Germline Mutations in High Penetrance Genes are Associated with Higher Pathologic Stage and Increased Cancer Recurrence in Patients with Non Small Cell Lung Cancer

Objective: To determine both the frequency of pathogenic mutations in high penetrance genes (HPGs) in patients with lung adeno or squamous cell carcinoma and whether the presence either HPGs or an elevated genetic risk score (GRS) is associated with different clinical phenotypes and oncologic outcomes.

Methods: Patients with NSCLC who had consented to participate in a prospectively collected linked clinical database and biorepository and had either a blood or tissue sample were included in the study. Their germline DNA was sequenced using a targeted next-generation sequencing panel that includes both cancer-associated HPGs genes and known lung cancer risk-associated SNPs to assess for the presence of HPGs and to calculate a GRS. This data was then linked to the corresponding clinical database to assess for association between germline mutations and clinical phenotype, including pathologic stage, tumor grade, and disease recurrence using Fisher's exact test and multivariable logistic regression.

Results: We analyzed 151 patients with either primary lung adenocarcinoma or squamous cell carcinoma. Pathologic stage breakdown was 96 (64%) stage I, 31 (20%) stage II, 17 (11%) stage III, and 7 (5%) stage IV. Fifty patients (33%) were carriers for any HPG mutation. GRS was missing in 5 patients. The GRS was >1.5 (23%) in 34 patients. The presence of an HPG mutation was strongly associated with higher pathologic stage and a higher risk of recurrence. Of patients with any HPG mutation 48% (24/50) were stage II or higher and 26% (13/50) were stage III or higher, compared to 31% (31/101, p=0.04) and 11% (11/101, p=0.02) of patients without an HPG mutation. For patients with both an HPG mutation and a GRS >1.5, 73% (8/11) were stage II or higher and 36% (4/11) were stage III or higher, compared to 33% (45/135, p=0.02) and 14% (19/135, p=0.07), respectively, of patients who did not have both an HPG mutation and an elevated GRS. Twenty-Two percent (11/50) of patients with an HPG mutation had cancer recurrence compared with 11% (11/101) of patients without (p=0.07). In multivariable analysis, the presence of a DNA repair HPG mutation was associated with higher stage (OR 3.34 for stage >1, p=0.02) and the presence of a cancer-related HPG mutation increased recurrence (OR 3.91, p=0.03) (Table 1). Higher tumor grade was not associated with the presence of an HPG mutation or an elevated GRS score.

Conclusion: The presence of mutations in HPGs is associated with presentation at higher pathologic stage and a higher risk of disease recurrence. Germline testing may be helpful in predicting who is at risk for recurrence, and therefore may eventually prove useful in appropriate delivery of adjuvant chemotherapy. Further large studies are needed to better delineate the role of HPGs in cancer recurrence and the potential benefit of adjuvant treatment in patients harboring such mutations.

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