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INTRODUCTION

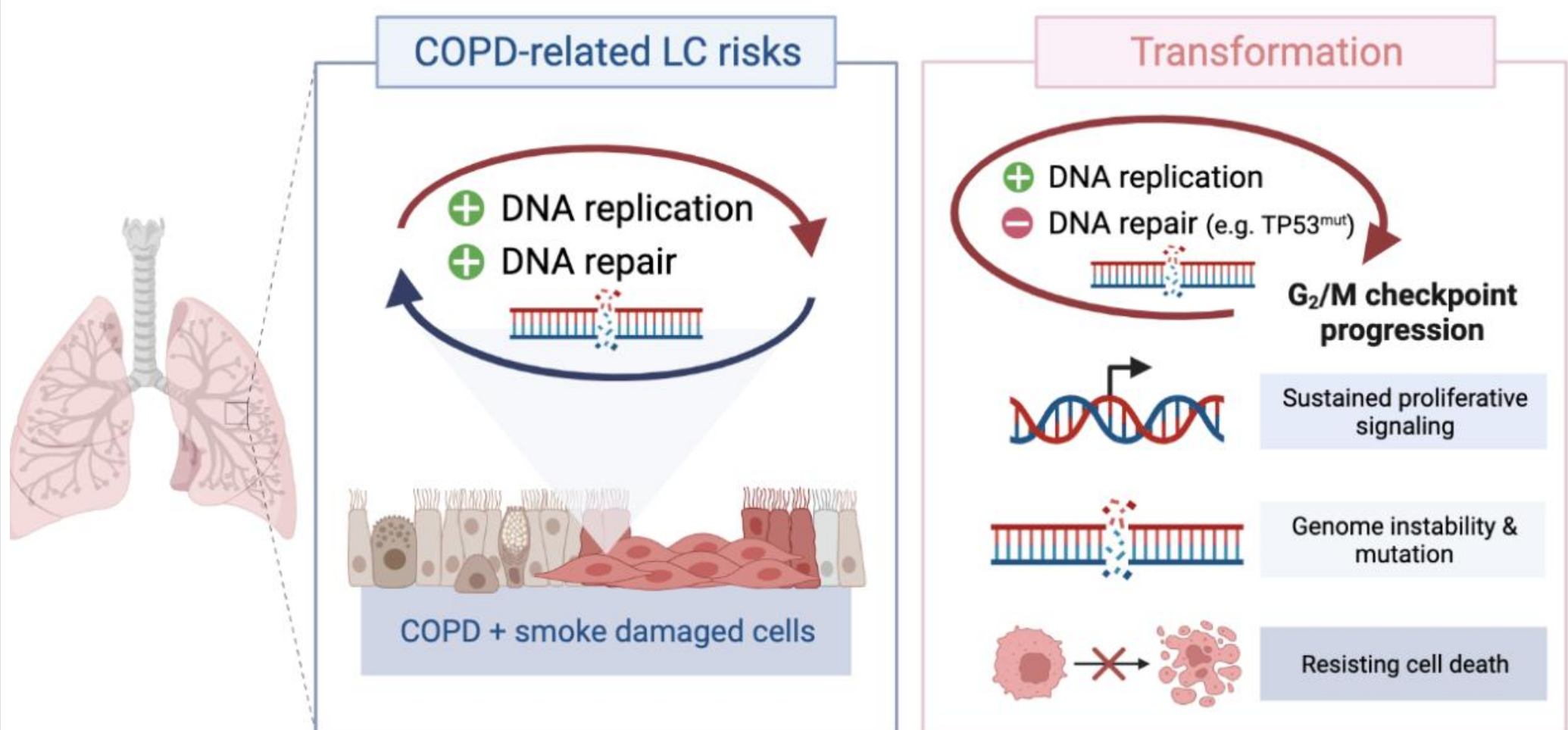
- Global burden:** Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, and lung cancer is the leading cause of cancer-related mortality.
- Independent risk:** Tobacco smoking is the primary risk factor for both diseases; however, COPD confers a 2- to 6-fold increased risk of lung cancer, independent of smoking history^{1,2}.
- Shared mechanisms:** COPD and lung cancer share overlapping pathogenic mechanisms, including chronic inflammation, oxidative stress, epithelial-mesenchymal transition, and genetic and epigenetic alterations³.
- Small Airways as Critical Site:** Small airway epithelium (SAE) is central to airflow obstruction, field cancerization, and a promising source of early detection biomarkers.
- Hypothesis:** We hypothesized that transcriptomic changes in COPD-affected small airways provide insights into the lung cancerization process.

METHODS

- Small airway epithelial cells**
n = 238 (Collected during bronchoscopy)
- Transcriptome profiling**
RNA
Affymetrix Human Gene 1.0 ST Array
- Gene co-expression network analysis (WGCNA)**
Expression programs associated with COPD and their preservation in lung adenocarcinoma tumors
- Prioritizing hub genes**
Module Membership
Gene Significance
Intra-Module Connectivity
• kME measures how strongly a gene follows the overall module expression pattern
• GS reflects the correlation of the gene with COPD diagnosis
• kWithin indicates how interconnected a gene is with other members of the module
- PLK4 overexpression in HBEC and H1299 cells, western blot + immunofluorescence**
- Cytological and morphological measurements**
Sample Collection and Analysis
Sputum Cytology
Bronchial Biopsies
Aneuploidy
n = 3270 subjects
n = 3258 subjects

DISCUSSION AND CONCLUSION

Proposed link between COPD and Lung Cancer (LC)



Left panel (COPD-related LC risks): Airway epithelial cells damaged by COPD and smoking are under constant proliferative pressure. These cells attempt to maintain tissue integrity by increasing DNA replication and DNA repair mechanisms. However, chronic injury and inflammation create a high baseline of DNA damage that the repair systems struggle to keep up with.

Right panel (Transformation): When repair pathways fail (such as with TP53 mutations) cells continue through the G₂/M checkpoint, replicating DNA despite unresolved damage. This leads to:

- Sustained proliferative signaling (cells keep dividing despite injury).
- Genome instability and mutation (errors accumulate in the genome).
- Resistance to cell death (mutated cells bypass apoptosis).

REFERENCES & ACKNOWLEDGEMENTS

- Gonzalez J, Marín M, Sánchez-Salcedo P, Zulueta JJ. Lung cancer screening in patients with chronic obstructive pulmonary disease. *Ann Transl Med*. 2016 Apr;4(8):160. doi: 10.21037/atm.2016.03.57. PMID: 27195278; PMCID: PMC4860483.
- Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. *Eur Respir J*. 2009 Aug;34(2):380-6. doi: 10.1183/09031936.00144208. Epub 2009 Feb 5. PMID: 19196816.
- Forder A, Zhuang R, Souza VGP, Brockley LJ, Lewarchuk ME, Telkar N, Stewart GL, Benard K, Marshall EA, Reis PP, Lam WL. Mechanisms Contributing to the Comorbidity of COPD and Lung Cancer. *Int J Mol Sci*. 2023 Feb 2;24(3):2859. doi: 10.3390/ijms24032859. PMID: 36769181; PMCID: PMC9918127.
- Tammemagi MC, Lam SC, McWilliams AM, Sin DD. Incremental value of pulmonary function and sputum DNA image cytometry in lung cancer risk prediction. *Cancer Prev Res (Phila)*. 2011 Apr;4(4):552-61. doi: 10.1158/1940-6207.CAPR-10-0183. Epub 2011 Mar 16. PMID: 21411501.
- Guillaud M, le Riche JC, Dawe C, Korbek J, Coldman A, Wistuba II, Park IW, Gazdar A, Lam S, MacAulay CE. Nuclear morphometry as a biomarker for bronchial intraepithelial neoplasia: correlation with genetic damage and cancer development. *Cytometry A*. 2005;63(1):34-40. doi: 10.1002/cyto.a.20101. PMID: 15614828.

Artificial Intelligence (AI) Use Disclaimer

No artificial intelligence tools were used in the development of this poster.

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Let's Connect

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Our Lab

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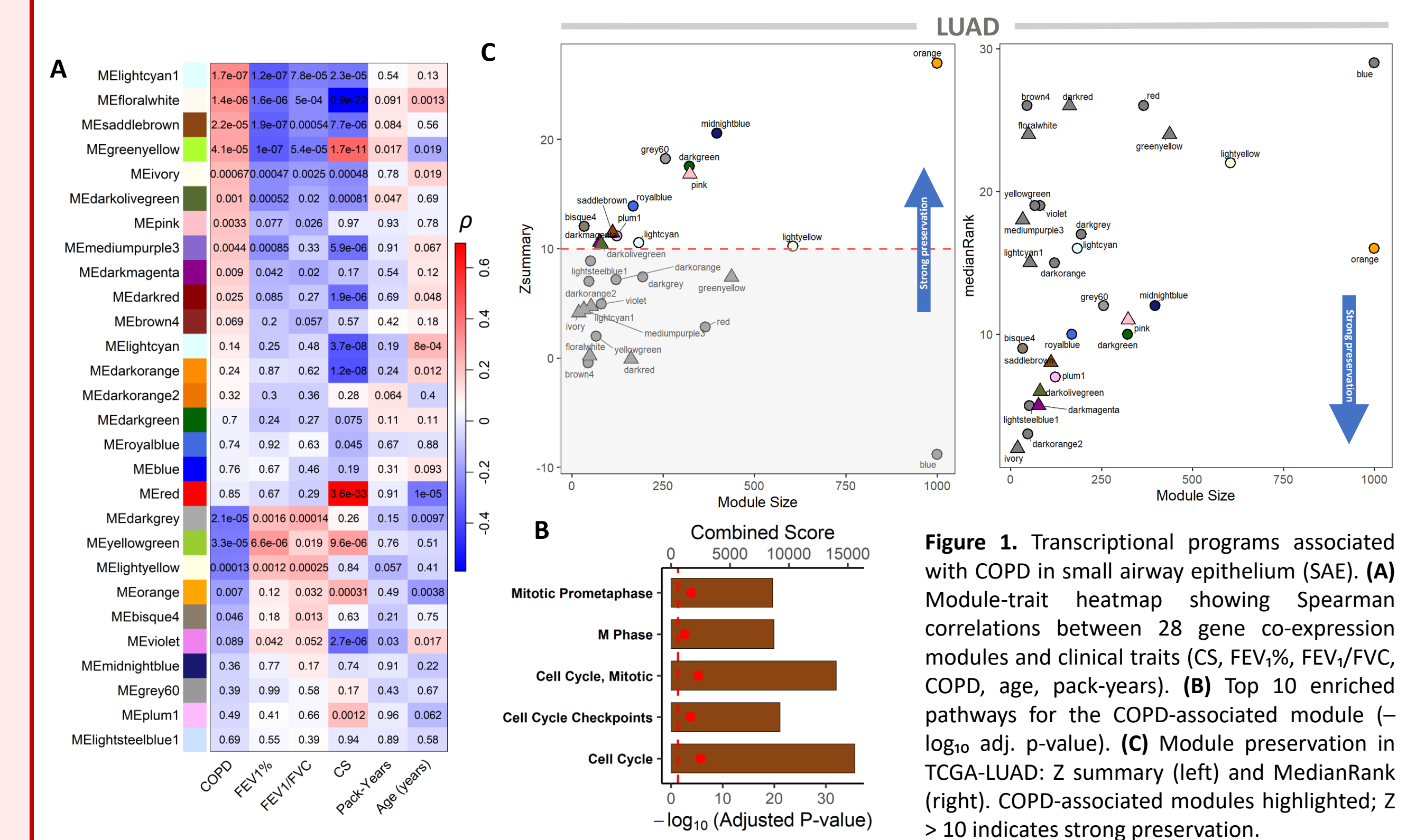
RESULTS

1 Cohort description

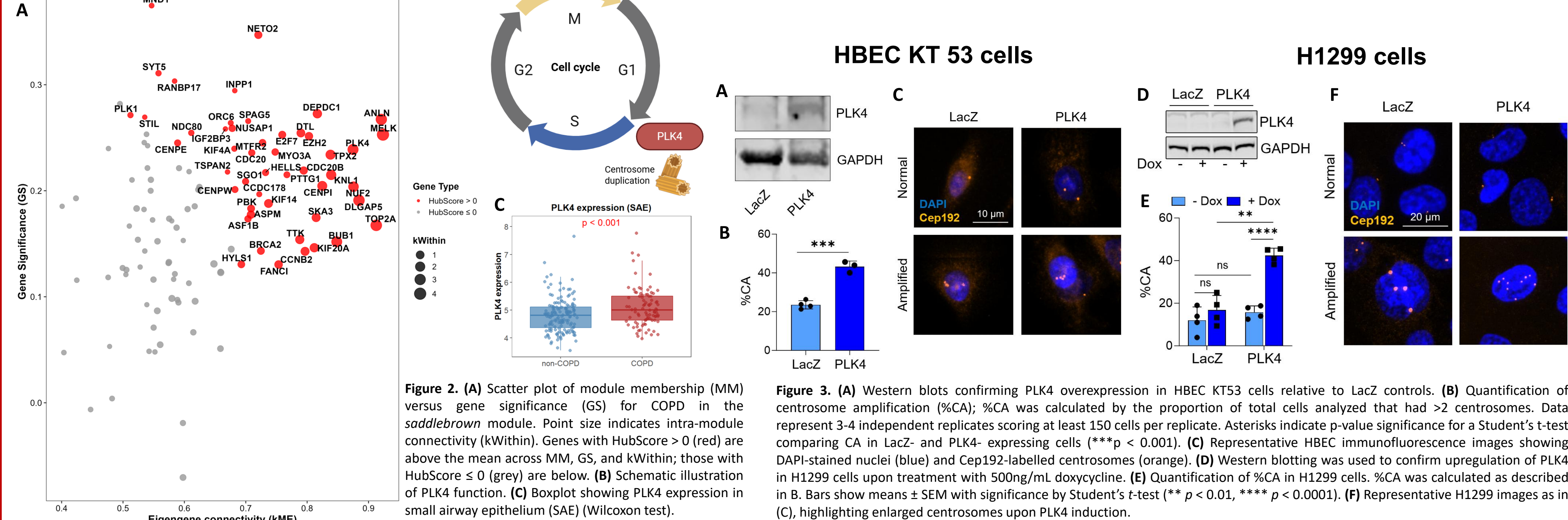
Table 1. Cohort Description				
		COPD (n = 105)	Non-COPD (n = 133)	P value†
Age (years) Average		64.1	65.1	0.17
Sex				
	Male	64	71	0.29
	Female	41	62	
Lung function				
	FEV1%	67.2	91.7	2.2e-16
	FEV1/FVC	60.1	76.4	2.2e-16
Smoking status				
	Current	43	56	0.96
	Former	62	77	
Pack-years		50.4‡	46.7‡	0.45

[†]Missing pack-years for 6 subjects with COPD and 10 subjects without COPD.
[‡]P-values were calculated using Chi-Square Tests for categorical variables (e.g., smoking status, history of asthma, inhaled medication usage) and Mann-Whitney U Tests for continuous variables (e.g., pack years, lung function measures) when normality assumptions were not met. Statistical significance was defined as p < 0.05, with significant values shown in bold.

2 A pro-mitotic transcriptional program links COPD and LUAD



3 Overexpression of genes in the pro-mitotic transcriptional program induces chromosomal instability in airway and lung cancer cells



4 A large cohort of precancerous lesions revealed marked nuclear irregularity and cellular aneuploidy in individuals with COPD, with these chromosomal instability metrics correlating with lung function and histological severity

