

Germline Alterations in Small Cell Lung Cancer Identified Through Blood-Based Profiling

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BACKGROUND

Small cell lung cancer (SCLC) is directly associated with repeated lung insults such as tobacco exposure, so inherited (germline) susceptibility is rarely considered.

Yet inherited risk may contribute to a subset of patients, especially those whose presentation is less typical for SCLC. Pathogenic germline variants in cancer-predisposition and DNA damage-repair genes have been reported in lung cancer, but their frequency and tumor context in SCLC remains poorly defined.

Buffy-coat sequencing within blood-based profiling provides an opportunity to identify germline-oriented findings and evaluate corresponding variants in linked tumor profiles.

OBJECTIVE

To characterize P/LP and risk-allele findings detected in buffy-coat DNA among patients in this SCLC blood-based profiling cohort and evaluate corresponding variants in linked solid-tumor profiles.

METHODS

Design: Retrospective patient-level analysis of this SCLC blood-based profiling cohort. Of 149 patients, 68 (45.6%) had linked solid-tumor profiling.

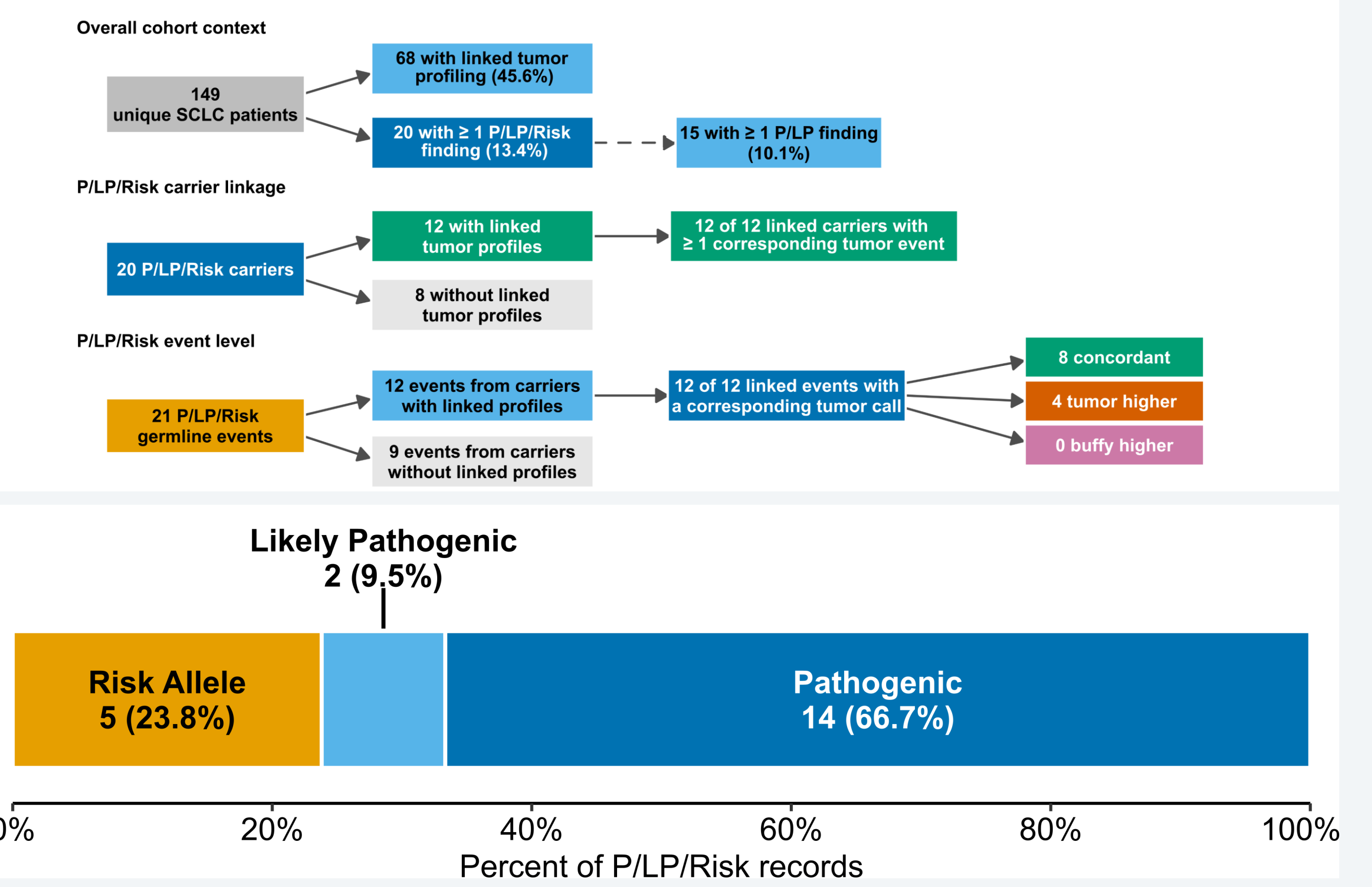
Germline findings: Reported buffy-coat findings were categorized as pathogenic, likely pathogenic, risk allele, VUS, likely benign, benign, or other/missing. Risk alleles were retained as a separate category and combined with P/LP only for prespecified descriptive summaries.

Linked tumor analysis: Blood and tumor profiles were linked by patient ID. Germline and tumor events were matched using genomic coordinates, with gene plus protein change used as a fallback. When multiple tumor calls corresponded to the same germline event, one tumor call was retained for downstream analysis.

VAF analysis: Buffy-coat and tumor VAFs were compared. Exploratory concordance required both an absolute VAF difference of no more than 15 percentage points and a tumor-to-buffy VAF ratio from 0.7 to 1.3.

Exploratory demographics: Age, sex, race, and tumor SBS4 burden were compared between patients with P/LP/Risk findings (n = 20) and patients with benign/likely benign variants (n = 8).

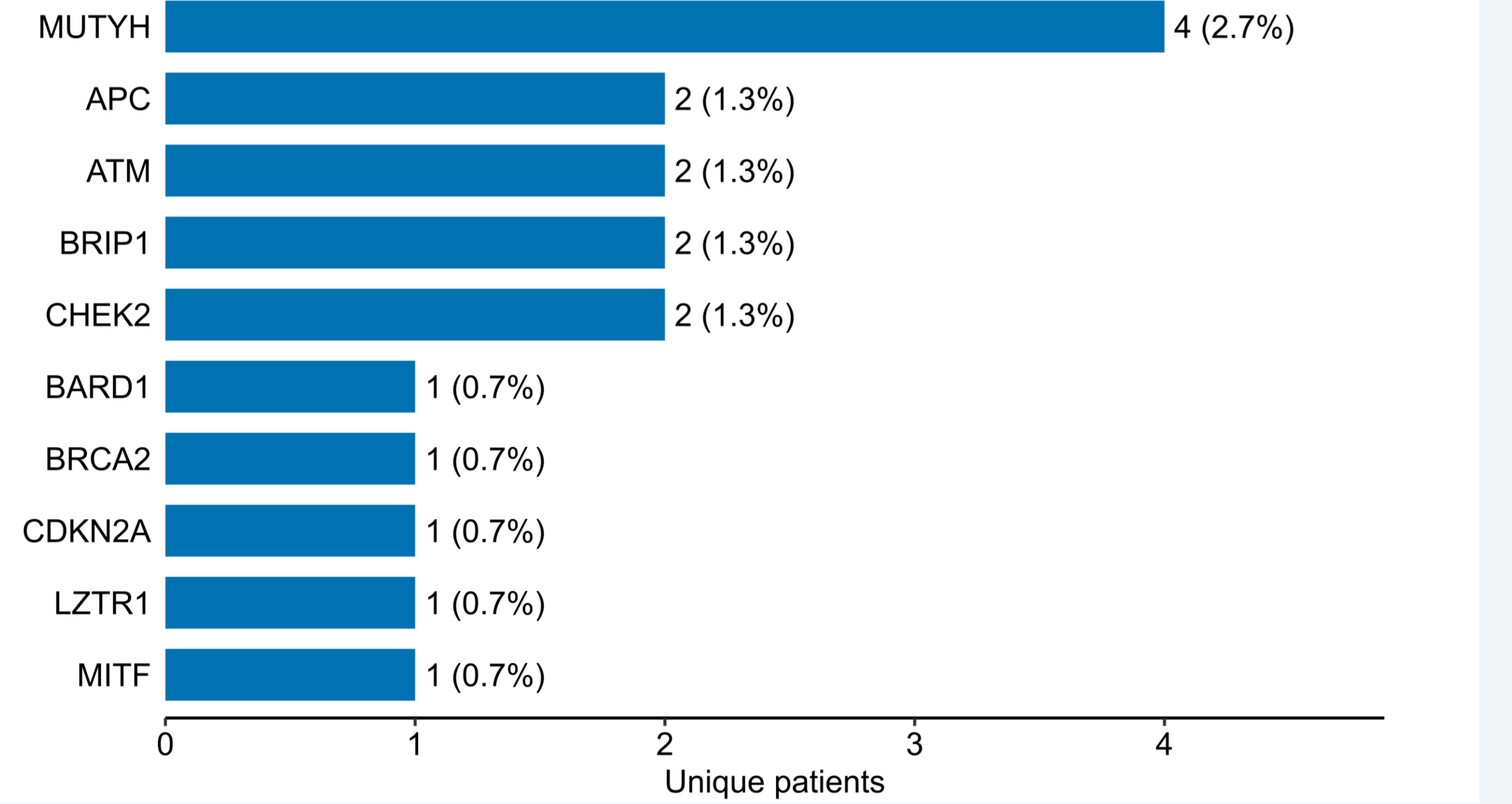
SCLC COHORT



Within this SCLC cohort of 149 unique patients, 15 patients (10.1%) had at least one P/LP finding and 20 patients (13.4%) had at least one P/LP/Risk finding.

Among 236 reported variant records, 190 (80.5%) were VUS and 21 (8.9%) were P/LP/Risk findings, including 14 pathogenic, 2 likely pathogenic, and 5 risk-allele records.

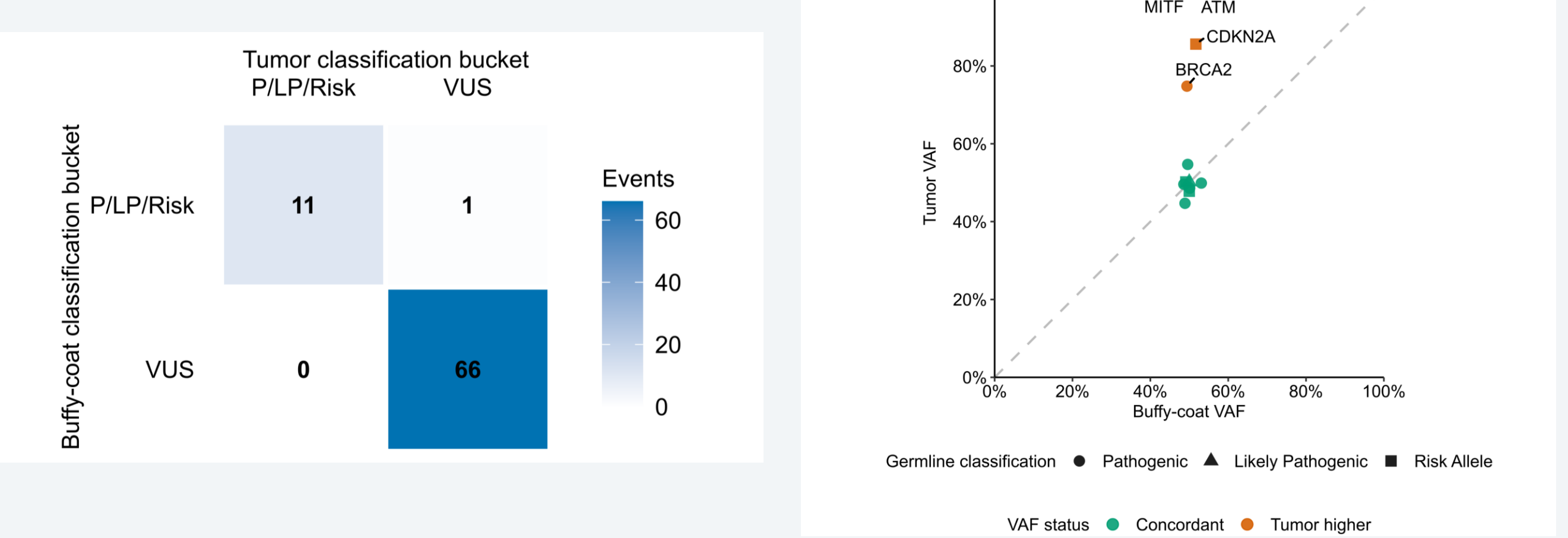
MOST FREQUENT P/LP/RISK GENES



Denominator was 149 unique patients. Each patient was counted once per gene but could contribute to more than one gene.



MATCHED TUMOR EVIDENCE



Among 12 P/LP/Risk events with a corresponding tumor call, 11 (91.7%) remained within the P/LP/Risk classification bucket in tumor profiling. One CDKN2A risk allele was classified as VUS in the tumor profile.

Exploratory VAF-concordance rates were 8 of 12 for P/LP/Risk and 43 of 66 for B/LB/VUS events. All four discordant P/LP/Risk events were tumor-higher.

CONCLUSIONS

- Within this SCLC cohort, 15 of 149 patients (10.1%) had at least one P/LP finding and 20 of 149 (13.4%) had at least one P/LP/Risk finding.
- Twelve of the 20 P/LP/Risk carriers had linked solid-tumor profiling, and all 12 had a corresponding tumor event. Eleven of the 12 corresponding events remained within the P/LP/Risk tumor-classification bucket.
- Findings support germline assessment in selected SCLC patients, with implications for genetic counseling and cascade testing; however, further testing and validation is needed.

CLINICAL IMPLICATIONS

Blood-based profiling with buffy-coat analysis may identify patients with SCLC who have P/LP findings in established hereditary cancer genes and warrant genetic counseling and confirmatory germline testing. Confirmed pathogenic findings may have implications for cascade testing of at-risk relatives.

Treatment implications were not evaluated in this study. Further work should define referral criteria using directly documented smoking history, age at diagnosis, family history, and confirmation that all blood-tested patients are represented in the denominator.