Inherited Germline *T790M* Mutation and Somatic Epidermal Growth Factor Receptor Mutations in Non-small Cell Lung Cancer Patients

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Five cases of non-small cell lung cancer, associated with germline transmission of epidermal growth factor receptor (*EGFR*)-*T790M* mutation, have been reported[1]; these patients had family histories of lung cancer. The activity of gefitinib was tested in only two patients, who were both refractory to this drug.[2] Herein, we describe a family of European descent in which two family members had non-small cell lung cancer associated with germline transmission of *T790M* mutation and who were treated with gefitinib (Figure 1*A*).

The proband was a 72-year-old female, never-smoker, who was diagnosed with an adenocarcinoma of the lung with bilateral pulmonary lesions. This patient was initially treated with chemotherapy for four courses, resulting in stable disease for 6 months, as determined by radiological examination. When the disease progressed, treatment with oral gefitinib at the dose of 250 mg/d was initiated, resulting in a partial response lasting for 9 months; subsequently, the patient developed pleural and cerebral progression of disease and died within 5 months.

A 74-year-old never-smoker sister of the proband was diagnosed with a poor differentiated locally advanced (stage IIIB for pleural effusion) carcinoma of the lung and was treated with a first-line chemotherapy, resulting in a partial response lasting for 12 months, after which new bone metastases were observed. As second-line treatment, oral gefitinib 250 mg/d was started, and a partial response was obtained that is lasting from 45 months; the patient is still alive and on treatment with gefitinib. No other members of this family developed lung cancer.

DNA was isolated from peripheral blood mononuclear cells or paraffin-embedded tumor samples, using the microDNA-kit (Qiagen, Hilden, Germany). Nested polymerase chain reaction to amplify *EGFR* (exons 18–21) and *K-RAS* (exon 1) and sequencing of polymerase chain reaction products on a ABI-3100 Genetic Analyzer was performed.

The *EGFR-T790M* mutation was found in the germline DNA of both patients (Figure 1*B*), whereas no mutations were detected in the *EGFR* exons 18, 19, and 21. In contrast, no *EGFR* mutations were observed in the two daughters of proband and in the two sons of individual II.

In the tumor tissue of individual I, we identified the deletion of *EGFR E746-A750* in exon 19 but no *EGFR* mutations in the exons 18, 20, and 21 (Figure 1*C*). In the tissue of individual II, no *EGFR* mutations in the exons 18, 19, and 21 were found, whereas the exon 20 could not be studied because no sufficient tumor tissue was present. No mutations were observed in codons 12 and 13 of *K-RAS* exon 1 in the tissues of both patients.

Our data support the hypothesis that an inherited *T790M* mutation confers an enhanced susceptibility to develop lung tumors[3]; moreover, the presence of a *T790M* germline mutation does not necessarily predict for resistance to EGFR-tyrosine kinase inhibitors.

The responses to gefitinib could possibly be due to the absence of *T790M* and *K-RAS* mutations and the occurrence of *EGFR*-activating mutations in the tumor tissues. However, other mechanisms, such as increased gene copy number,[4] may be responsible for response to gefitinib in the case of individual II.

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Disclosure: The authors declare no conflicts of interest.

The first two authors equally contributed to this study. Dr. Davide Torti contributed to the initial analysis.

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ISSN: 1556-0864/11/0602-0395

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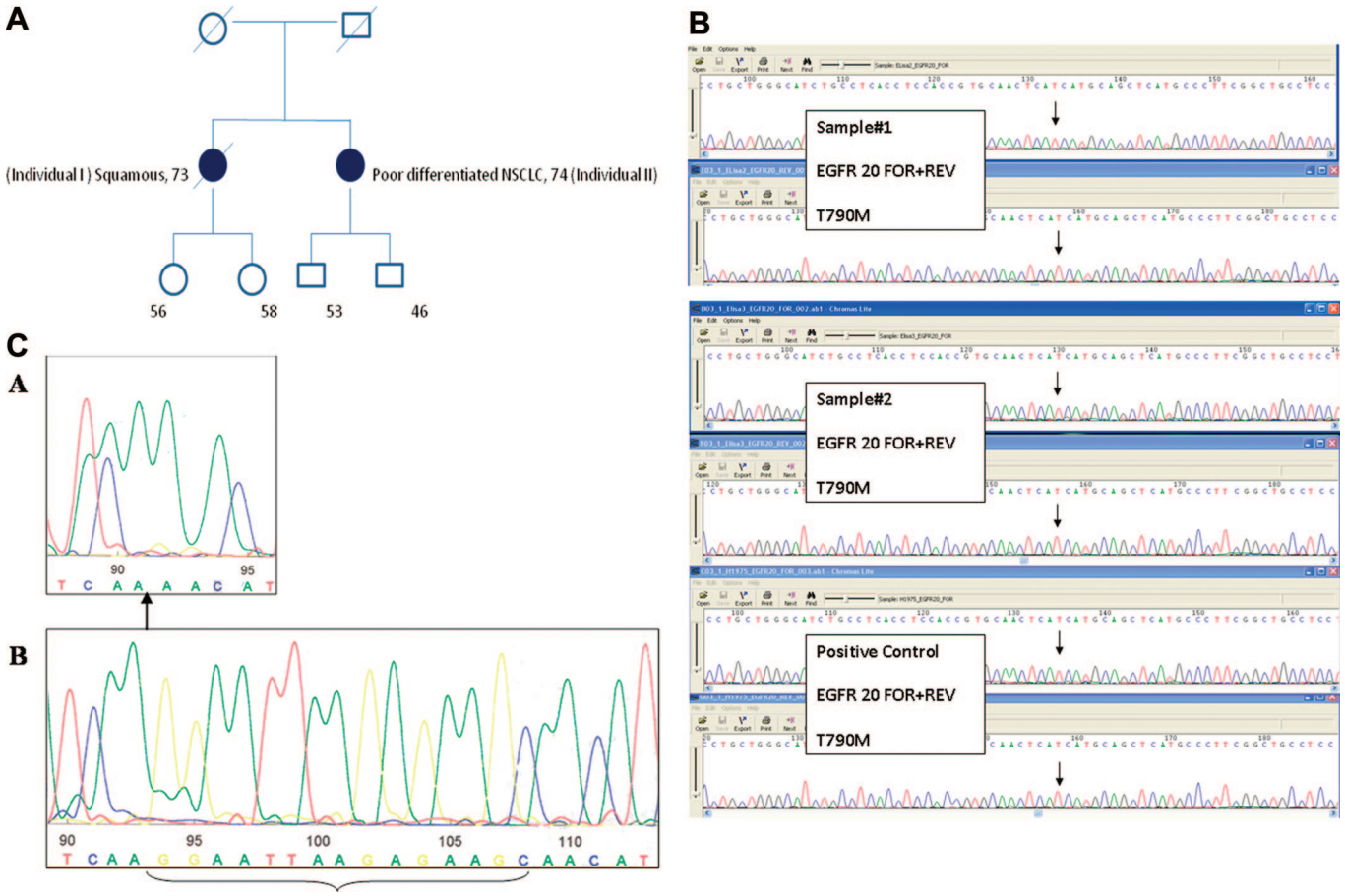

FIGURE 1. *A*, Pedigree of a family with cases of non-small cell lung cancers. *B*, Representative electropherogram for EGFR sequencing of the samples of the proband (sample #1) and her sister (sample #2). Sample #1 and #2 harbored a *T790M* mutation that was read from both the forward and reverse sequence. The figure also includes a positive control. Furthermore, the analysis included a sample with a known wild-type sequence at position 790, and a negative control (water), which was negative, excluding the chance of contamination. *C*, Representative electropherogram of the deletion *E746-A750* (ELREA) in *EGFR* exon 19 (panel *B*) in comparison with the wild-type sequence (panel *A*), as detected in the tumor tissue of the proband. EGFR, epidermal growth factor receptor.