Original Article

Using human genetics to understand the epidemiological association between neuroticism and lung cancer

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Background: Neuroticism, a personality trait characterized by emotional instability, has been linked to an increased risk of lung cancer (LC). However, the genetic underpinnings of this association remain poorly understood. This study aimed to comprehensively dissect the genetic link underlying neuroticism and LC.

Methods: We used genome-wide association study (GWAS) data to investigate the intricate genetic relationship between neuroticism and LC, along with specific histological subtypes: lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and small-cell LC (SCLC). Our analytical framework encompassed global and local genetic correlation, cross-trait meta-analysis, transcriptome-wide association study (TWAS), and bidirectional Mendelian randomization (MR) analysis.

Results: Notable genetic correlations were found between neuroticism and overall LC (r_g=0.15, P=2.24×10^{-5}), with stronger associations observed for LUSC (r_g=0.21, P=3.39×10^{-6}) and SCLC (r_g=0.16, P=2.50×10^{-3}). Partitioning the genome revealed additional genetic correlations in specific local genomic regions (including chr6q27 and chr6q16.2–q16.3) and functional categories (such as H3K27ac and H3K9ac). The cross-trait meta-analysis revealed 24 genetic loci that influenced both traits, including four novel ones. Looking into the gene-tissue level, TWAS identified 35 genes associated with both neuroticism and LC across multiple tissues, particularly in the nervous, respiratory, cardiovascular, and endocrine systems. MR analysis indicated a potential causal effect of neuroticism on overall LC [odds ratio (OR) =1.48, P=5.53×10^{-4}] and LUSC (OR =1.52, P=8.00×10^{-3}), but not on LUAD or SCLC. No reverse causality was observed.

Conclusions: This study reveals a genetic link between neuroticism and LC, offering new insights into LC risk assessment and potential prevention strategies for individuals with high neuroticism levels.

Keywords: Neuroticism; lung cancer (LC); cross-trait meta-analysis; Mendelian randomization (MR)

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Introduction

Neuroticism, a personality trait that reflects an individual's emotional instability, is characterized by a heightened tendency to experience anxiety, fear, over-sensitivity, and other negative emotions in response to stress (1). As a core dimension of the Five-Factor Model of personality, neuroticism has been linked to a range of both psychological and physical health conditions, including mental disorders (2), cardiovascular diseases (3,4), chronic pulmonary diseases (5), irritable bowel syndrome, and atopic eczema (6). Furthermore, neuroticism has also been linked to an increased risk of developing malignancies. The mechanisms underlying these associations may involve the prolonged activation of stress responses, which can disrupt immune and endocrine functions (7) and lead to chronic inflammation (8).

Lung cancer (LC) remains the leading incidence and mortality among all malignancies, representing a significant public health concern (9). While numerous studies have established that smoking is a primary risk factor for LC (10,11), epidemiological research has also suggested a potential association between neuroticism and the risk of developing LC. For instance, two prospective cohort studies by Nakaya *et al.* (12) and Wei *et al.* (13) found that individuals with high neuroticism scores were at greater risk of developing LC. However, these findings are not supported by an individual-participant meta-analysis of six prospective cohorts (14). These conflicting results may stem from limitations inherent in traditional epidemiological studies, such as potential biases, insufficient adjustment for confounding factors, or reverse causality, meanwhile conducting randomized trials to explore this link would be ethically unfeasible.

Using genetic data for phenotypic correlation analysis offers greater accuracy than observational studies by avoiding reverse causality and minimizing confounding factors. With the increasing availability of high-quality genome-wide association study (GWAS) data (15), researchers can investigate the links between neuroticism and LC and explore underlying mechanisms. In this regard, two studies employing Mendelian randomization (MR) have uncovered a causal relationship between neuroticism and LC by using genetic variants as instrumental variables (IVs) (13,16). However, significant gaps remain: prior studies did not explore the causal link between neuroticism and detailed histological LC subtypes, adjust for limited confounders, and have not addressed the reverse causal effect of LC on neuroticism.

Thus, utilizing the large-scale GWAS data, this study conducted a comprehensive genome-wide cross-trait analysis to characterize the global and local genetic correlations, identify shared genetic loci, and uncover potential causality between neuroticism and LC. *Figure 1* has outlined the design of this study. We present this article in accordance with the STREGA reporting checklist (17) (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-950/rc).

Highlight box

Key findings

- This study presents the first comprehensive investigation into the genetic link between neuroticism and lung cancer (LC), revealing significant genetic correlations and identifying shared loci. Additionally, it uncovers a potential causal relationship between neuroticism and both overall LC and its histological subtypes.

What is known and what is new?

- While previous observational studies suggested a potential link between neuroticism and LC, the underlying genetic mechanisms remained unclear, and no study had fully examined the association at the level of specific histological subtypes.
- This research fills that gap, providing genetic evidence of neuroticism's association with various LC subtypes and identifying specific pleiotropic loci and genes that may underlie this association.

What is the implication, and what should change now?

- Our findings suggest that individuals with high neuroticism levels may have an elevated risk of developing LC, highlighting the potential benefit of managing neuroticism as part of preventive strategies.

Methods

GWAS data sources

We obtained GWAS summary data for neuroticism from a study focusing on individuals of European ancestry. The phenotype was evaluated by summing up the neuroticism scores based on 12 dichotomous items of the Eysenck Personality Questionnaire Revised Short Form (EPQ-RS) (18), involving 380,060 participants from the UK Biobank, as detailed by Nagel *et al.* (19).

For LC, extensive GWAS data provided summary-level genetic associations for four distinct LC traits, sourced from a comprehensive analysis conducted by the International Lung Cancer Consortium (ILCCO) (20). This dataset

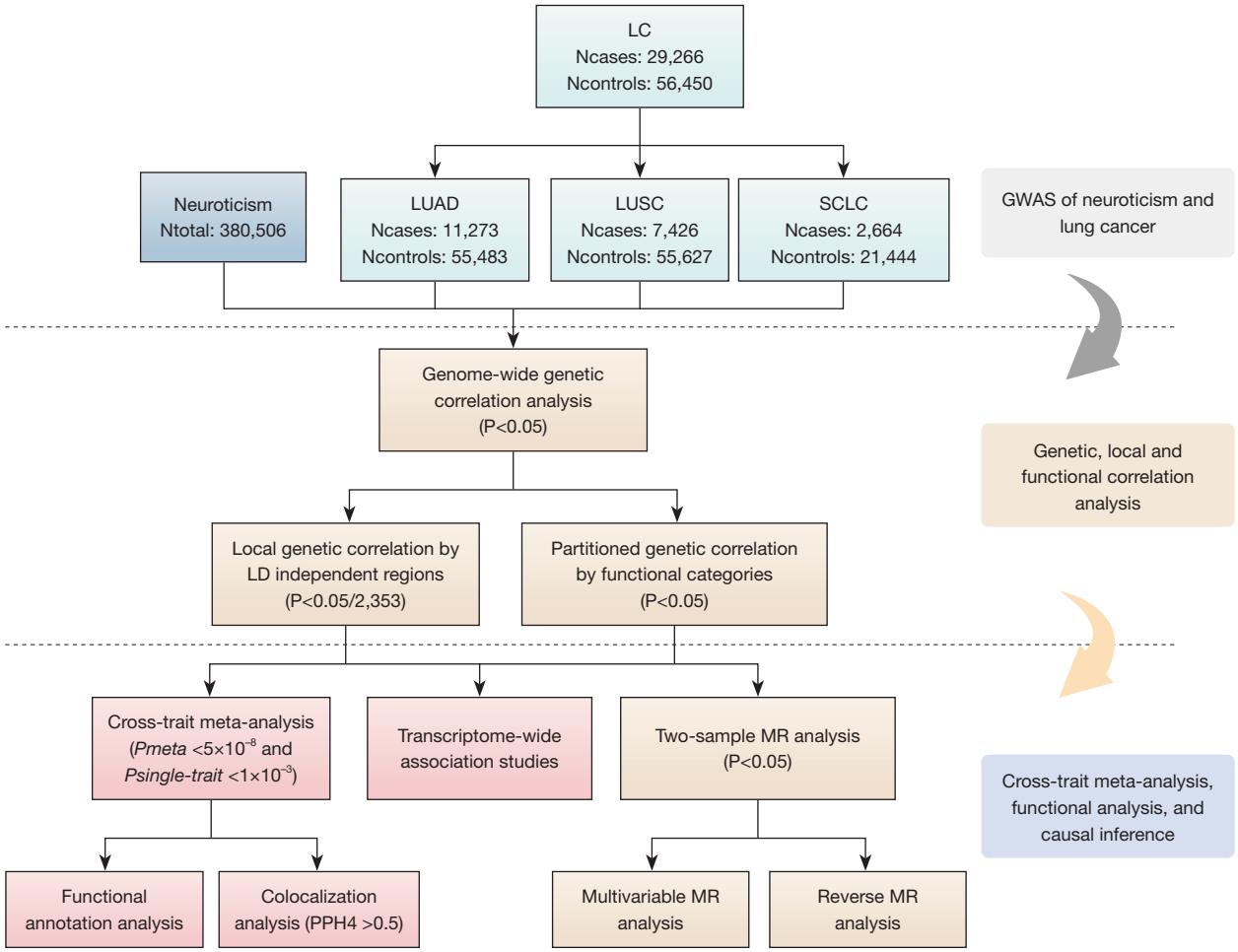

Figure 1 Overall study design of genome-wide cross-trait analysis. GWAS, genome-wide association study; LC, lung cancer; LD, linkage disequilibrium; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MR, Mendelian randomization; Ncases, number of cases; Ncontrols, number of controls; Ntotal, total sample size; PPH4, posterior probability for H4; SCLC, small-cell lung cancer.

comprised 85,716 participants, including 29,266 overall LC cases. When categorized by histological subtype, the data encompassed 11,273 cases for lung adenocarcinoma (LUAD), 7,426 for lung squamous cell carcinoma (LUSC), and 2,664 for small-cell LC (SCLC). Summary of data source of different traits is shown in *Table 1*. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analyses

Global and local genetic correlation

We assessed the genetic basis shared between neuroticism and LC using linkage disequilibrium (LD) score regression (LDSC) (25), which calculates r_g between traits utilizing GWAS summary-level data. It leverages the principle that a variant's effect size includes effects of all variants in LD with it. LDSC regression of chi-square statistics on LD scores derives genetic correlation, considering sample sizes, overlapping single nucleotide polymorphisms (SNPs), genetic covariance, and phenotypic correlation. We used precomputed LD scores based on well-imputed HapMap3 SNPs from European populations, covering around 1.2 million variants. Subsequently, to address potential population overlap, we implemented LDSC with a constrained intercept.

To further examine local genetic correlations, we used the SUPERGNOVA algorithm (26), which divides the genome into approximately 2,353 LD-independent blocks. This approach allows us to quantify shared local genetic

Table 1 Summary of data sources for different traits

Phenotype	Sample size†	Consortium	Population	Year	Data resources
Exposure and outcome					
Neuroticism	380,506	UK Biobank	European	2018	(19)
LC	29,266/56,450	ILCCO	European	2017	(20)
LUAD	11,273/55,483	ILCCO	European	2017	(20)
LUSC	7,426/55,627	ILCCO	European	2017	(20)
SCLC	2,664/21,444	ILCCO	European	2017	(20)
Confounding factors					
BMI	806,834	UK Biobank and GIANT	European	2019	(21)
Cigarettes smoked per day	337,334	GSCAN	European	2019	(22)
Drinking per week	941,280	GSCAN	European	2019	(22)
Physical activity	90,667	UK Biobank	European	2018	(23)
Sleep duration	446,118	UK Biobank	European	2019	(24)

†, continuous variables as total sample size, and categorical variables are shown as case/control. BMI, body mass index; GIANT, Genetic Investigation of ANthropometric Traits; GWAS, genome-wide association study; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; ILCCO, International Lung Cancer Consortium; LC, lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer.

effects in specific regions, revealing local correlations that might be masked in global analyses. To adjusting for multiple comparisons, we applied a Bonferroni correction with a stringent significance threshold at P<0.05/2,353.

Partitioned LDSC

Subsequently, we explored the genetic correlation between neuroticism and LC across multiple functional genomic categories by using partitioned LDSC (27). Our analysis focused on 11 common functional categories: conserved regions, DNase I hypersensitive sites (DHS), DNase I digital genomic footprinting (DGF) region, fetal DHS, histone marks (namely H3K27ac, H3K9ac, H3K4me1, and H3K4me3), promoter regions, transcription factor binding sites (TFBS), and transcribed regions (27,28). For each functional category, we recalculated LD scores for SNPs within that category to estimate the genetic correlation between neuroticism and LC.

Cross-trait meta-analysis

Next, we used Cross-Phenotype Association (CPASSOC) analysis to uncover genetic variants influencing both neuroticism and LC (29). CPASSOC provides two key statistics: S_{Hom}, which adjusts for trait correlations in fixed-effect meta-analysis, and S_{Het}, which improves power when genetic effect sizes differ across traits. Given potential genetic heterogeneity, we primarily relied on S_{Het}. We further employed PLINK v1.9 clumping (parameters: -clump-p1 5E-8, -clump-p2 1E-5, -clump-r2 0.2, -clump-kb 500) to obtain shared independent variants ($P_{CPASSOC}<5\times10^{-8}$ and $P_{single\text{-}trait}<1\times10^{-3}$). Novel shared SNPs referred to those meeting these thresholds but not reaching genome-wide significance in single-trait analyses ($1\times10^{-3}<P_{single\text{-}trait}<5\times10^{-8}$) and were independent ($r^2<0.2$) of those previously reported genome-wide significant SNPs from both single-trait GWAS (30). We then annotated the genes located nearest to the SNPs using the Ensembl Variant Effect Predictor (VEP) (31).

Colocalization analysis

To further validate these pleiotropic loci, colocalization analysis was conducted utilizing the coloc package (32), which employs a Bayesian framework to estimate posterior probabilities for five possible hypotheses: H0 (absence of causal variants), H1/H2 (one unique causal variant for each trait), H3 (two independent causal variants, each linked to one trait), and H4 (a shared causal variant affecting both traits). Our focus was the posterior probability for H4 (PPH4), identifying genetic loci with PPH4 >0.5 located within 500 kb of the lead SNP as shared variants.

Transcriptome-wide association study (TWAS) analysis

To determine tissues most relevant to the shared genes, we employed FUSION software for the TWAS analysis (33). This analysis aimed to discover links between neuroticism and LC by analyzing gene expression across 49 tissue types from the Genotype-Tissue Expression (GTEx) project (version 8). The TWAS methodology integrates GWAS summary statistics with expression quantitative trait loci (eQTL) data, enabling inference of gene expression levels and their associations with complex traits. This approach effectively identifies tissues where gene expression changes are most likely to impact both neuroticism and LC. To mitigate false positives, we utilized the Benjamini-Hochberg correction for multiple comparisons.

MR analysis

Finally, we conducted a bidirectional two-sample MR analysis to investigate potential causal links between neuroticism and LC. For neuroticism, we selected genetic instruments with a significance threshold of $P<5\times10^{-8}$ and clumped them for independent IVs using parameters of $r^2=0.001$ and a window size of 10 Mb. Similarly, we clumped SNPs for LC with the same significance threshold ($P<5\times10^{-8}$) but used $r^2=0.01$ within the same window size. The strength of the selected IVs was assessed using the F-statistic, with values below 10 indicating weak instruments (34).

Our primary method was the inverse-variance weighted (IVW) approach, which combines Wald ratio estimates of each SNP by dividing the SNP-outcome estimate by the SNP-exposure estimate (35). If no heterogeneity was detected, the fixed-effect IVW method was performed. To test the robustness of the findings against the assumption of balanced pleiotropy, we also used MR-Egger regression (36) and weighted median (37). Sensitivity analyses were conducted by excluding palindromic SNPs, removing pleiotropic SNPs associated with confounding traits, performing leave-one-out analysis, and applying the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) method (38) to detect and adjust for horizontal pleiotropy. To further address potential confounders, we employed a multivariable MR (MVMR) (39) approach accounting for body mass index (BMI) (21), smoking per day (22), drinking per week (22), physical activity (23), and sleep duration (24) (*Table 1*). Finally, we conducted a reverse-direction MR analysis to assess the potential reverse causality of genetically predicted LC on neuroticism.

Meta-analysis

To enhance statistical power, we conducted a meta-analysis combining our results with existing cohort studies on neuroticism and LC. A systematic PubMed search identified cohort studies before February 2, 2025, with additional references manually retrieved. Eligible studies were peer-reviewed, included European adults, and reported hazard ratio (HR) estimates with 95% confidence intervals (CIs). Studies with insufficient data or abstracts were excluded.

Data collected included sample size, follow-up, LC cases, and adjusted risk estimates. Study quality was assessed using the Newcastle-Ottawa scale, with all studies scoring ≥7. Pooled risk estimates were calculated, heterogeneity assessed with the Cochran *Q* test and I^2 statistic, and a fixed-effects model was used. Sensitivity analysis tested result robustness by omitting one study at a time. Statistical analysis was performed using R4.4.2.

Results

Global and local genetic correlation

Using both unconstrained and constrained LDSC, the global genetic correlations between neuroticism and LC were analyzed (*Figure 2*, Table S1). The unconstrained analysis revealed significant correlations for neuroticism with overall LC ($r_g=0.15$, $P=2.24\times10^{-5}$), LUSC ($r_g=0.21$, $P=3.39\times10^{-6}$), and SCLC ($r_g=0.16$, $P=2.50\times10^{-3}$). Under constrained conditions, these genetic correlations showed a slight decrease, along with reduced standard errors, enhancing the statistical robustness for overall LC ($r_g=0.10$, $P=6.20\times10^{-7}$), and different histological subtypes (LUAD: $r_g=0.05$, $P=3.28\times10^{-2}$; LUSC: $r_g=0.13$, $P=1.38\times10^{-7}$; SCLC: $r_g=0.12$, $P=1.72\times10^{-5}$).

By analyzing local genetic correlations across 2,353 LD-independent regions, significant associations were identified between neuroticism and LC (*Figure 3*). In the analysis, chr6: 167178790–168548525 showed significant correlations with both overall LC and LUAD, while chr6: 100287245–101862923 was significantly associated with SCLC. Notably, chr6: 167178790–168548525 on 6q27 includes the gene *CEP43* (20,40), and chr6: 100287245–101862923 on 6q16.2-q16.3 contains the gene *ASCC3* (19,41)—both previously linked to neuroticism and LC.

Partitioned LDSC

To explore the genetic overlap between neuroticism and

LC across multiple functional genomic elements, we conducted partitioned LDSC analysis (*Figure 4*, Table S2). Significant genetic correlations were found between neuroticism and overall LC in 10 out of 11 functional categories, with r_g values varying from 0.13 in transcribed regions to 0.26 in H3K27ac. For different histological LC subtypes, significant correlations were observed in seven out of 11 categories for LUAD, eight out of 11 for LUSC, and one out of 11 for SCLC. The strongest correlations were observed in TFBS for LUAD (r_g=0.14), H3K9ac for LUSC (r_g=0.26), and fetal DHS for SCLC (r_g=0.13).

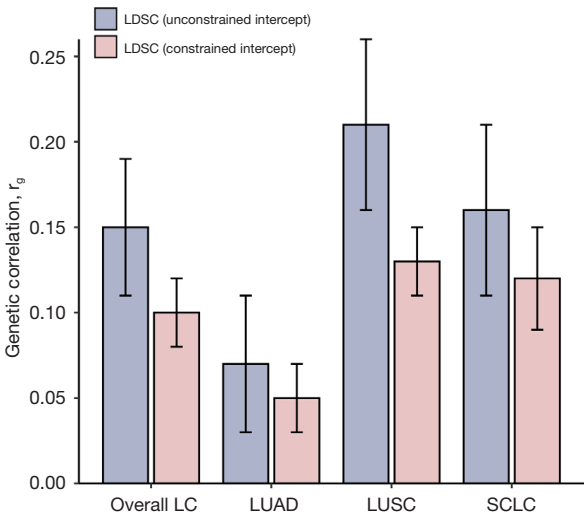

Figure 2 Summary of pairwise genetic correlations estimated using LDSC with and without constrained intercept. Bars represent the point estimates of genetic correlation for each disease pair. Error bars represent the standard error of genetic correlation. LC, lung cancer; LDSC, linkage disequilibrium score regression; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer.

Cross-trait meta-analysis and colocalization analysis

Given the strong genetic association between neuroticism and LC, we conducted a genome-wide meta-analysis using CPASSOC to identify shared significant genetic loci. This analysis revealed 24 independent loci that achieved genome-wide significance ($P_{CPASSOC}<5\times10^{-8}$ and $P_{single\text{-}trait}<1\times10^{-3}$). Among these, we found nine loci shared between neuroticism and overall LC, four with LUAD, nine with LUSC, and two with SCLC (*Table 2*). These SNPs are predominantly located in genomic regions 6p21 (harboring *SLC44A4*, *CYP21A2*, *HSPA1A*, *HSPA1L*, *TNXB*, and *HLA* gene), 6p22 (harboring *ZSCAN12*, *KRT18P1*, *SLC17A4*, and *ZNF322*), 6q27 (harboring *RNASET2*), 15q21.1 (harboring *SEMA6D*), and 17q21.31 (harboring *WNT3* and *CRHR1*). Excluding loci previously reported in single-trait GWAS or those in LD ($r^2\geq0.2$) with known loci, we identified four novel pleiotropic loci. Among these, two loci were shared between neuroticism and overall LC, and 2 between neuroticism and LUAD. The most significant SNP

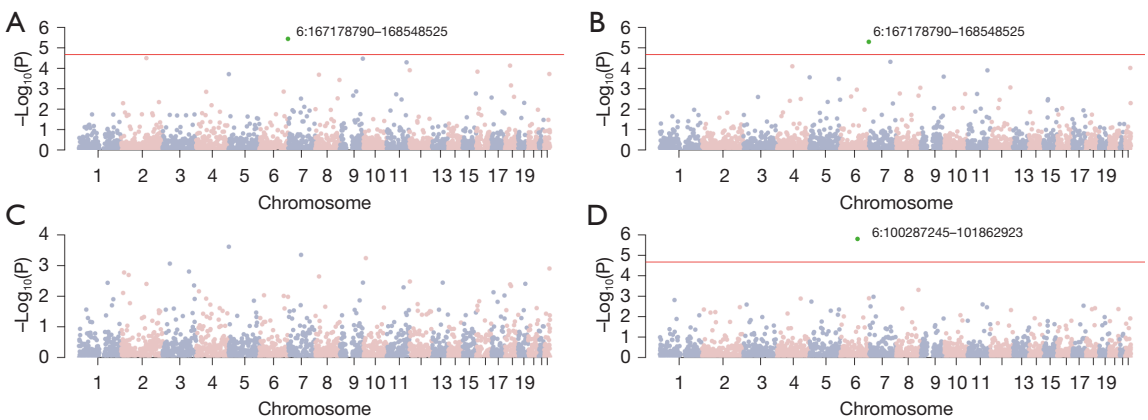

Figure 3 Manhattan plots for local genetic correlation between neuroticism with overall (A) LC, (B) LUAD, (C) LUSC, and (D) SCLC. The X-axis represents chromosomal positions across the human genome, while the Y-axis shows the $-\log_{10}$ of the P value. Each dot corresponds to an LD-independent genomic region, with green dots indicating significant regions. The red line represents the significance threshold of 0.05/2,353. LC, lung cancer; LD, linkage disequilibrium; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer.

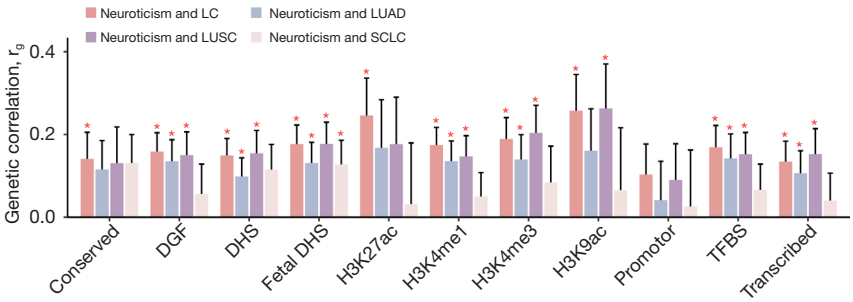

Figure 4 Partitioned genetic correlation between neuroticism and LC by genomic functional elements. Vertical axis represents genetic correlation. Horizontal axis represents 11 functional categories. Asterisks represent significance (*, P<0.05), while error bars represent the standard error of genetic correlation. DGF, DNase I digital genomic footprinting; DHS, DNase I hypersensitive sites; LC, lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer; TFBS, transcription factor-binding sites.

(rs2769345, $P_{CASSOC}=1.07\times10^{-8}$) mapped to *RNASET2*, a tumor suppressor involved in multiple cancers (42). Another significant SNP, rs2854275 ($P_{CASSOC}=1.96\times10^{-8}$), located within the *HLA* gene family, which plays a crucial role in immune regulation and is implicated in LC development and psychiatric disorders (43,44).

For colocalization analysis of shared pleiotropic loci, five out of nine SNPs, three out of four SNPs, six out of nine SNPs, and two out of two SNPs were found to be shared between neuroticism and overall LC, LUAD, LUSC, and SCLC, respectively (Table S3).

TWAS analysis

Results from tissue-specific TWAS revealed gene-level genetic overlap (Tables S4-S7). After multiple corrections, we determined a total of 35 independent transcriptome-wide significant shared genes (including 20 genes shared by neuroticism and overall LC, 13 genes shared by neuroticism and LUAD, five genes shared by neuroticism and LUSC, and four genes shared by neuroticism and SCLC). These gene-level genetic overlap was largely enriched in nervous, digestive, respiratory, cardiovascular, and endocrine system. Of note, three genes were located at pleiotropic loci identified in cross-trait meta-analysis, including *RNASET2* at 6q27 (enriched in brain, lung, adipose, whole blood, etc.), *SEMA6D* at 15q21.1 (enriched in brain), and *CRHR1* at 17q21.31 (enriched in brain and kidney cortex).

Bidirectional MR analysis

To investigate the causal link between neuroticism and LC, we conducted bi-directional MR instrumental analysis utilizing 94 neuroticism-associated SNPs (Table S8). The analysis using the IVW method indicated a significant association between neuroticism and overall LC risk [odds ratio (OR) =1.48, $P=5.53\times10^{-4}$]. This association was further supported by the Weight median (OR =1.59, $P=3.39\times10^{-4}$) and MR-PRESSO (OR =1.42, $P=1.24\times10^{-3}$) methods (*Figure 5*). Although the MR-Egger regression provided estimates that were directionally consistent, the results were not statistically significant (OR =1.19, P=0.81). After excluding palindromic SNPs (OR =1.50, $P=6.79\times10^{-4}$) or pleiotropic (OR =1.41, $P=7.02\times10^{-3}$), the results remained consistent. No significant outliers were identified in the leave-one-out analysis (Figure S1). For specific LC subtypes, a significant causal link was found in LUSC (OR_{IVW} =1.52, $P=8.00\times10^{-3}$), but not in LUAD (OR_{IVW} =1.27, P=0.10) or SCLC (OR_{IVW} =1.69, P=0.06), with these findings confirmed by sensitivity analyses. MVMR was conducted to control for potential confounding factors, resulting in consistent and statistically significant estimates. This indicates that the relationship between neuroticism with overall LC and LUSC remains unaffected by common confounders (Figure S2). In reverse-direction MR analysis using LC-associated SNPs (Table S9), no significant causal effect of LC on neuroticism was found: overall LC (OR_{IVW} =0.99, P=0.33), LUAD (OR_{IVW} =1.00, P=0.77), LUSC (OR_{IVW} =0.98, P=0.18), and SCLC (OR_{IVW} =1.00, P=0.85) (Figure S3).

Phenotypic association analysis

Integrating data from four existing cohort studies on

Table 2 Significant pleiotropic SNPs identified by cross-trait meta-analysis

Index SNP	Position	A1/A2	Neuroticism		LC		$P_{CPASSOC}$	Linear closest genes
			Beta	P value	Beta	P value		
Neuroticism and LC								
rs6545684	2p16.1	T/G	0.02	2.06×10^{-8}	–0.05	5.40×10^{-4}	8.12×10^{-10}	*LINC01122*
rs13213152	6p22.1	A/G	0.02	1.71×10^{-7}	0.15	5.58×10^{-12}	8.32×10^{-12}	*ZSCAN12*
rs148696809	6p22.1	T/C	0.02	2.21×10^{-7}	0.15	2.57×10^{-12}	3.71×10^{-12}	*KRT18P1*
rs2523573	6p21.33	C/G	0.01	1.06×10^{-5}	0.10	3.18×10^{-17}	2.70×10^{-17}	*HLA-B, XXbac-BPG248L24.12*
rs501942	6p21.33	T/C	–0.02	8.38×10^{-7}	0.17	8.40×10^{-19}	5.94×10^{-19}	*SLC44A4, CYP21A2*
rs6456701	6p22.2	T/C	0.01	6.14×10^{-4}	0.12	1.77×10^{-8}	3.64×10^{-8}	*SLC17A4*
rs1043618[†]	6p21.33	C/G	–0.01	9.88×10^{-7}	0.05	9.38×10^{-5}	3.55×10^{-8}	*HSPA1A, HSPA1L*
rs2769345[†]	6q27	T/C	0.01	1.72×10^{-6}	0.06	9.55×10^{-8}	1.07×10^{-8}	*RNASET2*
rs12903078	15q21.1	A/G	0.01	3.54×10^{-8}	0.06	3.17×10^{-7}	1.39×10^{-10}	*SEMA6D*
Neuroticism and LUAD								
rs1150753[†]	6p21.33	A/G	0.02	3.91×10^{-7}	0.10	2.69×10^{-4}	3.76×10^{-8}	*TNXB*
rs2854275[†]	6p21.32	A/C	–0.02	1.64×10^{-7}	0.10	8.58×10^{-4}	1.96×10^{-8}	*HLA-DQA1, HLA-DQB1*
rs113661667	17q21.31	T/C	–0.03	3.74×10^{-31}	–0.07	2.77×10^{-4}	3.44×10^{-34}	*CRHR1*
rs916888	17q21.31	T/C	–0.03	1.37×10^{-22}	–0.07	3.50×10^{-4}	5.86×10^{-25}	*WNT3*
Neuroticism and LUSC								
rs13201782	6p22.2	A/T	–0.02	4.59×10^{-6}	0.20	1.62×10^{-8}	8.66×10^{-9}	*ZNF322*
rs13213986	6p22.1	A/T	–0.02	1.72×10^{-7}	0.22	6.88×10^{-11}	1.78×10^{-11}	*ZSCAN12*
rs148696809	6p22.1	T/C	0.02	2.21×10^{-7}	0.22	3.77×10^{-11}	8.97×10^{-12}	*KRT18P1*
rs2853999	6p21.33	A/T	0.01	1.06×10^{-5}	0.25	3.51×10^{-16}	1.64×10^{-17}	*HLA-B, XXbac-BPG248L24.12*
rs36109883	6p22.2	A/G	–0.02	1.39×10^{-5}	0.25	6.16×10^{-12}	1.14×10^{-12}	*HIST1H2AC*
rs4713570	6p21.32	T/C	–0.01	1.44×10^{-5}	0.14	2.04×10^{-8}	1.12×10^{-8}	*HLA-DQA1, HLA-DQB1*
rs501942	6p21.33	T/C	–0.02	8.38×10^{-7}	0.26	3.06×10^{-17}	1.00×10^{-18}	*SLC44A4, CYP21A2*
rs707938	6p21.33	A/G	0.01	3.34×10^{-8}	0.07	3.35×10^{-4}	6.56×10^{-10}	*MSH5, SAPCD1, VWA7*
rs1327938	13q21.2	T/C	–0.01	2.49×10^{-7}	–0.07	3.52×10^{-4}	7.63×10^{-9}	*RPP40P2*
Neuroticism and SCLC								
rs4530683	4q28.3	A/G	–0.01	3.43×10^{-8}	–0.10	5.60×10^{-4}	1.59×10^{-8}	*SLC7A11-AS1, LINC00616*
rs12903078	15q21.1	A/G	0.01	3.54×10^{-8}	0.11	4.50×10^{-4}	1.61×10^{-8}	*SEMA6D*

[†], novel SNPs are shared SNPs not driven by a single trait and not in LD (r^2<0.2) with index SNPs from single-trait GWAS. CPASSOC, Cross-Phenotype Association; GWAS, genome-wide association study; LC, lung cancer; LD, linkage disequilibrium; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer; SNP, single nucleotide polymorphism.

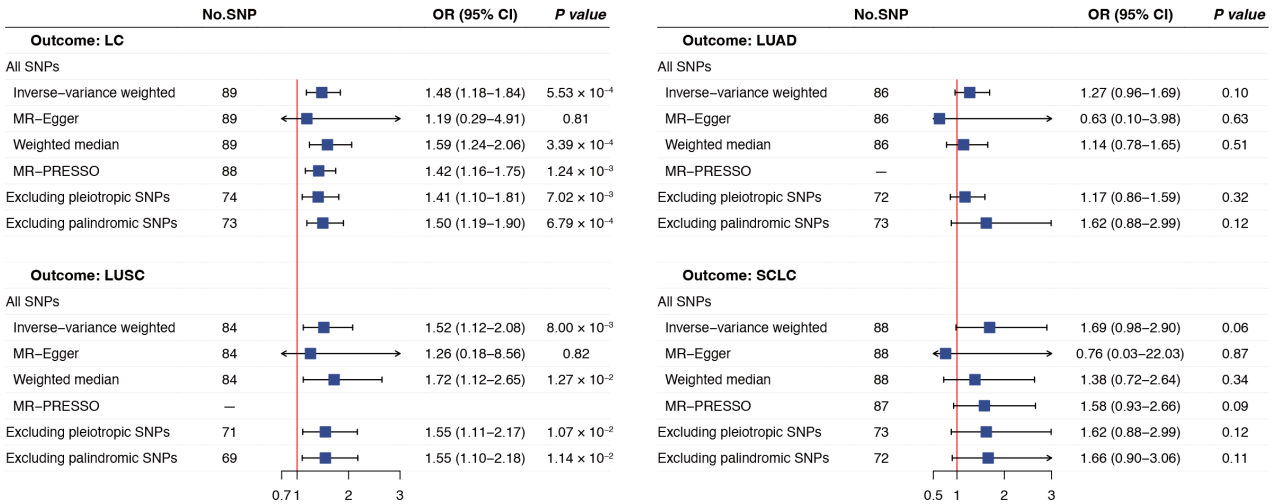

Figure 5 Forest plots of univariable MR of genetically predicted neuroticism on LC. The plots show the ORs and 95% CIs for the causal effect of neuroticism on LC and its histological subtypes. CI, confidence interval; LC, lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MR, Mendelian randomization; OR, odds ratio; PRESSO, Pleiotropy Residual Sum and Outlier; SCLC, small-cell lung cancer; SNP, single nucleotide polymorphism.

the association between neuroticism and LC incidence (12-14,45), the meta-analysis, which included over 490,000 participants, found a significant association (HR =1.06, 95% CI: 1.03–1.10), with no significant heterogeneity (P=0.48, I^2=0%) (Figure S4).

Discussion

In this study, we explored the shared genetic basis between neuroticism and LC by investigating genetic correlations, pleiotropic loci, tissue-gene expression, and causal relationships. Our analysis revealed a significant genetic link between neuroticism and LC, with additional insights gained from partitioning the genome into specific regions (including chr6q27 and chr6q16.2–q16.3), and functional areas such as H3K27ac and H3K9ac. The genetic basis was further dissected through two key mechanisms: pleiotropy and causality. Pleiotropic loci identified through CPASSOC highlighted shared genetic influences, while bidirectional MR analysis provided evidence for causality. Collectively, these results provide valuable insights into the complex genetic interplay between neuroticism and LC, indicating potential benefit for assessing LC risk in individuals with high levels of neuroticism.

The global genetic correlation between neuroticism and LC, revealed by LDSC, was confirmed through additional LDSC with a constrained intercept, which improves statistical power by assuming no sample overlap (25). Although the genetic correlation between neuroticism and LUAD was initially non-significant, it became marginally significant when the intercept was constrained to zero. When the genome was divided into 2,353 distinct regions, two specific genomic regions, chr6q27 and chr6q16.2–q16.3, were found to be significantly associated with both neuroticism and LC. The gene *ASCC3*, located at chr6q16.2–q16.3, has been shown to promote malignant phenotypes in LC and is associated with neuroticism (41,46). Partitioned LDSC further identified strong genetic correlations in functional regions like H3K9ac and H3K27ac, consistent with previous studies on the role of epigenetic modifications in psychiatric disorders and cancer (47,48). These findings suggest that neuroticism and LC share common genetic and epigenetic pathways.

To explore the underlying mechanisms, we performed a cross-trait meta-analysis, identifying 24 shared loci between neuroticism and LC. Many of these loci were previously associated with psychiatric disorders (*CRHR1*, *SLC17A4*, *SEMA6D*) (49-51), inflammatory responses (*HSPA1A*, *RNASET2*) (52,53), and cancer progression (*WNT3*, *TNXB*) (54,55). Notably, several genes, including *RNASET2* and the *HLA* gene family, showed strong associations, supported by significant colocalization evidence (PPH4 >0.5). Additionally, four novel loci were discovered, two linked to overall LC and two to LUAD, with *RNASET2* and the

HLA gene family emerging as prominent candidates.

RNASET2 is an RNase T2 enzyme present in humans and represents the only identified extracellular nuclease within its family (56). It has been recognized as a tumor suppressor gene, with reduced expression observed in primary ovarian tumors, melanoma, and non-Hodgkin's lymphoma (57). Additionally, gene eQTL analysis of 1,425 lung tissue samples has identified *RNASET2* as a potential susceptibility locus for LC (20). Beyond its role in cancer, *RNASET2* has also been linked to neuroinflammation, a process involved in several mental health disorders (58). These findings highlight *RNASET2* as a potential shared mechanism linking neuroticism and LC through its roles in both cancer progression and neuroinflammatory pathways.

The *HLA* gene family, a highly complex genetic system, plays a pivotal role in immune response and disease susceptibility, affecting various immuno-inflammatory disorders and cancers (59,60). Polymorphisms and expression of *HLA* molecules are associated with tumor occurrence and progression, as they regulate tumor cell proliferation and suppress antitumor immunity (59). Furthermore, recent studies have highlighted the critical role of *HLA*-related microglial expression in neurodegenerative disorders and aging (60,61). One potential mechanism by which *HLA* influences these conditions is through its effect on microglial function. Microglia are key players in the central nervous system, involved in neural circuitry development, brain blood vessel formation, and maintaining the blood-brain barrier architecture (62). Alterations in microglial function, such as microglial senescence and activation, have been linked to a wide range of psychiatric conditions, including psychosis, mania, depression, and anxiety (63). These results suggest the *HLA* gene family as another potential biological mechanism shared between neuroticism and LC. However, further fundamental research is required to validate these results and fully elucidate the underlying mechanisms.

By combining GTEx tissue expression data with GWAS findings at the gene-tissue level, TWAS analysis uncovered potential common mechanisms between neuroticism and LC. Both CPASSOC and TWAS pinpointed several genes—*RNASET2*, *SEMA6D*, *CRHR1*, and *SLC17A4*—as relevant across various tissues, particularly those involved in the nervous, respiratory, cardiovascular, and endocrine systems. Additionally, *CEP43*, located at 6q27, emerged in the local genetic correlation analysis. Other shared genes, such as *SERPINA1* and *IRF4*, were also detected by TWAS, and have been previously associated—either directly or indirectly—with mental health disorders and LC (64-67). Overall, the biological targets that overlap between neuroticism and LC point to potential therapeutic strategies for individuals with comorbid conditions.

Our bidirectional MR analysis identified a significant causal link between neuroticism and LC, particularly in overall LC and LUSC. These results align with findings from large-scale cohort studies (12,13) and recent MR studies (13,16). Our study builds upon these previous MR analyses in several key ways. Our study extends these previous analyses by exploring causal effects across specific LC histological subtypes. Sensitivity analyses confirmed the robustness of our results, and reverse-direction MR analysis revealed no significant causal effect of LC on neuroticism. These findings suggest that neuroticism may play a causal role in LC risk, emphasizing the need for targeted preventive strategies for individuals with high neuroticism. This underscores the importance of assessing LC risk and developing preventive strategies for individuals with high levels of neuroticism.

Several limitations of this study should be acknowledged. The genetic data that we used was derived from GWAS involving participants of European background, which may limit the generalizability of the results to other populations. Additionally, the relatively small sample size for LC histological subtypes may have restricted the ability to detect subtype-specific causal relationships. Self-reported neuroticism data at baseline could have introduced misclassification, although this is likely non-differential and would underestimate the true association. Furthermore, while our study focused on LC, neuroticism has been linked to other health conditions (e.g., chronic bronchitis, asthma), and future studies should explore these associations further. Lastly, although we identified potential genetic mechanisms and causal pathways, further clinical validation is necessary to confirm their practical applications in cancer prevention.

Conclusions

In conclusion, this study provides robust evidence for a shared genetic basis between neuroticism and LC, supported by pleiotropic loci and causal associations. Our findings suggest that neuroticism may contribute to LC risk, highlighting the importance of considering personality traits in LC risk assessment and prevention. This study advances the understanding of the genetic architecture underlying the relationship between neuroticism and LC and suggests potential avenues for future research and

cancer prevention.

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Footnote

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