Characterizing germline variants in patients with small cell lung cancer

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Introduction

Small cell lung cancer (SCLC) has traditionally been considered to arise from environmental and lifestyle factors. Recent evidence has shown that germline mutations may also impact the development of SCLC, however this remains understudied. We sought to identify novel germline mutations in SCLC including unexplored copy-number variations (CNVs) in our cohort of patients.

Methods

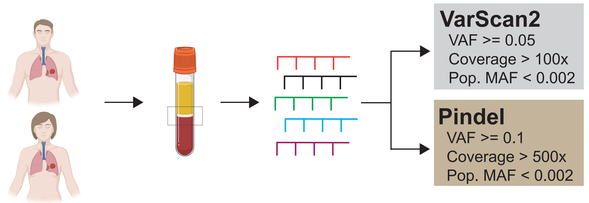

Figure 1. Overview of study and germline variant calling pipeline utilized. Pop. MAF, population mean allele frequency; VAF, variant allele fraction.

Results

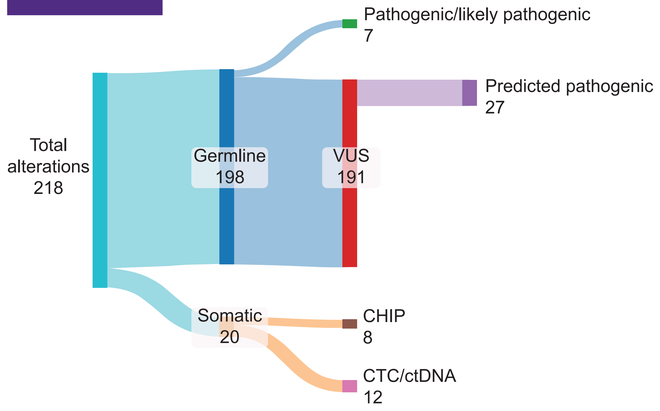

Figure 2. Overview of total variants identified in our cohort. VUS were annotated using MutationTaster, LRT, Polyphen2 HDIV, Polyphen2 HVAR, SIFT, PROVEAN, and Deepmind AlphaMissense. VUS, variants of uncertain significance; CHIP, Clonal hematopoiesis of ndeterminate potential; CTC/ctDNA, circulating tumour cells/circulating tumour DNA.

Results

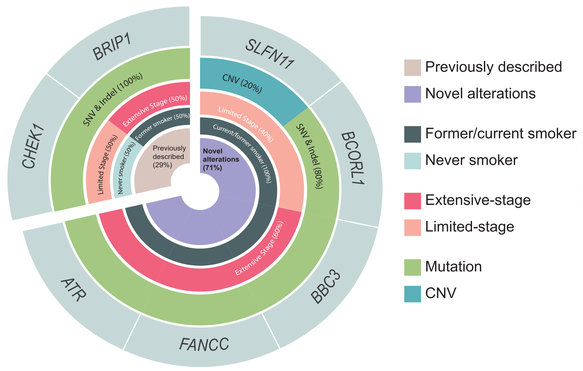

Figure 3. Clinical information and germline alteration categories of the 7 pathogenic/likely pathogenic alterations identified in the cohort. CNV, copy-number variation; Indel, insertion-deletion; SNV, single-nucleotide-variant.

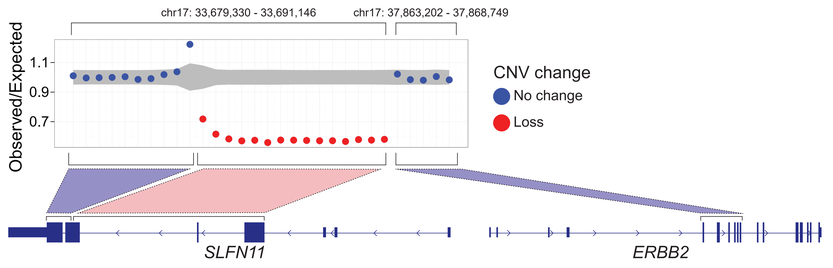

Figure 4. Copy-number deletion identified in exons 4-6 in the SLFN11 gene with a neighboring gene, ERBB2, for comparison. The y-axis examines the observed vs expected reads ratio for each hybrid-capture probe denoted by the blue and red circle symbols. Each probe targets a 120bp region of exons. DECoN was used to examine CNVs. CNV, copy-number variation

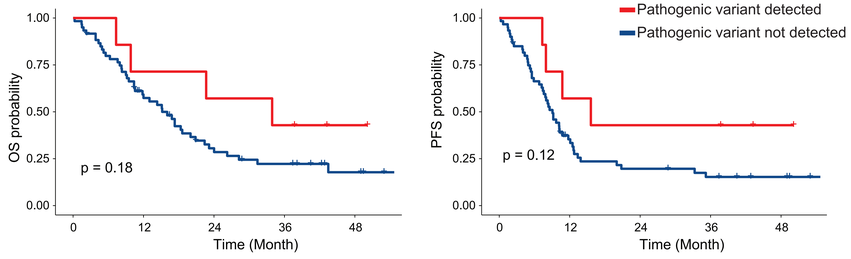

Figure 5. Overall survival (left, HR = 0.50, 95%CI = 0.18-1.39, p = 0.18) and progression-free survival (right, HR = 0.45, 95%CI = 0.16-1.24, p = 0.12) of patients with or without identified pathogenic variants. OS, overall survival; PFS, progression-free survival.

Results

Table 1. Patient demographics and clinical characteristics

		Pathogenic Variant Detected		
		No	Yes	Total
Total N (%)		N = 60 (89.6)	N = 7 (10.4)	N = 67
Age (years) Median (IQR)		68.0 (60.8 to 75.5)	62.2 (58.9 to 79.3)	68.0 (60.5 to 75.5)
Sex	Female	23 (38.3)	1 (14.3)	24 (35.8)
	Male	37 (61.7)	6 (85.7)	43 (64.2)
SCLC Diagnosis	De Novo SCLC	57 (95.0)	7 (100.0)	64 (95.5)
	Other Transformed SCLC	1 (1.7)	0 (0.0)	1 (1.5)
	EGFR transformed SCLC	2 (3.3)	0 (0.0)	2 (3.0)
Self-reported Ethnicity	Caucasian	38 (63.3)	6 (85.7)	44 (65.7)
	East Asian	4 (6.7)	-	4 (6.0)
	Southeast Asian	4 (6.7)	-	4 (6.0)
	Black	2 (3.3)	1 (14.3)	3 (4.5)
	Latin American	2 (3.3)	-	2 (3.0)
	Middle Eastern	1 (1.7)	-	1 (1.5)
	Not provided	9 (15.0)	-	9 (13.4)
Smoking Status	Current smoker	27 (45.0)	2 (28.6)	29 (43.3)
	Former smoker	27 (45.0)	4 (57.1)	31 (46.3)
	Never smoker	6 (10.0)	1 (14.3)	7 (10.4)
VA Staging at Diagnosis	Extensive-stage	35 (58.3)	4 (57.1)	39 (58.2)
	Limited-stage	25 (41.7)	3 (42.9)	28 (41.8)
Family History of Lung Cancer	Yes	18 (30.0)	2 (28.6)	20 (29.8)
	No	40 (66.7)	5 (71.4)	45 (67.2)
	Not provided	2 (3.3)	0	2 (3.0)
Family History of Cancer	Yes	37 (61.7)	5 (71.4)	42 (62.7)
	No	21 (35.0)	2 (28.6)	23 (34.3)
	Not provided	2 (3.3)	0	2 (3.0)
Relatives with Cancer	First-degree relatives	26 (43.3)	4 (57.1)	30 (44.8)
	More than two first-degree relatives	9 (15.0)	2 (28.5)	11 (16.4)
	Second-degree relatives	9 (15.0)	1 (14.3)	10 (14.9)

Conclusion

We have identified several novel germline alterations, including mutations and CNVs in patients with SCLC. In addition, we utilized in silico prediction models to categorize potential high-risk VUS. Our findings suggest that beyond tobacco exposure, germline alterations may also modulate the development of tumorigenesis in SCLC patients.