Clinical Cohort Analysis of Germline *EGFR* T790M Demonstrates Penetrance Across Ethnicities and Races, Sexes, and Ages

Darcy K. Berry, MS, CGC[1,2]; Xia Wang, MD, PhD[2]; Scott T. Michalski, MS, LCGC[3]; Hio Chung Kang, PhD[3]; Shan Yang, PhD[3]; Benjamin C. Creelan, MD[4]; Howard L. McLeod, PharmD[2]; and J. Kevin Hicks, PharmD, PhD[2]

INTRODUCTION

The epidermal growth factor receptor (*EGFR*) T790M mutation has been well studied in lung cancer as a somatically acquired mutation that is predictive of resistance to first- and second-generation EGFR tyrosine kinase inhibitors but sensitive to the third-generation kinase inhibitor osimertinib.[1-3] Rarely, *EGFR* T790M has been identified as a germline variant associated with hereditary lung cancer.[4,5] Only a limited number of germline *EGFR* T790M carriers have been described, mostly white female nonsmokers diagnosed with lung cancer.[6-9] The occurrence of lung cancer among germline *EGFR* T790M carriers is proposed to be higher in women potentially because of estrogen-EGFR pathway interactions.[8,10] Overall, the estimated risk of developing lung cancer among nonsmoking *EGFR* T790M carriers is 31%, compared with a 0.2% risk in a general population of nonsmokers and an approximately 23% risk in a general population of smokers.[6,11] However, the sparse clinical data among non–lung cancer cohorts could falsely elevate the estimated hereditary lung cancer risk as a result of ascertainment bias.

Two newly identified, unrelated families harboring germline *EGFR* T790M are presented. In addition, a clinical laboratory database consisting of > 65,000 patients who underwent germline hereditary cancer risk assessment, not enriched for lung cancer, was data mined to determine the incidence of *EGFR* T790M and associated patient demographics. A greater understanding of the clinical characteristics associated with germline *EGFR* T790M may allow for continued development of lung cancer screening strategies and surveillance plans.

CASE REPORTS

Kindred A

A never-smoker 43-year-old white woman with a family history of breast cancer (Fig 1) was incidentally diagnosed with atypical adenomatous lung hyperplasia and followed by surveillance. Radiographic changes prompted bilateral lung biopsies with pathology consistent for lung adenocarcinoma. Pretreatment somatic molecular analysis identified *EGFR* T790M (61% allele frequency) and *EGFR* L858R mutations (42% allele frequency). Shortly after the proband was diagnosed with lung cancer, her maternal cousin was diagnosed with breast cancer at age 47 years and underwent a germline hereditary cancer risk panel test (Invitae, San Francisco, CA). A deleterious *PALB2* mutation was reported and likely contributed to the family's breast cancer history.

The discovery of the *PALB2* mutation in a relative prompted the proband and her 39-year-old sister to undergo genetic testing (Invitae) for hereditary cancer risk assessment. No *PALB2* mutations were observed, but unexpectedly, both individuals were heterozygous for germline *EGFR* T790M. Evaluation for a family history of lung cancer revealed that the proband's sister, who is a never-smoker, was diagnosed with bilateral lower lobe lung nodules by computed tomography (CT) at age 38 years. Furthermore, a never-smoker maternal aunt had been diagnosed with metastatic lung cancer at age 43 years, and the maternal grandfather, who was a smoker, had been diagnosed with lung cancer at age 71 years (Fig 1). The proband and her sister were referred to the INHERIT EGFR study (ClinicalTrials.gov identifier: NCT01754025), with a recommendation that the proband's sister undergo annual low-dose lung CT screening. Because no increased pediatric lung cancer risk has been described to date, it was recommended that the children of the proband and the proband's sister have *EGFR* genetic testing in early adulthood.

Kindred B

A never-smoker 49-year-old white woman was diagnosed with poorly differentiated metastatic lung adenocarcinoma. Pretreatment somatic molecular analysis (Foundation Medicine, Cambridge, MA) reported several *EGFR* alterations, including *EGFR* amplification (copy number of 10.0), *EGFR* T790M (57.8% allele frequency), and *EGFR* L861Q (40.8% allele frequency). A *CHEK2* T367fs*15 (64% allele frequency) nonsense mutation and *FANCD2* loss of exons 2-18 were also reported. Additional molecular analysis was performed to

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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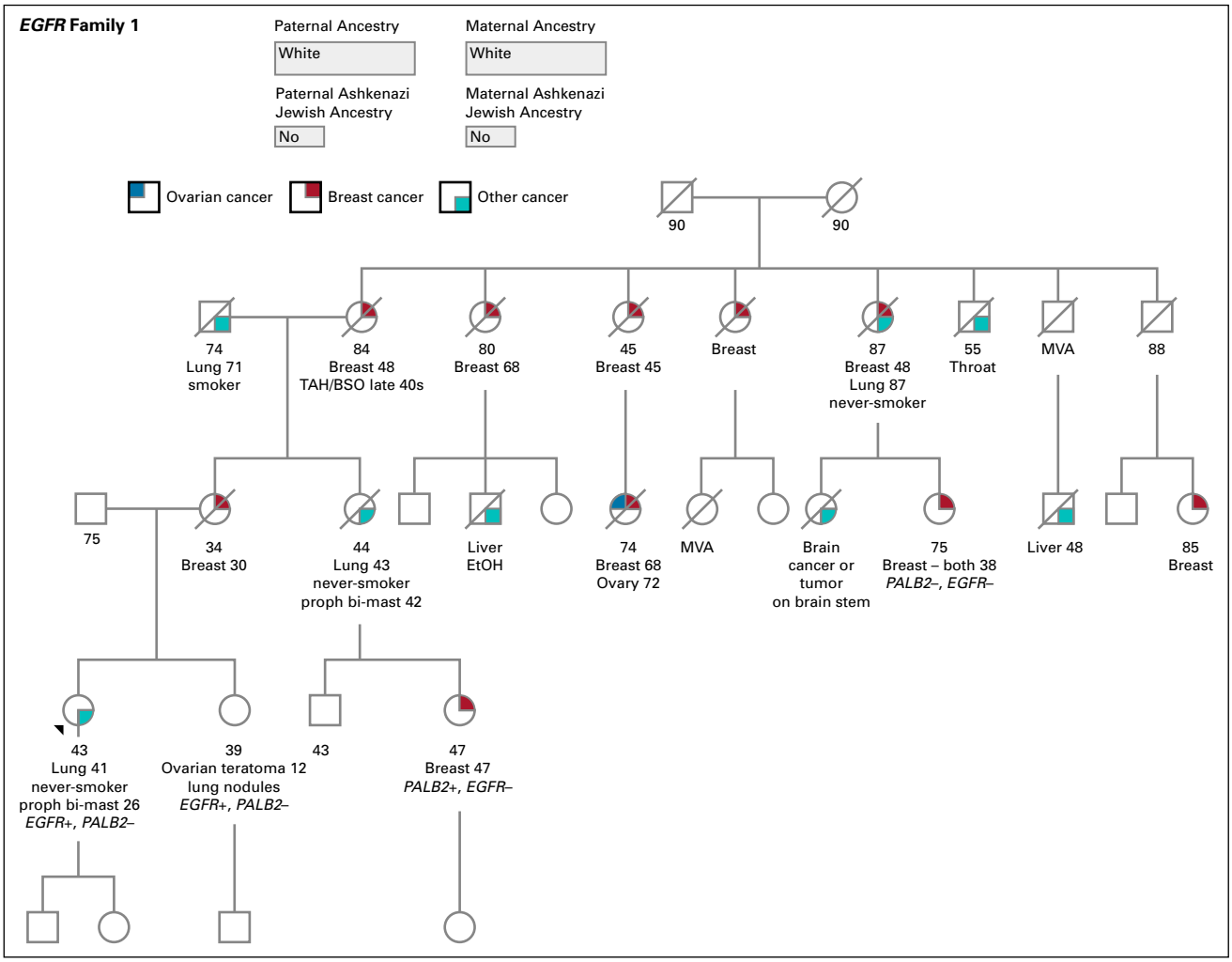

FIG 1. Pedigree of kindred A. The black arrow identifies the proband. BSO, bilateral salpingo-oophorectomy; EtOH, ethanol; MVA, motor vehicle accident; proph bi-mast, prophylactic bilateral mastectomy; TAH, total abdominal hysterectomy.

determine whether the reported mutations were somatic or germline alterations. Germline testing (Invitae) confirmed heterozygosity for *EGFR* T790M, *CHEK2* T367fs*15, and *FANCD2* deletion of exons 2-18. On the basis of the test results, the proband's 24-year-old daughter had germline testing performed and was found to have heterozygous *EGFR* T790M and *FANCD2* alterations (Fig 2). For the *EGFR* T790M variant, a recommendation was given to consider low-dose CT surveillance in the future.

CLINICAL COHORT ANALYSIS

Deidentified clinical data from a cohort of 65,218 individuals undergoing germline hereditary cancer risk assessment (Invitae) were analyzed for the incidence of *EGFR* T790M (methods described in Data Supplement). Although single-gene *EGFR* T790M germline testing was available, the clinical cohort consisted of individuals who were tested using an 83-gene cancer panel that included *EGFR* T790M. There was an overrepresentation of females (82.0%) and whites (59.6%) in the clinical cohort (Table 1). Age at time of germline testing was grouped into ranges to ensure confidentiality, with most patients having molecular analysis performed in the age range of 40-69 years (median, 54 years). A total of 29 individuals (0.04%) were found to be heterozygous carriers of *EGFR* T790M within this population of individuals undergoing hereditary cancer testing. There was no difference in incidence among males and females (P = .2; Table 2). Stratifying by race, 4 African Americans (0.13%), 19 whites (0.05%), and 6 individuals of mixed or unknown race (0.05%) were *EGFR* T790M carriers. The rate of incidence trended higher among African Americans, although it was not significant when compared with whites (P = .09) likely because of small sample sizes.

Cancer history was available for 26 individuals positive for *EGFR* T790M, with 14 (53.8%) having a history of lung cancer at time of genetic testing and 2 additional individuals having lung nodules (Data Supplement). The 26 individuals were found among 20 families. Thirteen

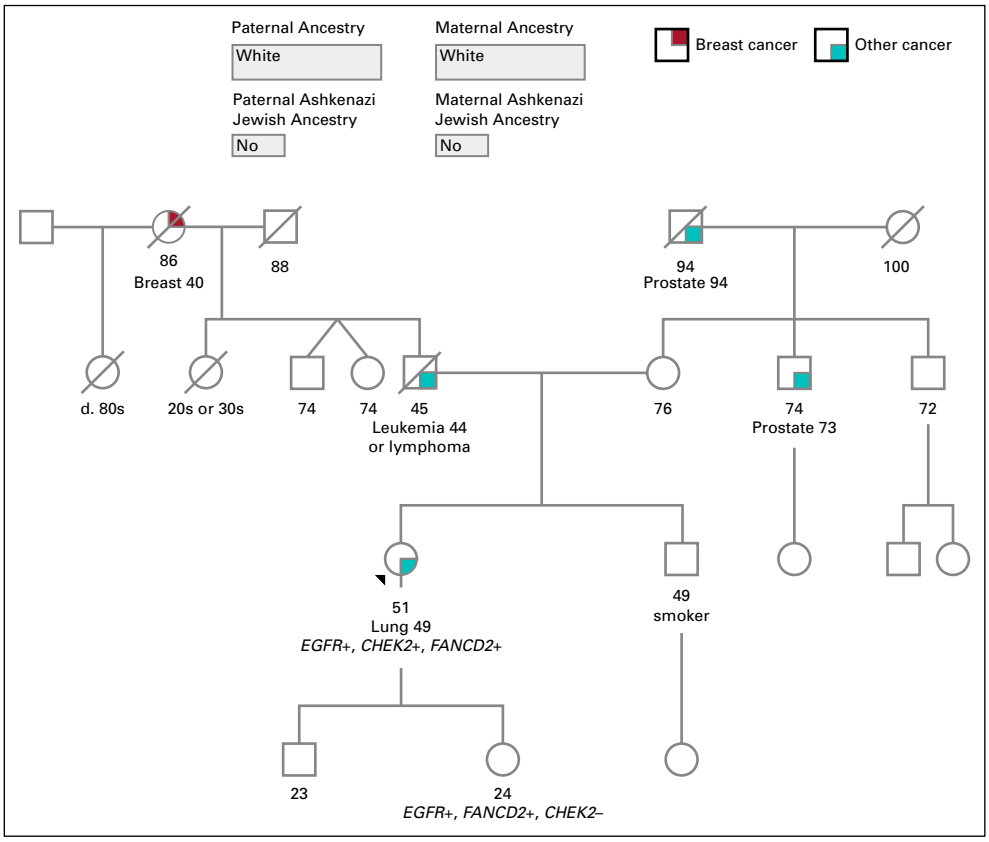

FIG 2. Pedigree of kindred B. Although the proband and her daughter are carriers of *EGFR* T790M, there was not a family history of lung cancer. The black arrow identifies the proband.

families had knowledge of an *EGFR* T790M variant discovered by somatic testing. On the basis of reported personal and/or family history, the remaining 7 families likely had genetic testing performed because of concerns regarding breast cancer risk. The mean age at lung cancer diagnosis was 56 years (range, 37-75 years; Data Supplement). No differences in rate of lung cancer diagnosis were observed among sex ($P = .2$) or age groups ($P = .2$; Table 2). The African American patients in the mutation-positive cohort were also impacted, with all 4 African Americans harboring *EGFR* T790M diagnosed with lung cancer.

DISCUSSION

A review of the literature found 14 studies describing histories of 38 patients with germline *EGFR* T790M.[4-9,12-19] Consistent with our case reports, 88.5% of individuals identified from the literature review for which race or ethnicity was reported were white. Sex was reported for 32 individuals, with 62.5% being female. Of the individuals with lung cancer for whom sex was reported, 71% were women. Taken together, prior studies consisting largely of familial lung cancer or lung cancer cohorts suggest that *EGFR* T790M hereditary lung cancer syndrome is more prominent among white females.

We analyzed a clinical database for incidence of *EGFR* T790M that consisted of > 65,000 patients, not enriched for lung cancer, who underwent germline hereditary cancer testing. Only 29 individuals were *EGFR* T790M carriers, consistent with prior studies suggesting that germline *EGFR* T790M is rare. The occurrence of *EGFR* T790M trended higher in African Americans. This observation is consistent with population studies showing *EGFR* T790M allele frequency of 0.02% in an African population and 0.004% in a European population.[20] Further epidemiologic studies are needed in African American populations, because confirmation would have important implications for screening strategies across patient groups in the United States.

Prior studies of *EGFR* T790M carriers suggest lung cancer development is observed in women of younger age. In the clinical cohort, development of lung cancer among those positive for *EGFR* T790M was comparable among men and women. Of the 22 patients identified in a literature review with age at lung cancer diagnosis provided, the median age was 57 years (range, 29-81 years). Consistent with historical data, the median age of cancer diagnosis in the clinical cohort was 56 years, ranging from 37-75 years. Taken together, the age at lung cancer diagnosis appears to be significantly younger for *EGFR* T790M carriers when compared with a median age of

TABLE 1. Invitae Clinical Cohort Demographic and Testing Characteristics

Characteristic	No. (%) of Participants (N = 65,218)
Sex	
Female	53,449 (82.0)
Male	11,767 (18)
Unknown	2 (0.003)
Self-declared race or ethnicity	
Ashkenazi Jewish	3,428 (5.3)
Asian	2,788 (4.3)
Black/African American	3,140 (4.8)
Hispanic	4,339 (6.7)
Mixed/other/unknown	12,670 (19.4)
White	38,853 (59.6)
Age at testing, years[a]	
0-39	11,998 (18.4)
40-69	43,690 (67)
≥ 70	9,530 (14.6)
EGFR T790M results	
Germline carrier	29 (0.04)

[a]Age at time of testing was grouped into ranges for confidentiality.

70 years at diagnosis for lung and bronchus cancer reported by SEER[21]; however, this finding may be a result of a testing bias toward individuals diagnosed at unusually young ages with lung cancer. Younger age of lung cancer onset should be considered when planning surveillance of unaffected mutation carriers.

Analysis of the clinical cohort had limitations, including a lack of race and sex diversity, unknown smoking status, small sample size as a result of the rarity of the mutation, and unknown testing indication for all individuals. Diagnosis of lung nodules or lung cancer after genetic testing was also not available for the clinical cohort. Penetrance could not be calculated because of incomplete family histories and limited genetic information among family members. Prevalence of germline *EGFR* T790M among a general population could not be inferred because our clinical cohort was enriched for those with personal and family histories suspicious for a hereditary cancer syndrome. These limitations do not diminish our findings that germline *EGFR* T790M and development of lung cancer are observed across races and ethnicities, sexes, and ages.

For both families described, *EGFR* T790M was initially discovered by somatic testing. The unexpected result of *EGFR* T790M in the pretreatment setting only prompted germline confirmation in the second family and was incidentally confirmed in the first family. A lack of germline *EGFR* T790M confirmation could prevent the consideration of screening and surveillance plans for family members that could potentially reduce the incidence of incurable metastatic lung cancer. Although there are currently no national surveillance recommendations for unaffected *EGFR* mutation carriers, previous studies have suggested implementing low-dose lung CT based on an observed reduction in lung cancer–associated mortality rates among smokers who underwent low-dose

TABLE 2. *EGFR* T790M–Positive Patients Stratified by Sex and Race or Ethnicity

Patient Characteristic	Total No. of Patients	No. of Patients (%)	
		EGFR T790M Positive	Diagnosed With Lung Cancer[a,b]
Sex			
Female	53,449	21 (0.04)	9 (0.02)
Male	11,767	8 (0.07)	5 (0.04)
Race or ethnicity			
Ashkenazi Jewish	0	0	0
Asian	0	0	0
Black/African American	3,140	4 (0.13)	4 (0.13)
Hispanic	0	0	0
Mixed/other/unknown	12,670	6 (0.05)	2 (0.02)
White	38,853	19 (0.05)	8 (0.02)
Age, years[c]			
0-39	11,998	5 (0.04)	1 (0.01)
40-69	43,690	19 (0.04)	9 (0.02)
≥ 70	9,530	5 (0.05)	4 (0.04)

[a]Lung cancer status as reported at the time of germline testing.
[b]Three patients found to carry *EGFR* T790M were excluded from further analysis as a result of state-specific confidentiality laws.
[c]Age at time of testing was grouped into ranges for confidentiality.

CT surveillance.[6,7,22] Both probands had lung cancer with activating somatic *EGFR* mutations. Among those with germline *EGFR* T790M who develop lung cancer, prior studies suggest the majority of individuals also have activating *EGFR* somatic mutations that potentiate cancer development.[8]

In the clinical cohort, > 60% of individuals with *EGFR* T790M were documented to have lung cancer or lung nodules. Because germline *EGFR* T790M can be identified incidentally and is clinically meaningful, individuals undergoing hereditary cancer risk assessment should be given the option to select a gene panel that includes *EGFR*. For individuals with a suspicious family history of lung cancer, *EGFR* testing should be strongly considered. Overall, our results support previous recommendations[5,15] that all individuals carrying somatic *EGFR* T790M mutations in the pretreatment setting or with high allele fraction on plasma cell-free DNA testing[3] be offered germline testing regardless of sex, ethnicity or race, or age.

AFFILIATIONS

[1]Navicent Health, Macon, GA
[2]Department of Individualized Cancer Management, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
[3]Invitae, San Francisco, CA
[4]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

CORRESPONDING AUTHOR

Darcy K. Berry, MS, CGC, H. Lee Moffitt Cancer Center, 10920 N McKinley Dr, MKC-Genetics, Tampa, FL 33612; e-mail: darcy.berry@moffitt.org.

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AUTHOR CONTRIBUTIONS

Conception and design: Darcy K. Berry, Scott T. Michalski, Howard L. McLeod, J. Kevin Hicks
Financial support: Howard L. McLeod
Administrative support: Howard L. McLeod
Provision of study material or patients: Benjamin C. Creelan
Collection and assembly of data: Darcy K. Berry, Scott T. Michalski, Hio Chung Kang, Shan Yang, Benjamin C. Creelan, Howard L. McLeod, J. Kevin Hicks
Data analysis and interpretation: Darcy K. Berry, Xia Wang, Scott T. Michalski, Shan Yang, Benjamin C. Creelan, Howard L. McLeod, J. Kevin Hicks
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Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Scott T. Michalski
Employment: Invitae
Stock and Other Ownership Interests: Invitae
Travel, Accommodations, Expenses: Invitae

Hio Chung Kang
Employment: Invitae, Guardant Health (I)
Stock and Other Ownership Interests: Invitae, Guardant Health (I)
Travel, Accommodations, Expenses: Invitae, Guardant Health (I)

Shan Yang
Employment: Invitae
Stock and Other Ownership Interests: Invitae
Travel, Accommodations, Expenses: Invitae

Benjamin C. Creelan
Consulting or Advisory Role: Boehringer Ingelheim, AbbVie, KSQ Therapeutics, BerGenBio, AstraZeneca/MedImmune, ARMO BioSciences, E.R. Squibb Sons, Gilead Sciences, GlaxoSmithKline
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Travel, Accommodations, Expenses: AstraZeneca

Howard L. McLeod
Leadership: Cancer Genetics
Stock and Other Ownership Interests: Cancer Genetics, Interpares Biomedicine
Honoraria: Genentech, Illumina
Consulting or Advisory Role: Gentris, Cancer Genetics, Saladax Biomedical, National Institutes of Health/National Cancer Institute, Admera Health, eviCore Healthcare, Pharmazam, Viecure
Speakers' Bureau: Genentech
Other Relationship: Northwestern University, Xiangya Hospital

J. Kevin Hicks
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