LETTER TO THE EDITOR

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Distribution Data of Epidermal Growth Factor Receptor Mutations Detected by Next-Generation Sequencing Method in Non-Small Cell Lung Cancer

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Despite significant developments made in early diagnosis and treatment, the incidence of lung cancer remains high both in Turkey and worldwide, and it is one of the leading causes of cancer-related deaths.[1] When we evaluate Turkey, according to the age-standardized cancer rate in males, lung cancer occupies first place with 57.7%, and in females, it is at fifth place with 9.8%. 80% of lung cancer cases are non-small cell lung cancer (NSCLC), most of them are diagnosed at an advanced stage, and only 19% of patients can live for five years or longer.[2] The dominant histological subtype in NSCLC is adenocarcinoma both in the world and in Turkey (47.1%).[3]

The molecular pathogenesis of NSCLC is very complex and heterogeneous. Specific mutations can cause, accelerate, or slow the formation of lung tumors. Remarkable advances have been made in the diagnosis and management of lung cancer over the last two decades, with the discovery of "driver" mutations that can be targeted by specific therapeutic inhibitors.[4] However, functionally insignificant "passenger mutations" can be detected in lung cancer.[5]

Epidermal growth factor receptor (EGFR), KRAS, BRAF, RET, MET, ERBB2 [HER2], and neurotrophic tyrosine receptor kinase mutations can be detected with tests performed with multiple genetic sequencing panels in laboratories with the next-generation sequencing (NGS) method, and multiple treatment options can be obtained. The histological types recommended for testing are adenocarcinoma, adenosquamous carcinoma, large cell carcinoma, and NSCLC not otherwise specified types. In the case of high clinical suspicion (individuals under 50 years, never smoked or smoked very little, adenocarcinoma component cannot be excluded due to insufficient tumor tissue), the test can be applied in histologies other than adenocarcinoma.[6]

EGFR, HER1/erbB1, a member of the HER/erbB growth factor receptor family, is a tyrosine kinase receptor found on the surface of epithelial cells and shows overexpression in several cancers. This cell surface protein consists of the extracellular part (to which the ligand is attached), the transmembrane part, and the intracellular tyrosine kinase parts. The binding of the ligand to the receptor activates receptor dimerization and tyrosine kinase autophosphorylation, increases cell proliferation, angiogenesis, and metastasis through intracellular signaling pathways such as Ras-Raf-MEK-ERK and PI3K-AKT-mTOR,

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and inhibits apoptosis. Overexpression of the ligand or receptor and mutations in the receptor may cause inappropriate activation of this receptor-signaling pathway.[7]

EGFR mutations have both predictive and prognostic value for NSCLC and are associated with some clinicopathological features (e.g., smoking, gender, age, ethnicity, histological type).[8] The presence of EGFR gene mutation in NSCLC varies according to society. It has been reported at a rate of 14% in the USA, 7% in Australia, 11% in France, and 8% in other western countries, and it is generally observed to be 2-14% in western societies.[9,10] Several studies have reported a high incidence (27-42%) of EGFR mutations in the Far East, such as 27% in Japan, 34% in Taiwan, and 30% in other East Asians.[9-11] The frequency of EGFR gene mutations is 2.9% in Saudi descent and between 2 and 5% in Arabian descent as reported in few studies.[12]

In the current study, the frequency of EGFR was 19% in 1,081 cases evaluated with the NGS method in the Turkish population. Exon 19 and 21 mutations, which constitute almost 90% of EGFR mutations, are defined as "classic" EGFR mutations, of which 45% are exon 19 deletions and 40% are exon 21 L858R point mutations.[13] In addition to these activating mutations, exon 19 insertions constitute up to 10% of all EGFR mutations; and exon 21 L861Q, exon 18 G719X, and exon 20 S768I point mutations are associated with sensitivity of small molecules [EGFR-tyrosine kinase inhibitors (TKIs)] such as erlotinib, gefitinib, afatinib, osimertinib, and dacomitinib.[13,14] Most exon 20 insertions and NSCLC with exon 20 T790M point mutations are unresponsive to EGFR-TKIs.[15] In advanced NSCLC with an activating EGFR mutation, a 67% response rate to EGFR-TKIs and overall survival of approximately 24 months have been reported.[16]

EGFR mutations are commonly analyzed by real-time polymerase chain reaction, Sanger sequencing, and NGS methods. The reporting period for all tests is recommended as 10 weekdays (2 weeks). In the NGS study, these analyses take 2-3 weeks.[6] With the increasing use of the NGS test, new EGFR variants are identified.

In this study, amplification was detected in 39 out of 215 cases evaluated by the NGS method, loss of EGFR in 5, intron 19 in three, intron 2 in two, and intron 1 in one case. Of the 165 patients with remaining EGFR mutations, EGFR mutations were detected in 10 different exons; five patients had exon 23 mutations, 54 (32.7%) had exon 21, 17 had exon 20, 72 (43.6%) had exon 19, four had exon 18, two had exon 17, one had exon 16, three had exon 15, and five patients had exon 5 mutations. One hundred and twenty-six (58%) patients had "classical" EGFR mutation. Exon 19 deletion was detected in 72 of these patients, and exon 21 point mutation in 46 patients with p.L856R (27.9%) mutation. Exon 20 c.2369C>T p.T790M mutation associated with resistance in TKI treatment was detected in only four (2.8%) patients. Table 1 shows the distribution of EGFR mutations in 165 patients.

Overall, the mutation distribution in the Turkish population showed similarity to that in other populations worldwide in literature. These mutations detected by NGS technology may help clinicians in their treatment decision. Rare mutations may be targets for preclinical drug development.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *İrfan Çiçin, İvo Gökmen;* ***Design:*** *İvo Gökmen;* ***Control/Supervision:*** *İrfan Çiçin;* ***Data Collection and/or Processing:*** *Sezin Sayın, Ali Gökyer, İvo Gökmen, Ebru Taştekin;* ***Analysis and/or Interpretation:*** *İrfan Çiçin;* ***Literature Review:*** *İvo Gökmen;* ***Writing the Article:*** *İvo Gökmen, Sezin Sayın;* ***Critical Review:*** *Ali Gökyer;* ***References and Fundings:*** *İvo Gökmen;* ***Materials:*** *İvo Gökmen, Ebru Taştekin.*

TABLE 1: Distribution of EGFR mutations in 165 patients.

Exon	EGFR mutation	Protein position		Number of patients (n=165)
23	c.2703G>T	p.6901G		2
	c.2709 T>A	p.T903T		3
21	c.2573T>G	p.L858R		46
	c.2582T>A	p.L861Q	1	
	C.2491 C>T	p.R831C	1	
	c.2490C>T	p.D830D	1	
	c.2582T>G	p.L861R		1
	c.2508 C>T	p.R836R	3	
	c.2580A>G	p.K860K	1	
20	c.2369C>T	p.T790M	4	
	c.2454G>A	p.v819v		1
	c.2319del	p.H773del		
	c.2319_2320insCACCCCCAC	p.H773_V774ins		1
	c.2361G>A	p.Q787Q	1	
	c.2286A>G	p.E762E		1
	c.2300_2308dup	p.A767_V769dup	1	
	c.2303_2311dup	p.S768_D770dup		2
	c.2311_2319dup	p.N771_H773dup	4	
	c.2303G>T	p.S768I		1
19	c.2235_2249 del	p.E746_A750del		72
18	c.2155G>T	p.G719C	1	
	c.2156G>C	p.G719A	2	
	c.2127_2129delAAC	p.E709_T710delinsD		1
17	c.2030G>a	p.R677H	1	
	c.2047C>T	p.L683L		1
16	c.1960G>A	p.V654M	1	
15	c.1821C>T	p.V607V	2	
	c.1802G>C	p.G601A	1	
13	c.1562G>A	p.R521K	3	
	c.1509C>T	p.G503G	2	
3	c.2703G>T	p.G.901G	1	
	c.379G>A	p.A127T	1	

EGFR: Epidermal growth factor receptor; NGS: Next-generation sequencing.

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