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ARTICLE

Pathogenic germline variants in small cell lung cancer: A systematic review and meta-analysis

Sami Ul Haq,[1,2,10] Aleem Aamir,[2,3,10] Chloe Mighton,[4,5] Katrina Hueniken,[2] Vivek Philip,[2] Raymond H. Kim,[2,6,7] Geoffrey Liu,[2,3,4,7] Peter Sabatini,[6,8] Scott V. Bratman,[3,9] and Benjamin H. Lok[3,7,9,11,12,*]

Summary

This systematic review and meta-analysis examined the prevalence and clinical impact of germline variants in small cell lung cancer (SCLC). Primary objectives included estimating the prevalence of germline variants in SCLC patients, while secondary objectives focused on their effects on patient outcomes. A comprehensive search was conducted in Ovid MEDLINE, EMBASE, and gray-literature databases (as of July 2024). Studies reporting germline variants in SCLC patients were included. Data were extracted to calculate pooled prevalence and hazard ratios (HRs). Study quality was assessed using the Translating ROBBINs tool, and heterogeneity was evaluated using the I^2 statistic. Of 6,117 screened studies, 124 met inclusion criteria, with 8% (10/124) reporting pathogenic/likely pathogenic (P/LP) findings. Meta-analysis using a random-effects model estimated the prevalence of P/LP germline variants in SCLC patients at 11% (95% CI: 5%–25%). Gene-level prevalence was estimated for *ATM* (pooled prevalence = 1%; 95% CI: 0%–5%), *BRCA1* (1%; 95% CI: 1%–3%), *BRCA2* (1%; 95% CI: 1%–3%), and *TP53* (1%; 95% CI: 0%–3%). Patients with P/LP variants in DNA damage repair genes showed a non-significant prognostic survival benefit (pooled HR: 0.8; 95% CI: 0.51–1.29, $I^2 = 8\%$). We have conducted a comprehensive systematic review of germline variants and their impact on clinical outcomes of SCLC patients. Our meta-analysis identified an estimated prevalence of P/LP variants in SCLC patients, suggesting a rationale for screening in the clinic.

Introduction

Small cell lung cancer (SCLC) is a highly aggressive malignancy characterized by rapid proliferation, early metastasis, and poor prognosis. Two-thirds of patients present with extensive-stage metastatic disease at diagnosis, with limited treatment options and poor survival outcomes.[1] The median survival for limited-stage patients is less than 2 years, whereas for those with extensive-stage disease, it is approximately 1 year.[1]

While environmental factors, predominantly including tobacco exposure, have traditionally been viewed as the primary cause of SCLC,[2] emerging evidence challenges this paradigm. Recent studies in 2021 and 2024 have highlighted the potential role of pathogenic germline variants in contributing to SCLC predisposition and pathogenesis.[3,4] This broader understanding introduces a more complex mechanism underlying SCLC etiology beyond tobacco exposure alone. Furthermore, these data have raised questions regarding the role of germline variants in SCLC, including how prevalent they are among patients and how they influence patient outcomes.

Molecularly, SCLC is characterized by a high tumor mutational burden, with near-ubiquitous concurrent loss of the tumor suppressor genes *TP53* and *RB1*.[5] Germline loss-of-function mutations in these genes, among others, have been linked to an increased predisposition to various cancer types.[6] In some cases, such as breast cancer, the identification of germline variants in *BRCA1* and *BRCA2* and their associations with biallelic *BRCA1* and *BRCA2* tumor mutations has enabled the use of targeted therapies such as PARP inhibitors, which exploit the unique synthetic lethal vulnerabilities created by these germline variants and associated tumor mutations.[7]

While the role of germline variants has been well established in other cancers,[8] and screening is recommended to guide patient management, the relevance of germline variants in SCLC remains poorly understood. The recent identification of germline variants within SCLC patient cohorts suggests that genetic predispositions may play a

[1]Schulich School of Medicine & Dentistry, Western University, 1151 Richmond St, London, ON N6A 5C1, Canada; [2]Princess Margaret Cancer Centre, 610 University Avenue, Toronto, ON M5G 2C1, Canada; [3]Department of Medical Biophysics, Temerty Faculty of Medicine, University of Toronto, Princess Margaret Cancer Research Tower, 101 College Street, Room 9-309, Toronto, ON M5G 1L7, Canada; [4]Dalla Lana School of Public Health, University of Toronto, 155 College Street, Room 500, Toronto, ON M5T 3M7, Canada; [5]St. Michael's Hospital, 30 Bond Street, Toronto, ON M5B 1C9, Canada; [6]Toronto General Hospital, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada; [7]Institute of Medical Science, Temerty Faculty of Medicine, 1 King's College Circle, Medical Sciences Building, Room 2374, Toronto, ON M5S 1A8, Canada; [8]Department of Laboratory Medicine & Pathobiology, Temerty Faculty of Medicine, University of Toronto, 1 King's College Circle, 6th Floor, Toronto, ON M5S 1A8, Canada; [9]Radiation Medicine Program, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, ON M5G 2C1, Canada
[10]These authors contributed equally
[11]Present address: Lok Lab, 13th floor, Princess Margaret Cancer Research Tower, 101 College St, Toronto, ON M5G 0A3, Canada
[12]Lead contact
*Correspondence: benjamin.lok@uhn.ca
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larger role than previously recognized. Despite these findings, the overall prevalence and clinical outcomes of germline variants in SCLC are still not well defined.

To address these gaps in understanding, we conducted a systematic review and meta-analysis to synthesize the available evidence on germline variants within SCLC. Our primary objective was to map the molecular landscape of tumors containing germline variants and clarify their prevalence within SCLC cohorts. In addition, we sought to explore associations between specific germline variants and clinical outcomes. A secondary goal was to determine whether there is sufficient evidence to suggest that SCLC patients should be screened for germline mutations.

Material and methods

Study design

The study protocol and data extraction for the systematic review and meta-analysis were designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement guidelines.[9] The research protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/; registration no. CRD42024556012).

Eligibility criteria

Any primary research studies, including cohort, case-control, and genome-wide association study, that profiled germline variants in patients with SCLC were considered. All germline alterations were considered. Only studies published in English were considered.

Search strategy

In July 2024, the databases Ovid MEDLINE, and Ovid EMBASE were queried. The MEDLINE and EMBASE search strategies are outlined in Table S1. A gray literature query was performed in July 2024, including the bioRxiv, medRxiv, and EMBASE repositories.

Study selection process

Studies identified from the search strategy and available in English were imported to Covidence review software, screened, and reviewed by two independent reviewers (S.U.H. and A.A.). A first round of screening was performed based on study title and abstract, and full texts from selected studies were uploaded to Covidence and used for a second round of screening. Studies were selected if they reported germline variants (including single-nucleotide variants, insertions or deletions, and copy-number variations) in SCLC patients. Any disagreement between reviewers was mediated by B.H.L.

Data extraction and synthesis

Study data were extracted in Microsoft Excel by two independent authors (S.U.H. and A.A.). The following variables were collected: total number of SCLC patients, percentage of limited stage, sex, median age, percentage of never smokers, percentage with personal history of cancer, percentage with family history of cancer, ethnicity, American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology criteria, gene details, frequency of variant in cohort, odds ratio reported for each germline variant, hazard ratio (HR) of overall survival, and median overall survival. Germline pathogenicity classifications were extracted from the articles if provided. If no classification was provided in the study, then a separate query was performed in ClinVar to determine the pathogenicity of the reported variants. Studies were divided into two broad categories: variant level and genotype level. Variant-level studies summarized variants and their effects at a variant level whereas genotype-level studies stratified their data for each genotype of the variant. Risk of bias and study quality were assessed independently by each reviewer using the Translating-ROB tool developed by Casolino et al.[10]

Statistical analyses

Descriptive statistics were used to quantify the frequencies of germline variants. A random-effects meta-analysis was carried out on the HR and prevalence data to calculate the pooled event rate. Study-specific outcomes with 95% confidence intervals (CIs) were graphically represented in a forest plot. Cochran's Q test for heterogeneity was carried out reporting the I^2 statistic, which indicates the percentage of variation across studies due to heterogeneity rather than chance. Statistical analysis was performed with the "meta" and "metafor" packages in R (version 4.4.0). Publication bias was assessed based on funnel plot diagram and Egger's test.

Results

Studies identified

We utilized the search strategy outlined in the material and methods section. Our criterion was to identify any study that examined germline variants in SCLC. A total of 6,117 studies were identified across 3 different databases, including MEDLINE, EMBASE, and PubMed (Figure 1). We were unable to identify any relevant studies in the gray literature. After removing duplicates, we screened 5,942 studies by abstract and title, excluding 5,781 studies based on predefined criteria. The most common reason for exclusion was studies focused on non-SCLC (NSCLC) rather than SCLC or lung cancer regardless of histology. This left 161 studies that were retrieved for full-text review. After full-text review, 37 studies were excluded, primarily due to lack of germline variant data, leaving a total of 124 studies (Table S2). The 124 studies were divided into 2 different categories: studies that reported their findings by gene level (n = 35; Table S3) and by specific genotype level (n = 89; Table S4). The studies were separated because the goal of this meta-analysis was to identify general consequences associated with gene alterations rather than granular allele-level changes. Prior to performing meta-analyses, we further restricted to 10 studies because they specifically identified a pathogenic/likely pathogenic (P/LP) variant deemed to be clinically relevant (Table S3).

Cohort and germline gene alteration prevalence

Ten studies (10/124) were included for the meta-analysis for germline variant[11] prevalence because they identified

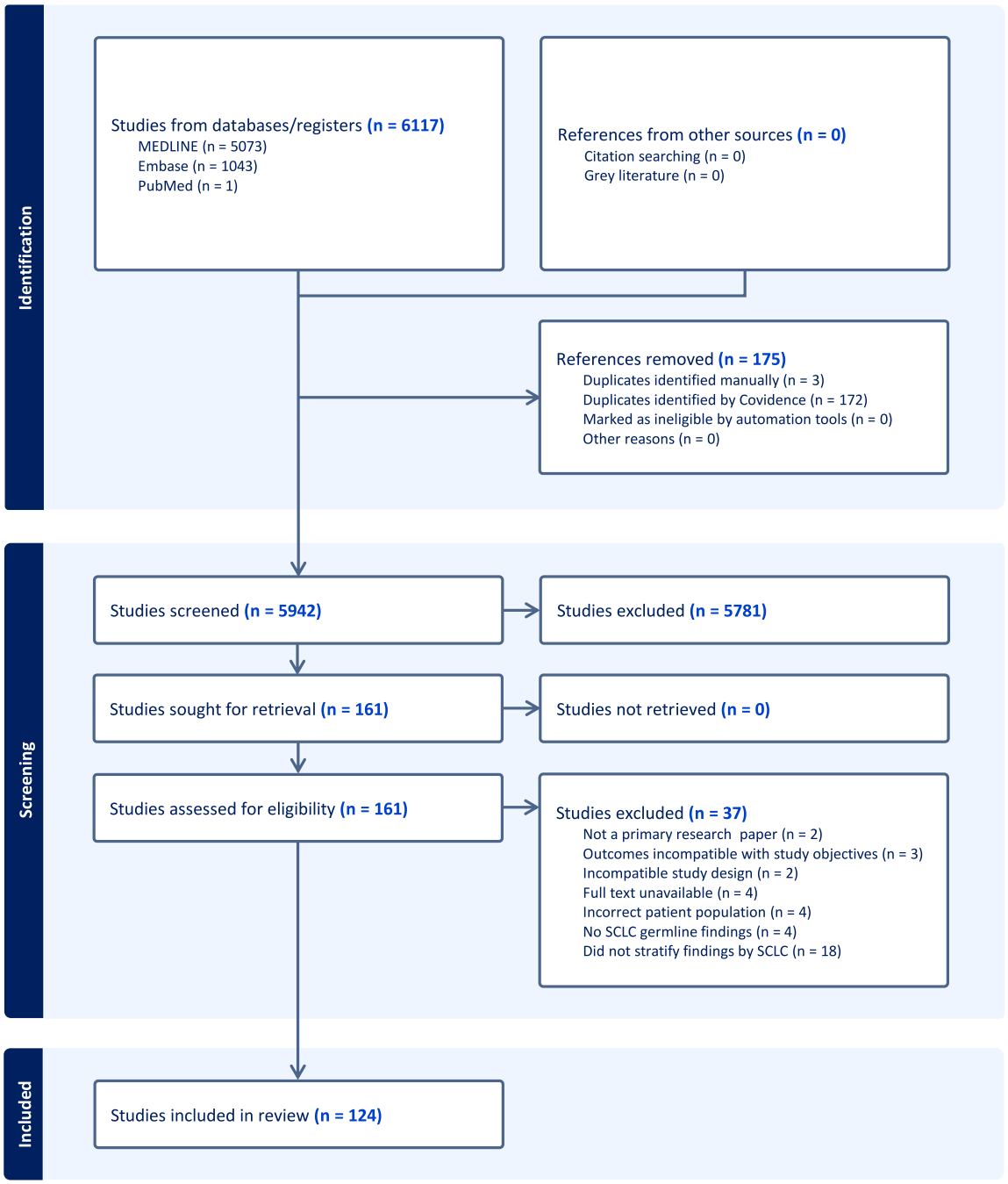

Figure 1. PRISMA workflow diagram of study selection process

clinically relevant P/LP variants (Table S3). Prevalence refers to number of patients within a cohort that had a P/LP variant. Meta-analysis of the pooled prevalence data identified a generalized prevalence of 11% (95% CI: 5%–25%) using the random-effects model (Figures 2 and S2A). Between-group heterogeneity was high across studies (I^2 = 94%). We also performed a sensitivity analysis by excluding two potential outlier studies[3] and identified a generalized prevalence of 7% (95% CI: 4%–12%), with a substantially reduced between-group heterogeneity (I^2 = 63%).

We also examined prevalence on a per-gene level. For this, we restricted the meta-analysis to germline genes reported in the above 10 studies and kept genes that were examined in at least two studies/cohorts. Notable germline genes and their pooled prevalences for SCLC-specific genes were as follows: *ATM* (pooled prevalence = 1%, 95% CI: 0%–5%, n = 2 studies), *BRCA1* (pooled prevalence = 1%, 95% CI: 1%–3%, n = 5), *BRCA2* (pooled prevalence = 1%, 95% CI: 1%–3%, n = 7), and *TP53* (pooled prevalence = 1%, 95% CI: 0%–3%, n = 3) (Figures 3A–3D). Other genes included *BRIP1* (pooled prevalence = 2%, 95% CI: 1%–6%, n = 2),

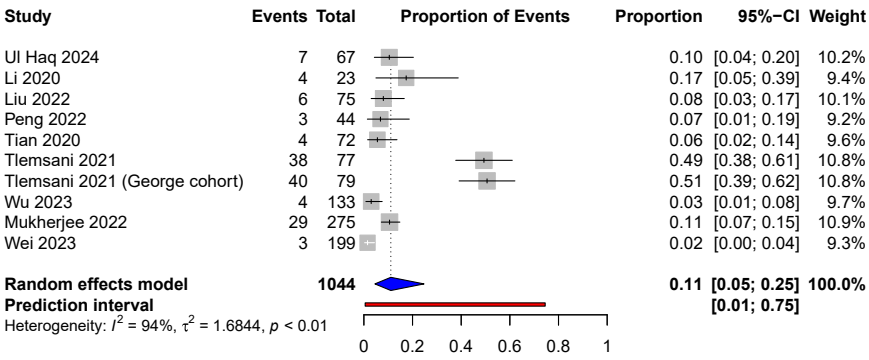

Figure 2. Forest plot of pathogenic/likely pathogenic germline variant prevalence across studies, with 95% confidence intervals (95%-CI) and *p* values from random-effects meta-analysis

CHEK1 (pooled prevalence = 2%, 95% CI: 1%–6%, $n = 2$), *CHEK2* (pooled prevalence = 1%, 95% CI: 0%–2%, $n = 3$), *GJB2* (pooled prevalence = 3%, 95% CI: 1%–7%, $n = 2$), *MUTYH* (pooled prevalence = 3%, 95% CI: 2%–5%, $n = 3$), *PARK2* (pooled prevalence = 1%, 95% CI: 0%–3%, $n = 3$), *POLQ* (pooled prevalence = 4%, 95% CI: 2%–9%, $n = 2$), and *SLFN11* (pooled prevalence = 1%, 95% CI: 0%–5%, $n = 2$) (Figures S1A–S1H).

Prognostic relevance

Two studies (2/124) were included for the meta-analysis for HR of overall survival because these were the only studies that reported outcomes for the associated P/LP variants (Table S3); both studies examined DNA damage response and repair germline mutations associated with SCLC.[3,4] Given the limited number of studies, the range of the CI (95% CI: 0.51–1.29) may provide more meaningful information than the pooled estimate itself. The meta-analysis reported non-statistically significant difference in survival, with a pooled HR of 0.8 (95% CI: 0.51–1.29, $I^2 = 8\%$) (Figures 4 and S2B).

Discussion

We have examined the germline landscape for SCLC with a specific focus on prevalence and patient outcomes. We conducted a systematic assessment of multiple databases and gray literature, identifying 124 studies and synthesizing knowledge on the prevalence of germline variants in SCLC. Importantly, we were limited by the small number of eligible studies and the variability in methodologies used, and this contributes to the observed heterogeneity in our meta-analysis.

Our meta-analysis of the variant-level germline variant prevalence in the SCLC population suggests 11% of all patients with SCLC may harbor a P/LP variant (Figure 2). On a per-gene basis, the prevalence of DNA damage response and repair genes like *BRCA2* or *MUTYH* was identified to be 1% (Figures 3 and S1), with similar estimates also identified for other genes, including *CHEK2*, *POLQ*, *SLFN11*, and *TP53* (Figures 3 and S1). Our analysis aligns with previous studies[12–14] that also highlighted the challenge of identifying P/LP germline variants in SCLC. We also identified a non-significant association with survival for patients with SCLC harboring germline variants (Figure 4).

Germline variants are important prognostic factors in several cancers.[8] Across cancer types in The Cancer Genome Atlas, 8% of all patients have a P/LP variant,[15] but this varies by cancer type. Comparing the pooled prevalence estimate from our study of 11% to other lung cancers, lung adenocarcinoma and squamous cell carcinoma, both subtypes of NSCLC, have a reported germline variant prevalence of 5%–6%.[15] While P/LP variants in NSCLC patients have some therapeutic implications,[16] the clinical implications of such variants in SCLC is underexplored. Our estimate is similar to pancreatic adenocarcinoma, where 14.1% of patients have a P/LP variant.[15] Various studies have also reported the prevalence of germline variants in other cancer types. For example, germline *BRCA1/2* variants are detected in 8% of prostate cancer,[17] 15% of ovarian cancer, and 5% of breast cancer.[18] Similarly, *GJB2* germline variants are detected in 1% of pediatric/young adult solid tumors.[19]

A major implication of this systematic review is a newfound understanding of the prevalence of P/LP variants in SCLC patients. This is especially important because it sheds light on important questions such as whether SCLC patients should be opted-in for germline testing strategies. Currently, SCLC patients are not offered germline testing. In other cancers, including prostate cancer,[20,21] breast cancer,[22] pancreatic cancer,[23] germline variants have prognostic value.[8] However, in contrast to these cancers, the evidence for germline testing in SCLC is unclear. Our findings do not establish a definitive rationale for screening but suggest that additional studies are needed to inform therapeutic/prognostic or risk-stratification strategies in SCLC patients. Another major implication is to understand whether there are specific treatment strategies or to investigate whether there is greater potential for toxicity to radiotherapy for SCLC patients with P/LP variants. For instance, a mutation-based therapeutic strategy has been identified in colorectal cancer patients harboring germline *POLQ* variants.[24]

Our analysis also raises the question of why patients with P/LP variants in DNA damage response and repair genes have a trend for better overall survival. We speculate that this is likely due to platinum chemotherapy being the backbone of therapy for SCLC and patients with these germline variants having SCLC tumors with functional defects in DNA repair, potentially making them more

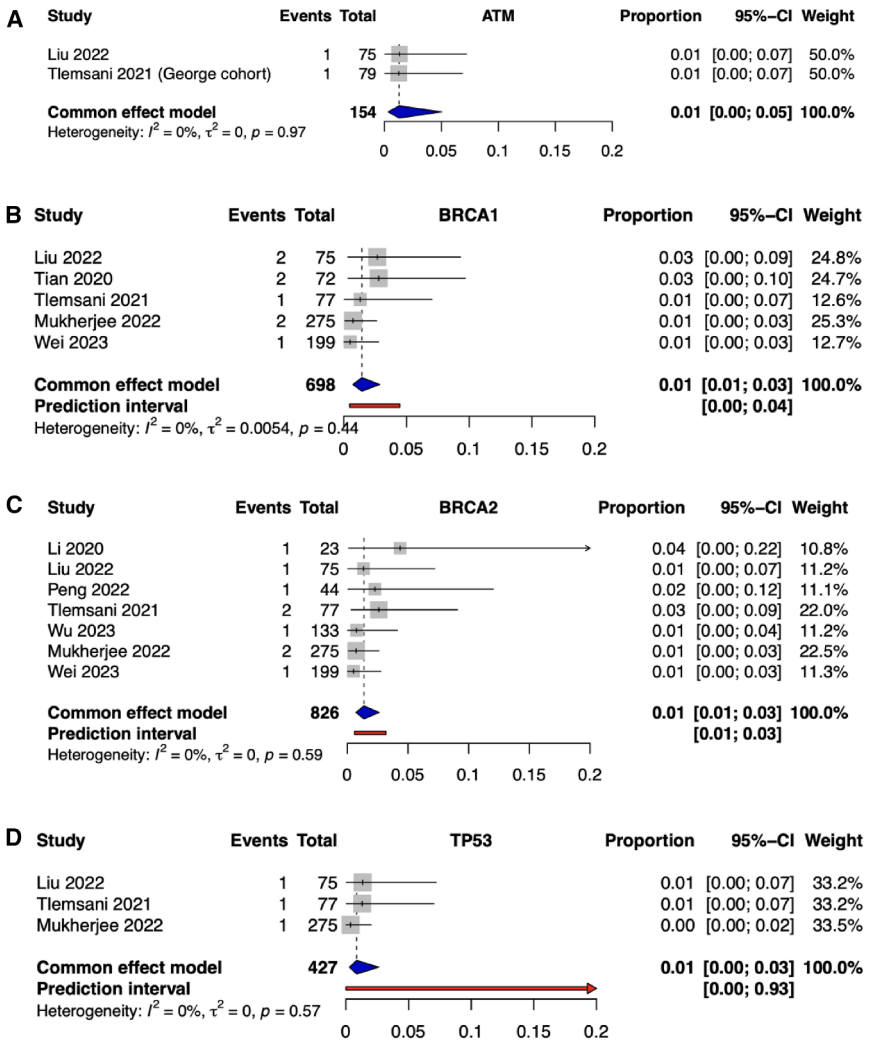

Figure 3. Forest plot of pathogenic/likely pathogenic germline variant prevalence across studies, with 95% confidence intervals (95%-CI) and *p* values from common-effect meta-analysis

(A) *ATM*, (B) *BRCA1*, (C) *BRCA2*, and (D) *TP53*.

responsive to this therapy. However, additional studies are needed to directly elucidate the mechanism behind variants in these genes and their effect on SCLC tumorigenesis and improved survival. Eventually, this may influence risk stratification and personalized treatment approaches for patients with SCLC.

Our systematic review is subject to certain limitations. One key limitation is the small cohort sizes across the included studies, which reduces statistical power and limits the generalizability of our study. Also, there is a high degree of heterogeneity in our meta-analysis, particularly in the prevalence analysis, likely due to variability in the genes examined across studies,[12–14] as no standardized gene panels currently exist for germline testing in SCLC. These limitations have been observed in some of the studies we examined,[12–14] further underscoring the need for more standardized and large-scale studies in germline variants in SCLC. However, our heterogeneity is not as high when subsetting our analysis to similar genes (Figures 4 and S1).

When examining methods used in our analysis, a common-effects model was utilized for both the HR and the per-gene prevalence meta-analysis due to the limited number of studies. Common-effects estimates underestimated the variance of our estimates, especially considering the high level of heterogeneity present. Similarly, it was necessary to restrict our meta-analysis to 6% of all the studies we retrieved because the variants reported in most studies were not found to be P/LP by the authors or by our independent cross-reference in ClinVar; most SNPs were benign or did not exist in ClinVar (Table S3). Moreover, ClinVar is not a complete database and may have classifications supported by varying qualities of evidence.

One particular concern is the interpretation of our pooled prevalence estimate of 11% (Figure 2). While this provides a summary of germline variant prevalence in SCLC, it should be interpreted with caution due to the wide variation in individual study estimates. Two studies reported substantially higher germline variant prevalence (49% and 51%), likely reflecting differences in study design, sample selection bias, or methodology. To assess the impact of these outliers, we conducted a sensitivity analysis excluding these two studies, which resulted in a revised pooled prevalence of 7% and an improved measure of heterogeneity from I^2 of 94% to 63% (Figure S3). This highlights the extent to which individual studies can influence meta-analytic estimates and underscores the need for standardized approaches in future research.

Similarly, our meta-analysis of overall survival included only two studies. Pooled estimates from few studies are highly sensitive to individual study characteristics and may not reflect the true effect size. In this case, the wide CI (95% CI: 0.51–1.29) may offer more meaningful insight than the pooled HR of 0.8, and the uncertainty in this association highlights the need for additional studies to clarify the relationship between germline variants and survival in SCLC.

Another limitation is the difference in methods used by the primary studies analyzed. Most studies used PCR-based techniques, while a minority utilized next-generation

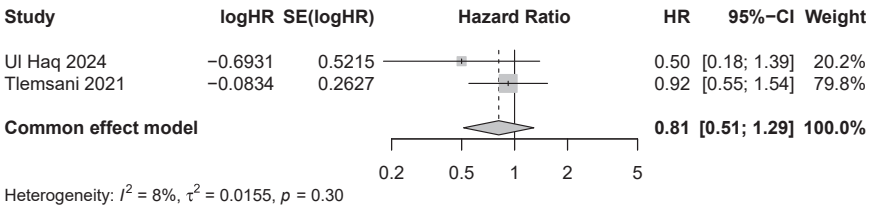

Figure 4. Forest plot of hazard ratios (HR) for overall survival in patients with pathogenic/likely pathogenic germline variants across studies, with 95% confidence intervals (95%-CI) and *p* values from common-effect meta-analysis

sequencing. Similarly, there is no standardized set of genes examined across studies. This lack of methodological consistency makes direct comparisons challenging and highlights the need for future research using whole-exome or whole-genome sequencing (WES/WGS) approaches. Lastly, most studies did not examine longitudinal patient outcomes, which limited our meta-analysis of overall survival significantly.

Based on these observations of heterogeneity in primary study design and reporting, to increase our understanding of the relevance of germline variants in SCLC, future studies could consider implementing WGS/WES SCLC-specific gene panels that include DNA response and repair genes, and identifying P/LP variants as defined by ACMG and/or ClinVar. Moreover, it may be valuable to include, when possible, longitudinal patient outcomes and include the available family history of cancer in patients with SCLC; also, an effort made toward including ethnically and racially diverse populations would improve global generalizability. In addition, there is a need for functional studies to understand how the identified germline variants in the studies impact SCLC development. Lastly, further work is needed to understand how environmental exposures (i.e., tobacco) affect patients with P/LP variants compared to those without.

In conclusion, we have examined the landscape of germline variants and their impact on clinical outcomes in SCLC. We performed a meta-analysis and identified an estimate of prevalence of P/LP variants in SCLC patients, suggesting a potential but not yet definitive rationale for screening in the clinic. Importantly, our work highlights a paucity of studies that comprehensively examine family history and P/LP germline variants in SCLC patients, and we hope future research can address this gap. While our findings do not provide direct evidence to change clinical guidelines at this time, they underscore the need for larger well-designed studies to evaluate the clinical relevance of germline variants in SCLC.

Data and code availability

The data and code generated during this study for meta-analyses are available at GitHub: https://github.com/sulhaq97/sclc_germline_meta_systematic.

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Declaration of interests

S.V.B. is an inventor on patents related to cell-free DNA mutation and methylation analysis technologies that have been licensed to Roche and AdelaBio, respectively, and is co-founder of, has ownership in, and serves in a leadership role at AdelaBio. G.L. reports grants and personal fees from AstraZeneca and Takeda, grants from Boehringer Ingelheim, and personal fees from Hoffman La Roche, Merck, Bristol Myers Squibb, and Pfizer outside the submitted work. B.H.L. reports grants from Pfizer and grants, personal fees, and nonfinancial support from AstraZeneca, and personal fees from Daiichi-Sankyo outside the submitted work.

Supplemental information

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