

Oliver Shutkever^{1,2}, Robert Bentham^{1,3}, Kerstin Haase^{1,2}, Carlos Martínez-Ruiz^{1,4}, Charlotte Grieco^{1,4}, Daniele Marinelli^{1,2,3}, Lorelle Brownlee¹, Sophia Ward^{1,4,5}, Selvaraju Veeriah¹, Lizi Manzano¹, Fiona Blackhall^{6,7,8}, Colin R. Lindsay^{6,7,8}, TRACERx Consortium, Charles Swanton^{1,4,9}, Nicholas McGranahan^{1,3}, David A. Moore^{1,4,10}, Mariam Jamal-Hanjani^{1,2,9}

1. Cancer Research UK Lung Cancer Centre of Excellence, University College London Cancer Institute, London, UK. 2. Cancer Metastasis Laboratory, University College London Cancer Institute, London, UK. 3. Cancer Genome Evolution Research Group, University College London Cancer Institute, London, UK. 4. Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London, UK. 5. Genomics Science Technology Platform, The Francis Crick Institute, London, UK. 6. Cancer Research UK Lung Centre of Excellence, The University of Manchester, Manchester, UK. 7. Division of Cancer Sciences, The University of Manchester, Manchester, UK. 8. Department of Oncology, The Christie NHS Foundation Trust. 9. Department of Oncology, University College London Hospitals, London, UK. 10. Department of Cellular Pathology, University College London Hospitals, London, UK

Correspondence: David Moore; d.moore@ucl.ac.uk

Introduction

- Pulmonary neuroendocrine tumours (NETs) exhibit diverse clinical behaviours and biological features
- Carcinoid tumours are typically indolent and frequently lack driver alterations
- Small cell lung carcinomas (SCLCs) and large cell neuroendocrine carcinomas (LCNECs) represent aggressive malignancies and are associated with a poor prognosis
- Knowledge of the molecular heterogeneity of pulmonary NETs may improve understanding of these tumours and support better prognostic stratification
- This study aims to characterise the genomic heterogeneity of NETs in a sub-cohort of patients recruited to the TRACERx study

Methods

- Classical/typical carcinoids (CCs), atypical carcinoids (ACs), SCLCs and some LCNECs were ineligible for the main TRACERx study, and were opportunistically sequenced due to the availability of fresh frozen tissue
- Multi-regional sampling of tumour tissue (77 regions from 26 patients) was performed alongside peripheral blood sampling
- Histological diagnoses were confirmed with subspecialist thoracic pathological central review
- Whole-exome sequencing of paired tumour and blood samples was performed prior to processing of genomic data with the TRACERx bioinformatic pipeline

Results and discussion

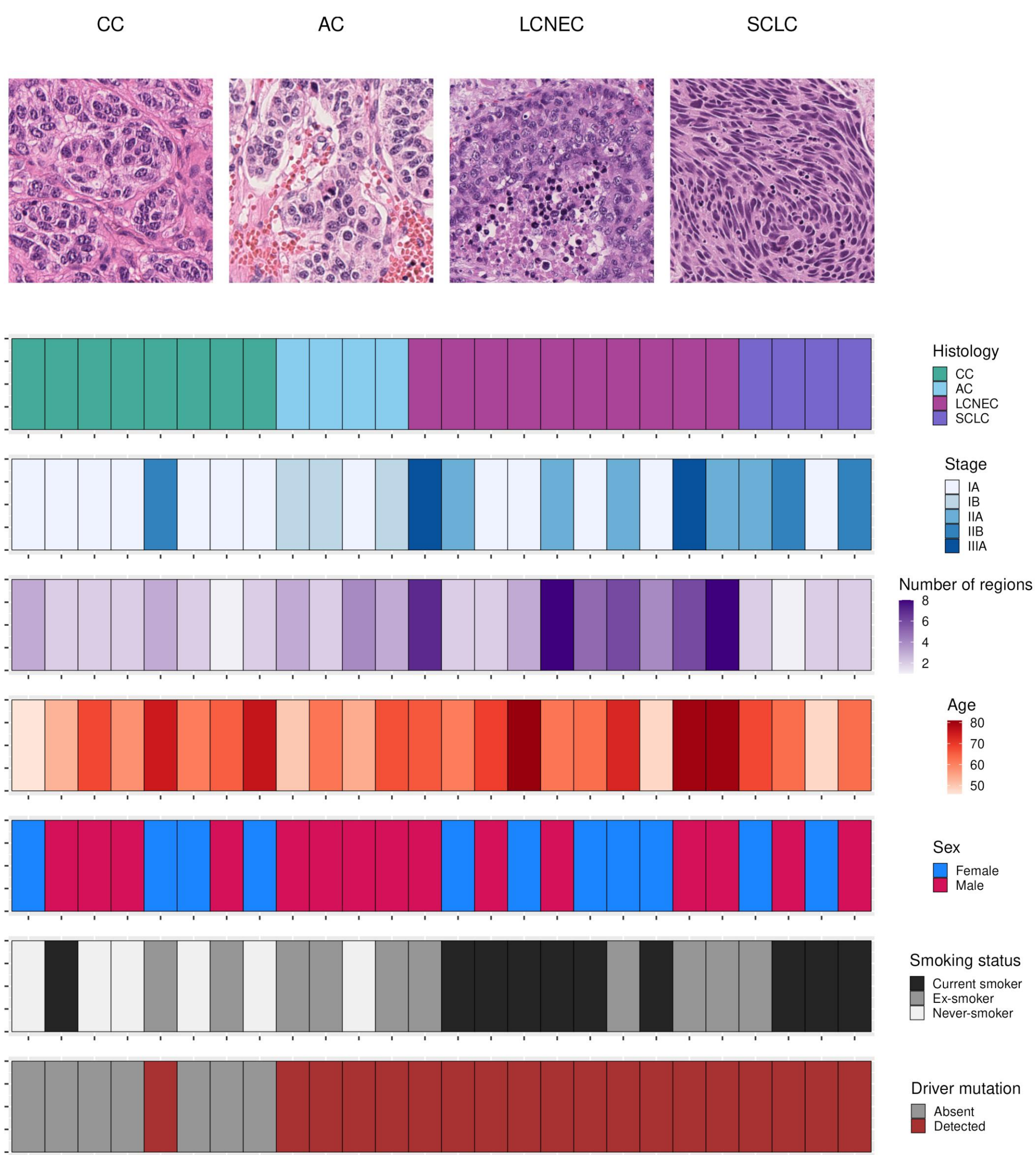
- CCs and ACs were characterised by a low burden of mutations and copy number alterations and limited genomic heterogeneity
- LCNEC and SCLC appeared more heterogenous, with more prominent branching of phylogenetic trees and increased chromosomal instability
- TP53* and *RB1* driver alterations were occasionally subclonal in LCNEC, which could impair tumour subtyping
- Analysis of synchronous SCLCs revealed two genetically unrelated tumours in the presence of a pathogenic germline *BRCA2* variant, highlighting the importance of driver profiling in this clinical scenario
- The possibility of earlier driver events and parallel evolution should be explored in larger LCNEC cohorts

Acknowledgements

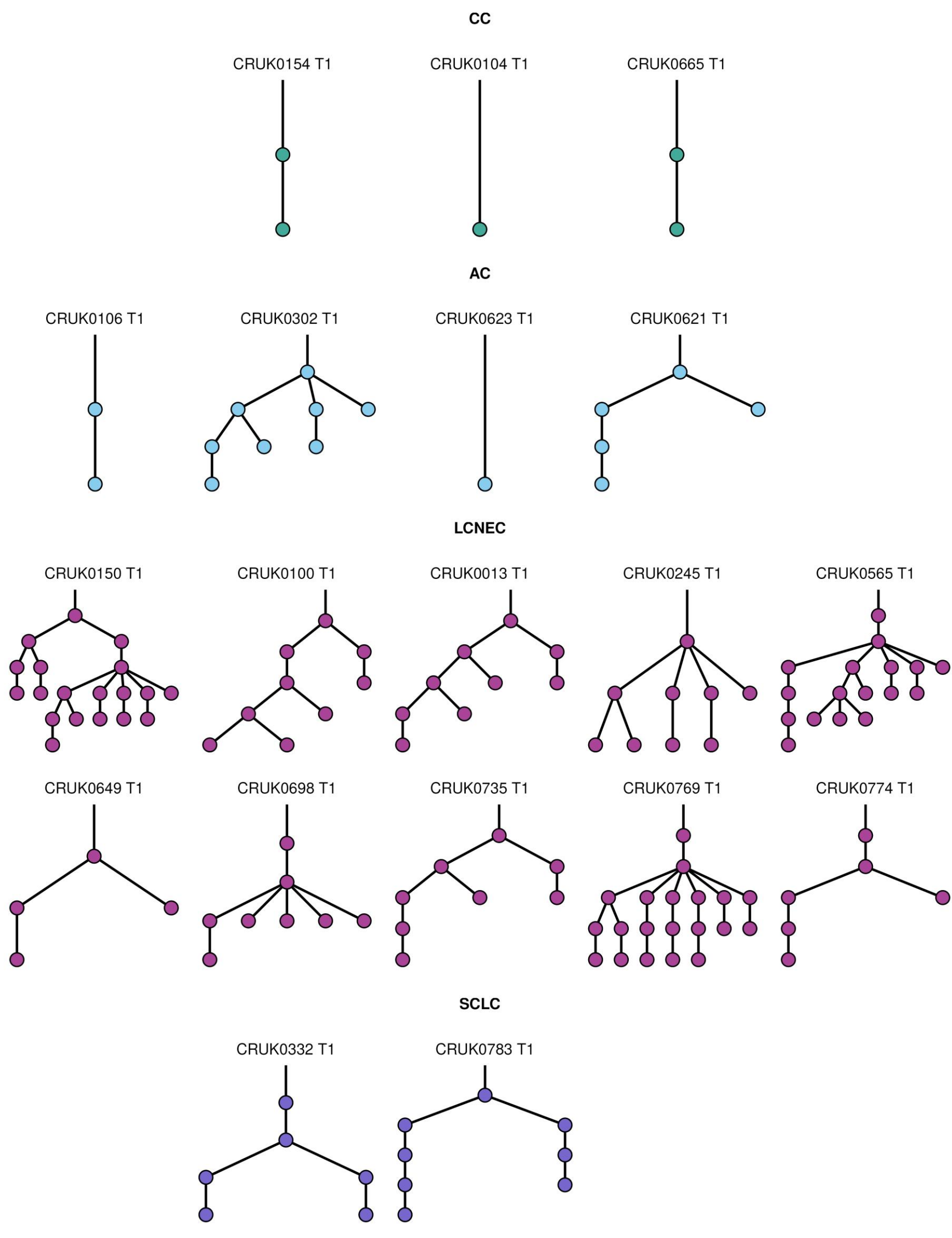
Cancer Research UK City of London Centre Award [CTRQQR-2021\100004]
Cancer Research UK Lung Cancer Centre of Excellence
UK and Ireland Neuroendocrine Tumour Society



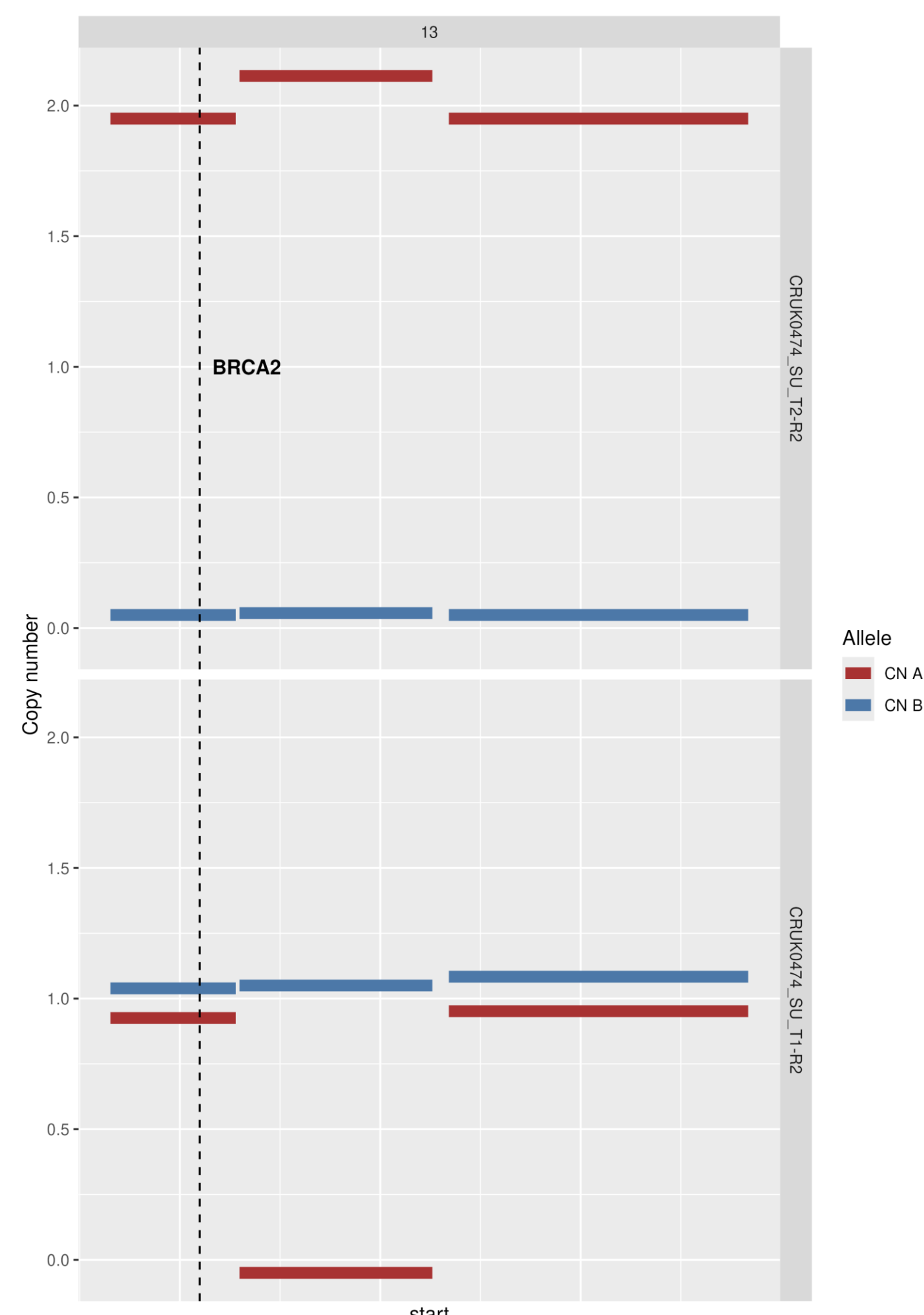
Cohort characteristics



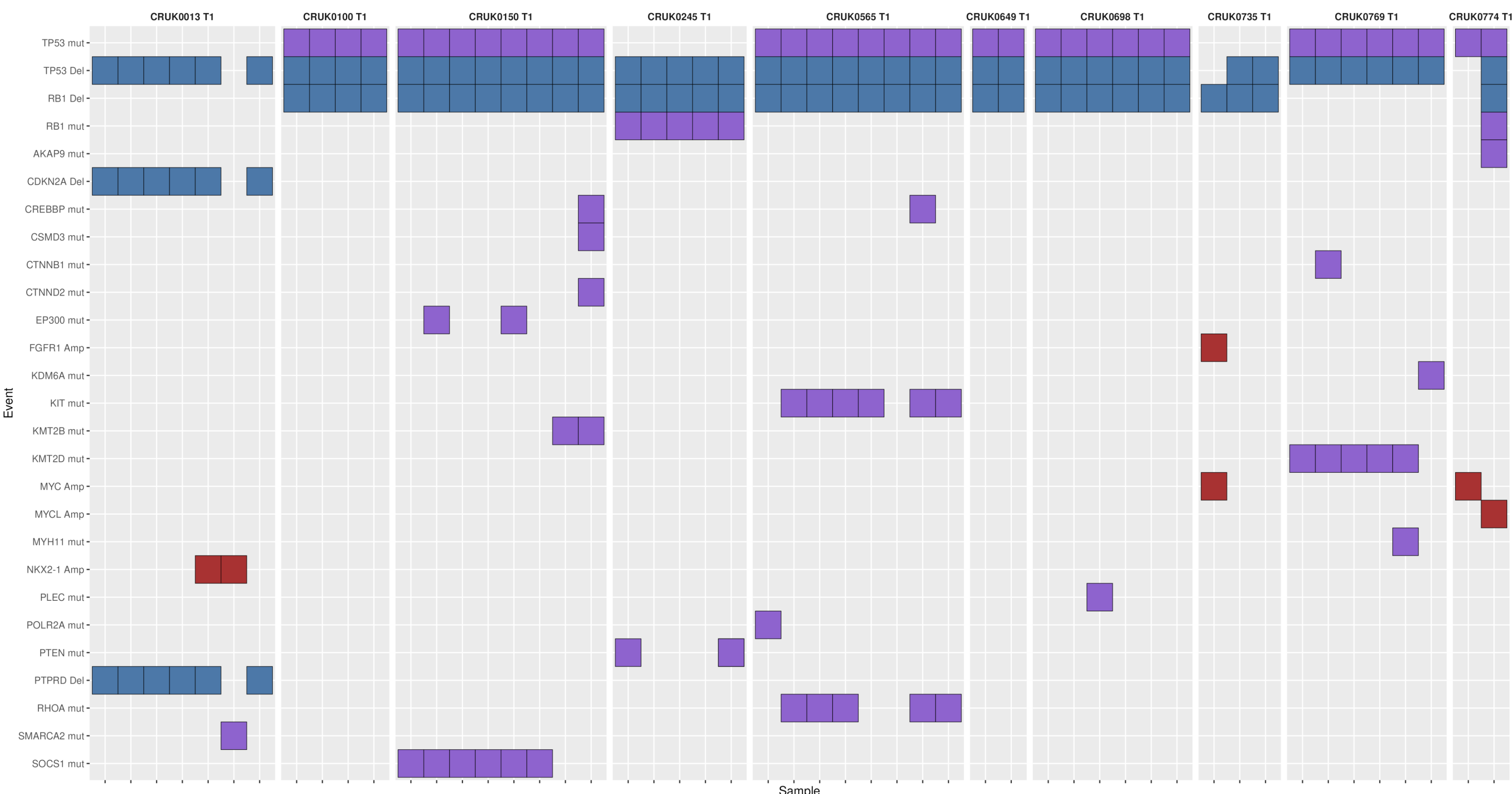
Reconstruction of clonal phylogenies



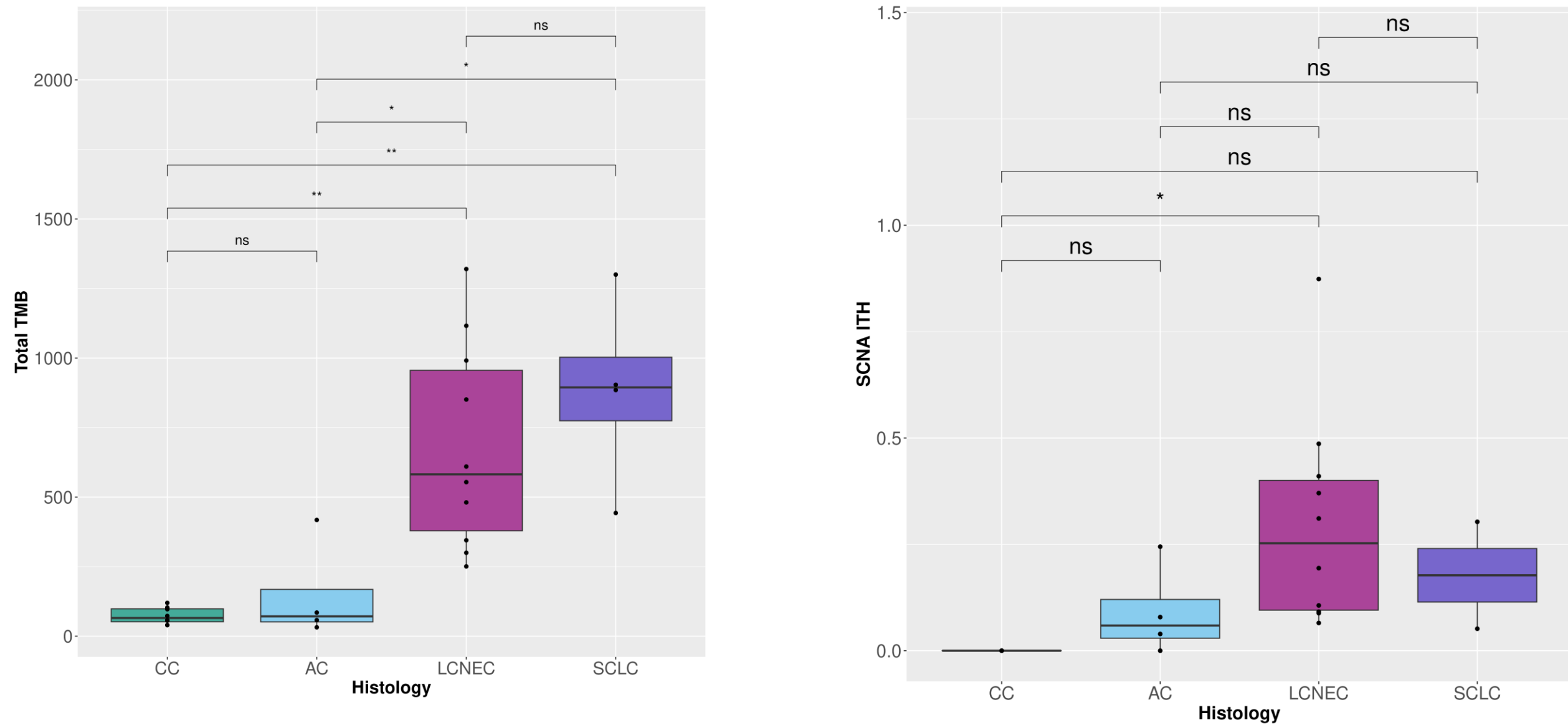
Synchronous small cell carcinomas associated with germline *BRCA2* variant



Driver events in LCNEC



TMB and SCNA heterogeneity



References

Williams JF, Vivero M. Diagnostic criteria and evolving molecular characterisation of pulmonary neuroendocrine carcinomas. *Histopathology*. 2022 Aug 2;81(5):556–68. doi:10.1111/his.14714

Frankell AM, Dietzen M, Al Bakir M, Lim EL, Karasaki T, Ward S, et al. The evolution of lung cancer and impact of subclonal selection in TRACERx. *Nature*. 2023 Apr 12;616(7957):525–33. doi:10.1038/s41586-023-05783-5

Rafnar T, Sigurjonsdottir GR, Stacey SN, Halldorsson G, Sulem P, Pardo LM, et al. Association of *BRCA2* K3326* with small cell lung cancer and squamous cell cancer of the skin. *JNCI: Journal of the National Cancer Institute*. 2018 May 14;110(9):967–74. doi:10.1093/jnci/djy002