Frequency of *EGFR* mutations in Non-Small-Cell Lung Cancer (NSCLC) from Greek patients

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Background: Iressa (Gefitinib) has recently received license for the treatment of first line NSCLC patients harboring activating somatic mutations within the tyrosine kinase (TK) domain of the epidermal growth factor receptor (*EGFR*). Treatment of patients harboring *EGFR* mutations with gefitinib leads to improved response and survival outcomes, therefore screening for *EGFR* mutations has entered routine clinical practice. Several clinico-pathological factors correlate with these mutations including gender, smoking history, and histology. The frequency of *EGFR* mutations is also ethnicity-dependent, wherein the incidence in Asian populations is ~30%, while in Caucasians (Whites) it is lower, ~15%. However, limited data is available on intra-ethnic differences throughout Europe.

Aim: The aim of this study was to determine the frequency and spectrum of *EGFR* mutations in an unselected group of Greek NSCLC patients.

Methods: We set up High Resolution Melting (HRM) assays to identify mutations in exons 18-21 of the *EGFR* gene. Validation of the sensitivity of the HRM analysis (HRMA) was tested by making serial dilutions of a sample with a known mutation and tumor cell content (TCC) (Fig.1).
Formalin-fixed paraffin embedded (FFPE) tissue samples from 698 patients were analyzed for somatic *EGFR* mutations. HRMA was used for initial screening and the mutation status was verified by bi-directional sequencing (Figs. 2 and 3). Pathological review was obtained for all samples and macro-dissection was used to ensure a tumor cell content (%TCC) of >75% in all possible cases.

Figure 1: HRMA Sensitivity

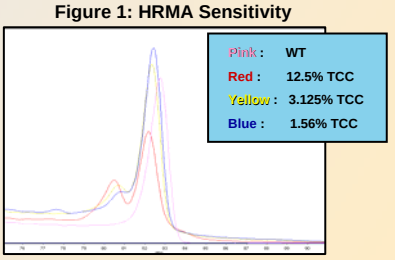


Figure 2: ex.19 delE746-

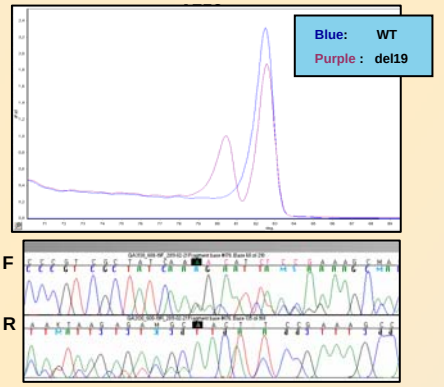
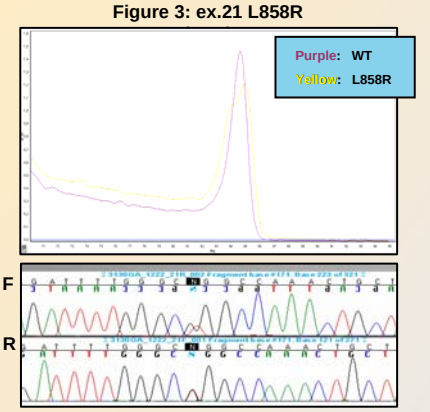


Figure 3: ex.21 L858R

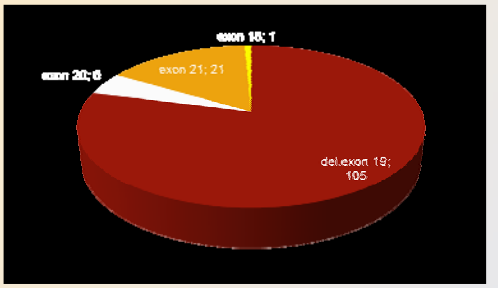


Results: The sensitivity of our HRM assays was found to be ≤1.5% (Fig.1).

In the entire cohort (n=698) the frequency of activating mutations was **19.05%** (133 mutations);

- 105 x exon 19
- 21 x exon 21
- 6 x exon 20
- 1 x exon 18 (Fig.4)

Figure 4: Mutation distribution among *EGFR* exons 18-21



Conclusions: Applying a very sensitive mutation detection technique in a large cohort of unselected Greek NSCLC patients in routine diagnostic practice, we obtained an overall mutation frequency of **19.05%**. This mutation frequency is similar to that found by the SLADB and EURTAC studies in European populations.

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