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Research Article

NEU1 Inhibitors and Risk of Malignancy: Mendelian Randomization Insights in Drug Targeting Studies

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Abstract

Background: Rheumatoid Arthritis (RA) is associated with an increased risk of cancer, and celecoxib is a commonly used drug for treating both RA and cancer. Celecoxib, a NEU1 inhibitor, exerts its anti-cancer effects by modulating NEU1 expression. This study employs Mendelian randomization to explore the therapeutic potential of NEU1 in cancer treatment.

Methods: We collected Single Nucleotide Polymorphisms (SNPs) of NEU1 from published genome-wide association study data and conducted drug-target Mendelian Randomization (MR) analysis to examine the causal relationship between NEU1 inhibitors and various malignant tumors. The main outcomes included lung cancer, Gastric Cancer (GC), Esophageal Cancer (EC), Colorectal Cancer (CRC), Breast Cancer (BC), Pancreatic Cancer (PC) and Cervical Cancer (CC). MR methods (Egger, IVW, MR-PRESSO) and colocalization analysis were employed to analyze these seven types of cancer.

Results: NEU1 inhibition significantly reduced the risk of gastric cancer (OR [95% CI] = 0.55 [0.36 to 0.84], $p < 0.001$) and lung cancer (OR [95% CI] = 0.90 [0.83 to 0.96], $p < 0.001$). Initial data showed a reduced risk of cervical cancer (OR [95% CI] = 0.61 [0.49 to 0.78], $p < 0.001$), while in the repeat analysis, the result was OR = 0.44 with $p = 3.34$. Colocalization analysis confirmed the reduction in cervical cancer risk with NEU1 inhibition.

Conclusion: The Neu1 inhibitors significantly reduced the risk of gastric cancer, lung cancer, and cervical cancer.

Keywords: Cancer; Celecoxib; Drug-target Mendelian randomization; NEU1; Rheumatoid arthritis

Background

In today's world, the incidence of malignant tumors accounts for approximately 12% of the global population, posing a significant psychological and economic burden not only on patients but also on their families [1]. It has also become one of the major challenges faced by the medical community. In the field of cancer treatment, targeted therapy has emerged as an important approach, providing patients with more precise and effective treatment options [2]. However, despite the great promise that targeted therapy brings to cancer treatment, there are still many unknown potential mechanisms of disease onset and treatment targets. Therefore, there is an urgent need to delve into the mechanisms of tumor development, discover new treatment targets, and better prevent and treat diseases related to tumors.

Rheumatoid Arthritis (RA) is a chronic inflammatory disease associated with an increased risk of certain cancers, such as lung cancer and lymphoma [3]. The etiology of this increased cancer risk may be multifactorial, including shared risk factors as well as chronic inflammation. Rheumatoid arthritis may be related to the incidence and progression of malignant tumors, and the effects of various drugs used to treat rheumatoid arthritis on malignant tumor diseases warrant further investigation. RA and malignant tumors commonly present with pain, and celecoxib is a selective nonsteroidal anti-inflammatory drug (NSAID) commonly used to treat patients with rheumatoid arthritis as well as those with tumor-related pain. Celecoxib is a potent COX-2 selective inhibitor and has been reported to exhibit anti-cancer activity. For instance, it can prevent hypoxia-induced Epithelial-Mesenchymal Transition (EMT) in colon cancer cells [4], induce cell cycle arrest [5], and inhibit proliferation and depolarization of mitochondrial membrane potential expression in human colon rectal adenocarcinoma HT-29 cells [6]. Although some studies have reported the anti-tumor activity of celecoxib [7], its underlying mechanisms are still unclear.

Neuraminidase 1 (NEU1), as the target of celecoxib treatment, exerts anti-tumor effects by modulating the activation of several Receptor Tyrosine Kinases (RTKs) and Toll-like receptors and their downstream signaling pathways [8]. This study aims to explore the causal relationship between NEU1 inhibitors and malignant tumors, using Mendelian randomization methods to investigate the therapeutic effects of NEU1 gene simulation inhibition on malignant tumors. Our research not only seeks to provide new insights and approaches for the treatment of malignant tumors but also contributes to the development of the field of targeted therapy.

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Methods

Selection of NEU1 instrumental variable

The summary data for rheumatoid arthritis were derived from a meta-analysis of a genome-wide association study (GWAS) involving 417,256 individuals of European descent. Instrumental variables targeting NEU1 for the treatment of rheumatoid arthritis were identified to simulate the effect of NEU1 inhibitors. These instrumental variables were selected from single nucleotide polymorphisms (SNPs) located within 100kb of the NEU1 gene locus and associated with rheumatoid arthritis disease (Figure 1). To mitigate the impact of strong linkage disequilibrium (LD), an LD threshold was set at r2 < 0.3. Ultimately, 16 significant SNPs related to NEU1 were retained (Additional file 1: Table S1). A repeat analysis was conducted using summary data from another GWAS study involving 178,616 individuals of European ancestry to ensure the stability of the results (Additional file 1: Table S2).

Source of outcomes

We conducted drug-target Mendelian Randomization (MR) analysis on nine diseases as targets. These datasets were sourced from European populations. The dataset for lung cancer was obtained from a GWAS meta-analysis, comprising 4,444 cases and 174,282 controls. Additionally, we collected GWAS summary datasets for Gastric Cancer (GC), Esophageal Cancer (EC), Colorectal Cancer (CRC), Breast Cancer (BC), Pancreatic Cancer (PC), and Cervical Cancer (CC) as primary outcomes.

MR analysis

We harmonized the exposure-relevant drug-target instrumental variables with the outcome dataset and then conducted analyses using several MR methods, including Egger regression, weighted median, inverse variance-weighted (IVW), simple mode, weighted mode, and MR-PRESSO. IVW was the most commonly used method [9]. Heterogeneity testing was performed using Cochran's Q value through Egger and IVW methods, where a p-value>0.05 indicated no significant heterogeneity. Egger regression was employed to assess the level of pleiotropy in the genetic instruments, where a p-value > 0.05 indicated no horizontal pleiotropy [10]. The MR assumption requires that SNPs are not directly related to the outcome (Figure 1). Therefore, the Phenoscanner online tool (http://www.phenoscanner.medschl.cam.ac.uk/) was used to identify traits directly related to the instrumental variable SNPs, excluding SNPs associated with LC, GC, EC, CRC, BC, PC, and CC. After testing for outliers with MR-PRESSO, sensitivity analyses were conducted. To ensure that our results were not significantly influenced by specific SNPs, we performed a leave-one-out analysis, sequentially removing each SNP, and compared the results of the IVW method with all variants. Data analysis was conducted using R version 4.2.1 with the MRPRESSO and TwoSampleMR packages [11].

Colocalization analysis

To confirm the association between NEU1 and cervical cancer, we employed the Mendelian randomization (MR) method. Specifically, we conducted MR analysis on expression quantitative trait loci (eQTLs) with estimated causal effects. These were defined as having IVW p-values, if available, with MR-PRESSO<0.05. We also performed colocalization analysis using the R package Coloc [12]. The variants most closely associated with the MR analysis, those with the lowest p-values, were selected as reference variables. A 100 kb region around these reference variants was considered as the colocalization region. Colocalization evidence was defined as a posterior probability greater than 0.95 for shared causal variants (posterior probability >0.95 under hypothesis 4) [13].

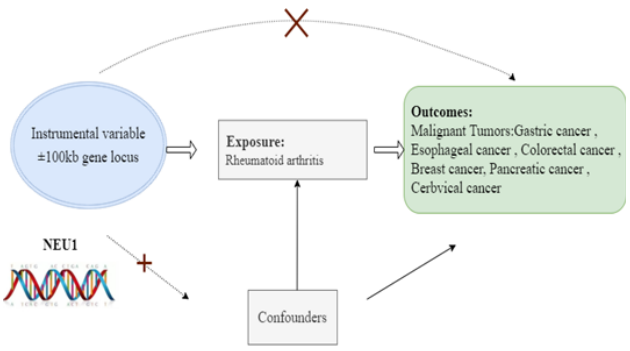

Figure 1: Research overview and design of drug target Mendelian randomization analysis. In order to verify the existence of causal correlation, it is necessary to meet the conditions as follows: (1) the instrumental variables are not related to the confounders (dashed line), (2) the instrumental variables are related to the exposure factor (solid line), and (3) the instrumental variables are not directly related to the outcome (dashed line).

Results

Causal Relationship between NEU1 Gene Inhibition and Malignant Tumors

The IVW method results showed that NEU1 inhibition significantly reduced the risk of gastric cancer (OR [95% CI] = 0.55 [0.36 to 0.84], p <0.001), and lung cancer (OR [95% CI] = 0.90 [0.83 to 0.96], p <0.001) (Figure 2). Results from Egger's, simple mode, weighted mode, and MR-PRESSO are shown in additional file 1: table S3. Similar results were obtained in a repeat analysis using another GWAS dataset (Additional file 1: Table S4). Cervical cancer risk was significantly reduced (OR [95% CI] = 0.61 [0.49 to 0.78], p < 0.001) in the initial GWAS dataset. However, in a repeat analysis using another GWAS dataset, the results showed a different level of risk reduction (OR [95% CI] = 0.44 [0.34 to 0.57], p = 3.34). To further validate these findings and reconcile the inconsistencies, we conducted colocalization analysis.

Sensitivity analysis

Several sensitivity analyses were conducted to examine and correct for the presence of pleiotropy in causal estimates. Cochran's Q-test and funnel plot showed no evidence of heterogeneity or asymmetry among these SNPs in the causal relationship. The results of sensitivity analyses indicated no heterogeneity and horizontal pleiotropy in all other outcomes (p > 0.05) (Supplementary Table S5). The MR-PRESSO global test did not detect potential horizontal pleiotropy (Supplementary Table S6). To verify the impact of each SNP on the overall causal estimates, we performed a leave-one-out analysis (Supplementary Figure S2). After systematically removing each SNP, we conducted the MR analysis again for the remaining SNPs. The results remained consistent, indicating that all SNPs contributed significantly to the causal relationship. Leave-one-out analysis demonstrates that removing any SNP related to the cancer diseases does not significantly alter the results (Figure 3). Furthermore, another GWAS related to rheumatoid arthritis was used to reselect NEU1

Outcome	Target	Method	NSNP	p-value	OR Visualization	OR (95% CI)
CRC	NEU1	MR Egger	8	0.8466		0.9581 (0.6327 – 1.4509)
		Weighted median	8	0.0920		0.8646 (0.7300 – 1.0241)
		Inverse variance weighted	8	0.0928		0.8949 (0.7862 – 1.0186)
		Simple mode	8	0.2164		0.8222 (0.6199 – 1.0905)
		Weighted mode	8	0.1566		0.8466 (0.6892 – 1.0399)
LC	NEU1	MR Egger	15	0.1781		0.8886 (0.7402 – 1.0667)
		Weighted median	15	<0.001		0.9260 (0.8541 – 1.0040)
		Inverse variance weighted	15	<0.001		0.8958 (0.8325 – 0.9640)
		Simple mode	15	0.0183		0.7808 (0.6387 – 0.9545)
		Weighted mode	15	0.0043		1.0009 (0.8629 – 1.1609)
GC	NEU1	MR Egger	12	0.0207		0.5474 (0.3560 – 0.8418)
		Weighted median	12	<0.001		0.7069 (0.6271 – 0.7968)
		Inverse variance weighted	12	<0.001		0.7186 (0.6311 – 0.8183)
		Simple mode	12	0.0024		0.7305 (0.6241 – 0.8549)
		Weighted mode	12	<0.001		0.6991 (0.6109 – 0.8001)
PC	NEU1	MR Egger	15	0.7187		0.9192 (0.5869 – 1.4396)
		Weighted median	15	0.4997		0.9320 (0.7595 – 1.1436)
		Inverse variance weighted	15	0.2601		0.9164 (0.7872 – 1.0668)
		Simple mode	15	0.9343		1.0155 (0.7084 – 1.4558)
		Weighted mode	15	0.7288		1.0619 (0.7612 – 1.4815)
EC	NEU1	MR Egger	15	0.4102		1.2683 (0.7337 – 2.1923)
		Weighted median	15	0.3877		1.0823 (0.9046 – 1.2949)
		Inverse variance weighted	15	0.2662		1.1039 (0.9274 – 1.3140)
		Simple mode	15	0.4358		1.1145 (0.8552 – 1.4522)
		Weighted mode	15	0.3141		1.1321 (0.8969 – 1.4291)
CC	NEU1	MR Egger	15	0.0879		0.5052 (0.2446 – 1.0434)
		Weighted median	15	<0.001		0.6035 (0.4783 – 0.7614)
		Inverse variance weighted	15	<0.001		0.6173 (0.4883 – 0.7804)
		Simple mode	15	0.3283		0.7493 (0.4286 – 1.3099)
		Weighted mode	15	0.0049		0.4557 (0.2872 – 0.7232)
BC	NEU1	MR Egger	15	0.8754		1.0071 (0.9231 – 1.0988)
		Weighted median	15	0.0393		1.0406 (1.0020 – 1.0808)
		Inverse variance weighted	15	0.0036		1.0452 (1.0145 – 1.0769)
		Simple mode	15	0.1046		1.0537 (0.9933 – 1.1179)
		Weighted mode	15	0.1600		1.0461 (0.9856 – 1.1104)

Figure 2: The effect of NEU1 inhibitor on 7 types of malignant tumors. NSNP, number of single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; NEU1: neuraminidase 1; LC: Lung Cancer; GC: Gastric Cancer; EC: Esophageal Cancer; CRC: Colorectal Cancer; BC: Breast Cancer; HC: Hepatocellular Carcinoma; PC: Pancreatic Cancer; CC: Cervical Cancer.

instrumental variables, and repeating the aforementioned approach indicates stable results can be obtained (Supplementary File 1: Table S7).

Figure 3: Sensitivity analysis of NEU1 across 7 cancer diseases: LC (Lung Cancer), GC (Gastric Cancer), EC (Esophageal Cancer), CRC (Colorectal Cancer), BC (Breast Cancer), HC (Hepatocellular Carcinoma), PC (Pancreatic Cancer), and CC (Cervical Cancer).

Colocalization analysis

We conducted SNP-level colocalization analysis to assess evidence for shared causal variants between the NEU1 gene and cervical cancer using Coloc. Each configuration generating a posterior probability in the colocalization analysis includes five hypotheses: H0, no association with either trait; H1, associated with Trait 1 but not Trait 2; H2, associated with Trait 2 but not Trait 1; H3, associated with both Trait 1 and Trait 2, two independent single nucleotide polymorphisms; and H4, associated with both Trait 1 and Trait 2, a shared SNP. We performed Bayesian colocalization analysis, focusing on SNPs located within 100 kb of the NEU1 gene locus and associated with cervical cancer risk. The colocalization analysis indicated a posterior probability of 99.12% for shared causal variants between SNPs associated with cervical cancer and the NEU1 gene (Figure 4).

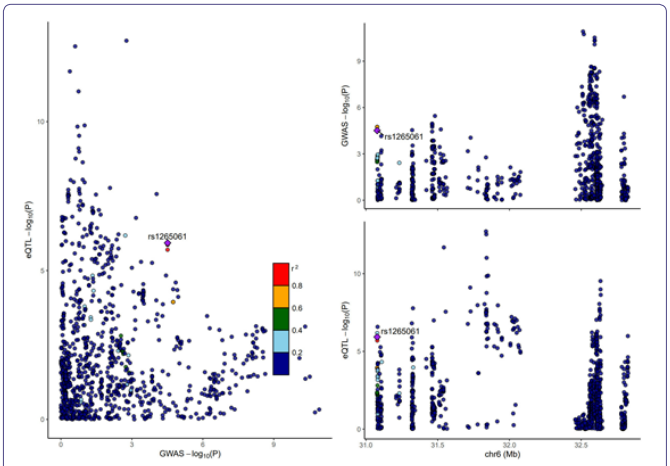

Figure 4: Highly supported evidence of colocalization between NEU1 and Cervical Cancer. NEU1: neuraminidase 1.

Discussion

Neuraminidase 1, a lysosomal sialidase, exerts significant influence on adverse biological processes. In addition to its role in lysosomes [14], NEU1 is found on the plasma membrane where it modulates the activation levels of various receptors, including Receptor Tyrosine Kinases (RTKs), integrins, and Toll-like receptors [15-22]. The aging process induces degradation of elastic fibers through mechanical stress and enzyme actions (such as matrix metalloproteinases, serine proteases, or cysteine proteases), resulting in the production of Elastin-Derived Peptides (EDPs) [23-26]. These bioactive EDPs interact with a single-cell surface receptor complex called the Elastin Receptor Complex (ERC), triggering diverse biological responses. NEU1's action is intricately linked to signaling through the ERC and the biological effects induced by EDPs [27-31]. Notably, in the context of tumor development, EDPs have been implicated in promoting processes such as cell proliferation, survival, invasion, angiogenesis, and the expression of Matrix Metalloproteinases (MMPs) [32].

Studies have highlighted NEU1's pivotal role in various cancer types, suggesting its potential as a promising target for cancer therapy [33-36]. Dysregulation of NEU1 has been associated with increased invasiveness, metastasis, and treatment resistance in tumors. Our research findings corroborate a significant protective effect of NEU1 inhibitors against gastric cancer, lung cancer, and cervical cancer, as indicated by the Odds Ratio (OR) and 95% Confidence Interval (CI). Sensitivity analyses were conducted, including leave-one-out analysis and tests for heterogeneity and pleiotropy, to assess the robustness of these results. These analyses confirmed the stability and validity of our findings, indicating a consistent reduction in the risk of gastric cancer, lung cancer, and cervical cancer with NEU1 inhibition.

Lung cancer is a leading cause of cancer-related deaths, histologically classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately

80%-85% of cases [37,38]. NEU1 mRNA expression has been linked to the overall survival of NSCLC patients, with higher NEU1 mRNA expression generally correlating with lower overall survival rates. Additionally, NEU1 is identified as a downstream target of p53-R273H, playing a crucial role in p53-R273H-induced migration of NSCLC cells [39]. Integrin β4, an important member of the integrin family, suppresses cancer metastasis by inhibiting Epithelial-Mesenchymal Transition (EMT) and promoting cell-cell and cell-matrix adhesion [40]. Interestingly, NEU1 has been reported to modulate signaling mediated by ITGB4 [41]. The activation of EGFR is pivotal in NSCLC development, making EGFR a promising therapeutic target [42]. EGFR Tyrosine Kinase Inhibitors (TKIs) such as erlotinib or gefitinib have shown significant benefits for NSCLC patients [43]. However, EGFR-TKI resistance remains a major challenge in NSCLC treatment. It has been reported [44] that NEU1 and MMP-9 form complexes on the cell surface with EGFR, which is crucial for EGFR activation. Thus, NEU1 inhibitors hold potential as therapeutic agents to overcome drug resistance in NSCLC treatment.

Gastric cancer, a common malignancy, has been associated with the crucial role of MicroRNAs (miRNAs) in cancer development and progression. Specifically, miR-125b is upregulated in gastric cancer tissues compared to non-tumor tissues, promoting in vitro migration, invasion, and in vivo metastasis of gastric cancer cells. NEU1 has been identified as a direct target gene of miR-125b, with this miRNA suppressing NEU1 expression and thereby facilitating gastric cancer proliferation, invasion, and migration [45]. Our experimental findings support a protective effect of NEU1 inhibitors against gastric cancer, although this contradicts some existing experiments. However, current research on NEU1 in gastric cancer is limited and requires further exploration. Studies by Kalliopi I Pappa [46] and colleagues have demonstrated NEU1 overexpression in various cervical cancer cell lines. A recent study [47] found that HDAC1 interacts with NRF2 to downregulate NEU1 expression, and NEU1 knockdown counteracted the effects of Trichostatin A (TSA) while enhancing the aggressiveness of cervical cancer cells. This suggests a complex interplay of NEU1 in cancer progression, necessitating deeper investigation into its role in gastric and cervical cancers.

Our study did not observe a causal relationship between NEU1 inhibitors and the risk of pancreatic cancer, esophageal cancer, colorectal cancer, or breast cancer. However, supporting evidence from related experiments exists. Haxho and colleagues highlighted the crucial role of NEU-1 in the sialyltransferase-mediated tumorigenesis of pancreatic cancer [48]. They demonstrated that increased NEU-1 expression is essential for MMP-9-EGFR signaling, promoting cancer progression and metastasis. Oseltamivir, an FDA-approved NEU inhibitor for preventing and treating influenza A and B infections, has shown potential in cancer treatment [49]. Osse's team showed that oseltamivir inhibits NEU-1 activity, suppressing the survival signaling of drug-resistant pancreatic cancer (PANC1) cells [50]. Additionally, sialidase inhibitors like oseltamivir modulate EGF-induced receptor tyrosine kinase activation in a dose and time-dependent manner, highlighting the significant role of NEU-1 in pancreatic cancer cell survival [51]. However, Bera and colleagues' research indicated increased expression of miR-125b in epithelial-mesenchymal transition (EMT) and chemoresistance in gemcitabine-resistant Pancreatic Ductal Adenocarcinoma (PDAC) cell models, partly due to reduced NEU-1 expression. In colorectal cancer, quantitative RT-PCR analysis of NEU-1 expression in human colon cancer tissues revealed lower levels compared to adjacent non-cancerous mucosa. Interestingly, within the same cancer tissues, NEU-1 activity appeared inversely correlated with invasion depth and degree of differentiation [52]. Furthermore, overexpression of NEU-1 in colon adenocarcinoma HT-29 cells reduced cell migration and invasion, while NEU-1 gene knockdown increased these aggressive behaviors. Several studies have explored the role of NEU-1 in breast cancer cells. Inhibiting or downregulating NEU-1 with oseltamivir phosphate impaired proliferation, apoptosis, and epithelial-mesenchymal transition of breast cancer cells, altering sialic acid levels [53]. In esophageal cancer, Sphingosine-1-phosphate transporter 1 (SPN S1) emerged as a significantly differentially expressed gene (DEG) in Esophageal Squamous Cell Carcinoma (ESCC). Transcriptomic sequencing revealed NEU1 as an important DEG influenced by SPNS1, positively correlated with SPNS1 expression. Oseltamivir Phosphate (OP), an NEU1 inhibitor, significantly reversed 5-FU resistance, migration, and proliferation induced by high SPNS1 expression both in vivo and in vitro. These findings suggest that SPNS1 may promote ESCC progression by upregulating NEU1 expression and affecting chemotherapy sensitivity [54].

Acknowledging the limitations of our study is important. Firstly, while Mendelian randomization analysis is a powerful tool, it cannot replace clinical trials. It serves as a method to analyze the causal relationship between exposure and outcome, but the actual clinical effects require verification through more rigorous clinical trials. Therefore, despite our study's findings suggesting that NEU1 inhibitors may reduce the risk of certain cancers, further clinical research is necessary to confirm the effectiveness and safety of this treatment strategy. Secondly, our study solely relied on GWAS data from European populations. Given the genetic heterogeneity among different races, the effects of NEU1 inhibitors may vary in other populations. Future studies should conduct subgroup analyses in diverse populations to comprehensively assess the effects and potential side effects of NEU1 inhibitors. Additionally, our sample size was relatively limited, and the data on specific cancer types may not be sufficiently comprehensive. Larger sample sizes and more comprehensive clinical data could provide a more accurate evaluation of the impact of NEU1 inhibitors on different types of cancer. Lastly, our study requires further cell and animal model experiments to validate the mechanism of action and biological effects of NEU1 inhibitors. Such experiments can offer a deeper understanding of NEU1's exact role in cancer development and treatment, laying a more profound foundation for future clinical research.

Conclusion

After conducting drug target MR analysis, we found that genetic prediction of inhibition of NEU1 significantly reduced the risk of lung cancer, gastric cancer, and cervical cancer.

Acknowledgement

The GWAS summary data were obtained from the online public platform (https://gwas.mrcieu.ac.uk/). The analyses of GWAS summary data were performed under application R version 4.2.1.

Author's Contribution

SJR designed the research study, collected data, analyzed and interpreted the data, and drafted the manuscript. CZW and QJ provided guidance and support throughout the research process, assisted in data collection and analysis, and participated in manuscript revision and editing. All authors have read and approved the final manuscript.

Every author and contributor listed above have reviewed and approved the final version of the manuscript.

Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declarations

Ethics approval and consent to participate: The GWAS summary data used in this study were all from the online public platform (https://gwas.mrcieu.ac.uk/). The study protocols were approved by respective local ethics committees, and participants have provided written informed consent.

Consent for Publication

All authors are aware of and agree to the publication. Not application.

Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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Supplementary Table

SNP	Effect_allele.exposure	Other_allele.exposure	Effect_allele.outcome	Other_allele.outcome
rs115699278	T	C	T	C
rs116508221	T	C	T	C
rs147906938	A	T	A	T
rs188605322	T	C	T	C
rs2844454	T	C	T	C
rs2844455	T	C	T	C
rs35570187	G	C	G	C
rs35875104	C	T	C	T
rs372313241	A	T	A	T
rs506770	C	G	C	G
rs611902	A	G	A	G
rs62395849	C	G	C	G
rs62395851	C	G	C	G
rs6905149	T	C	T	C
rs79928938	A	T	A	T

Table 1: 16 Significant SNPs related to NEU1 were retained.

SNP	Effect_allele.exposure	Other_allele.exposure	Effect_allele.outcome	Other_allele.outcome
rs115699278	T	C	T	C
rs116508221	T	C	T	C
rs12614	T	C	T	C
rs147906938	A	T	A	T
rs2072633	G	A	G	A
rs2763979	T	C	T	C
rs3020644	G	A	G	A
rs401775	C	T	C	T
rs506770	C	G	C	G
rs616634	G	A	G	A
rs66804014	A	G	A	G
rs6905149	T	C	T	C
rs693906	C	G	C	G
rs79928938	A	T	A	T
rs9461726	T	C	T	C

Table 2: A repeat analysis was conducted using summary data from another GWAS study involving 178,616 individuals of European ancestry to ensure the stability of the results.

Outcome	Target	method	nsnp	pval	or	or_lci95	or_uci95	orDrug	or_lci95Drug	or_uci95Drug
CRC	NEU1	MR Egger	8	0.846602	1.04369	0.689221	1.580465	0.958139	0.632725	1.450914
		Weighted median	8	0.092049	1.156613	0.976503	1.369942	0.864594	0.729958	1.024062
		Inverse variance weighted	8	0.092832	1.117451	0.981711	1.271959	0.894894	0.786189	1.01863
		Simple mode	8	0.216385	1.216287	0.917002	1.61325	0.822175	0.619867	1.09051
		Weighted mode	8	0.156592	1.181161	0.961591	1.450868	0.846625	0.689242	1.039943
LC	NEU1	MR Egger	15	0.178136	1.234	0.923821	1.648324	0.888558	0.74017	1.066693
		Weighted median	15	9.96E-06	1.261165	1.137797	1.39791	0.926035	0.854098	1.004031
		Inverse variance weighted	15	0.000468	1.177586	1.074536	1.290519	0.895804	0.832468	0.963958
		Simple mode	15	0.018254	1.308775	1.074281	1.594454	0.780803	0.638725	0.954485

		Weighted mode	15	0.004257	1.315357	1.123444	1.540053	1.000887	0.862944	1.16088
GC	NEU1	MR Egger	12	0.020686	1.826692	1.187874	2.809056	0.547438	0.355992	0.84184
		Weighted median	12	1.37E-08	1.41461	1.254971	1.594557	0.706908	0.627133	0.796831
		Inverse variance weighted	12	6.16E-07	1.391617	1.222094	1.584656	0.718588	0.631052	0.818268
		Simple mode	12	0.002422	1.368996	1.169711	1.602233	0.730462	0.624129	0.854912
		Weighted mode	12	0.000294	1.430393	1.249867	1.636994	0.699109	0.610876	0.800085
PC	NEU1	MR Egger	15	0.718679	1.087928	0.694624	1.703924	0.919179	0.586881	1.439627
		Weighted median	15	0.499729	1.073015	0.874429	1.316702	0.931953	0.759473	1.143604
		Inverse variance weighted	15	0.260079	1.091258	0.93739	1.270383	0.916374	0.787164	1.066792
		Simple mode	15	0.934278	0.984692	0.686918	1.41155	1.015545	0.708441	1.455778
		Weighted mode	15	0.728846	0.94168	0.674971	1.313778	1.061931	0.761164	1.481545
EC	NEU1	MR Egger	15	0.410161	0.788483	4.56E-01	1.362989	1.268258	0.733682	2.192338
		Weighted median	15	0.387693	0.923996	7.72E-01	1.105516	1.082255	0.904555	1.294865
		Inverse variance weighted	15	0.266199	0.905877	7.61E-01	1.078322	1.103903	0.927367	1.314044
		Simple mode	15	0.435776	0.897299	6.89E-01	1.169251	1.114456	0.855249	1.452223
		Weighted mode	15	0.314133	0.883289	7.00E-01	1.115012	1.132132	0.896852	1.429136
CC	NEU1	MR Egger	15	0.087898	1.979433	9.58E-01	4.088126	0.505195	0.244611	1.04338
		Weighted median	15	2.07E-05	1.657094	1.313295	2.090893	0.603466	0.478265	0.761443
		Inverse variance weighted	15	5.53E-05	1.619931	1.281326	2.048016	0.61731	0.488277	0.780441
		Simple mode	15	0.328314	1.334616	0.763443	2.333113	0.749279	0.428612	1.309855
		Weighted mode	15	0.004905	2.19422	1.382707	3.482013	0.455743	0.28719	0.723219
BC	NEU1	MR Egger	15	0.875428	0.992921	0.910112	1.083265	1.007129	0.923135	1.098766
		Weighted median	15	0.039308	0.960979	0.925283	0.998052	1.040605	1.001952	1.08075
		Inverse variance weighted	15	0.003636	0.95672	0.928612	0.985679	1.045238	1.014529	1.076877
		Simple mode	15	0.104573	0.949019	0.894565	1.006787	1.05372	0.993259	1.117862
		Weighted mode	15	0.160032	0.955897	0.900607	1.014582	1.046137	0.985627	1.110362

Table 3: Results from Egger's, simple mode, weighted mode, and MR-PRESSO.

Outcome	Target	method	nsnp	pval	or	or_lci95	or_uci95	orDrug	or_lci95Drug	or_uci95Drug
CRC	NEU1	MR Egger	11	0.383607	1.086325	0.909927	1.296919	0.920535	0.771058	1.098989
		Weighted median	11	0.309362	1.056332	0.950412	1.174056	0.946672	0.851748	1.052176
		Inverse variance weighted	11	0.724773	1.014879	0.934775	1.101848	0.985339	0.907566	1.069777
		Simple mode	11	0.632647	1.043746	0.88038	1.237428	0.958087	0.808128	1.135873
		Weighted mode	11	0.542357	1.047048	0.907655	1.207849	0.955066	0.827918	1.10174
LC	NEU1	MR Egger	15	0.227233	1.125419	0.937476	1.35104	0.888558	0.74017	1.066693
		Weighted median	15	0.055564	1.079873	0.998173	1.168259	0.926035	0.855974	1.00183
		Inverse variance weighted	15	0.00327	1.116316	1.03739	1.201247	0.895804	0.832468	0.963958
		Simple mode	15	0.035348	1.280733	1.039982	1.577216	0.780803	0.634028	0.961555
		Weighted mode	15	0.991042	0.999114	0.858223	1.163135	1.000887	0.859745	1.165199
GC	NEU1	MR Egger	15	0.00161	1.48297	1.220594	1.801746	0.674322	0.555017	0.819273
		Weighted median	15	5.99E-21	1.449839	1.341676	1.566723	0.689732	0.638275	0.745337
		Inverse variance weighted	15	8.06E-14	1.352029	1.24915	1.463382	0.739629	0.683349	0.800545
		Simple mode	15	3.05E-05	1.521375	1.32764	1.74338	0.6573	0.573599	0.753216
		Weighted mode	15	2.42E-05	1.513695	1.327007	1.726648	0.660635	0.579157	0.753575
PC	NEU1	MR Egger	15	0.781137	1.036675	0.808272	1.329621	0.964622	0.752094	1.237208
		Weighted median	15	0.756845	0.978439	0.852337	1.123199	1.022036	0.890314	1.173246

		Inverse variance weighted	15	0.433074	1.042843	0.939006	1.158164	0.958917	0.863436	1.064956
		Simple mode	15	0.592284	0.933299	0.729134	1.194632	1.071468	0.837078	1.37149
		Weighted mode	15	0.585263	0.935637	0.740848	1.181642	1.06879	0.84628	1.349805
EC	NEU1	MR Egger	15	0.910818	0.988146	8.05E-01	1.212548	1.011996	0.824709	1.241815
		Weighted median	15	0.137471	0.918478	8.21E-01	1.027552	1.088757	0.973186	1.218052
		Inverse variance weighted	15	0.464048	0.968781	8.90E-01	1.054624	1.032225	0.948205	1.123689
		Simple mode	15	0.233224	0.885746	7.32E-01	1.072002	1.128992	0.932834	1.366399
		Weighted mode	15	0.211024	0.893524	7.55E-01	1.057343	1.119164	0.945766	1.324351
CC	NEU1	MR Egger	15	0.033338	1.760229	1.10E+00	2.804421	0.568108	0.35658	0.905118
		Weighted median	15	1.03E-05	1.470771	1.239052	1.745826	0.679915	0.572795	0.807069
		Inverse variance weighted	15	1.38E-04	1.455259	1.199914	1.764942	0.687163	0.566591	0.833393
		Simple mode	15	0.002329	1.954464	1.371805	2.7846	0.511649	0.359118	0.728966
		Weighted mode	15	0.009181	1.599509	1.179223	2.169588	0.625192	0.460917	0.848016
BC	NEU1	MR Egger	15	0.108537	0.945691	0.887496	1.007703	1.057428	0.992356	1.126766
		Weighted median	15	0.122931	0.975477	0.945183	1.006741	1.02514	0.993304	1.057996
		Inverse variance weighted	15	0.632831	0.993031	0.964946	1.021934	1.007018	0.978537	1.036328
		Simple mode	15	0.193074	0.960642	0.90691	1.017557	1.040971	0.982746	1.102646
		Weighted mode	15	0.185074	0.964128	0.915855	1.014946	1.037206	0.985274	1.091876

Table 4: Results were obtained in a repeat analysis using another GWAS dataset.

Out-come	Target	egger_ intercept	se	pval	Q	Q_ df	Q_pval
CRC	NEU1	0.017548	0.051688	0.745798	5.474797	6	0.484508
					5.59006	7	0.588344
LC	NEU1	-0.05592	0.037645	0.168246	9.66141	10	0.470684
					11.86805	11	0.373643
GC	NEU1	-0.03663	0.054346	0.512062	54.35551	13	5.24E-07
					56.25544	14	5.26E-07
PC	NEU1	0.000794	0.055971	0.988894	9.105273	13	0.764947
					9.105475	14	0.824235
EC	NEU1	0.034956	0.066466	0.607795	26.66852	13	0.053807
					27.23595	14	0.057938
CC	NEU1	-0.05007	0.129068	0.705438	17.58507	11	0.091721
					17.82571	12	0.121086
BC	NEU1	-0.00979	0.010987	0.389325	17.36675	13	0.183076
					18.42636	14	0.188046

Table 5: The results of sensitivity analyses indicated no heterogeneity and horizontal pleiotropy in all other outcomes ($p > 0.05$).

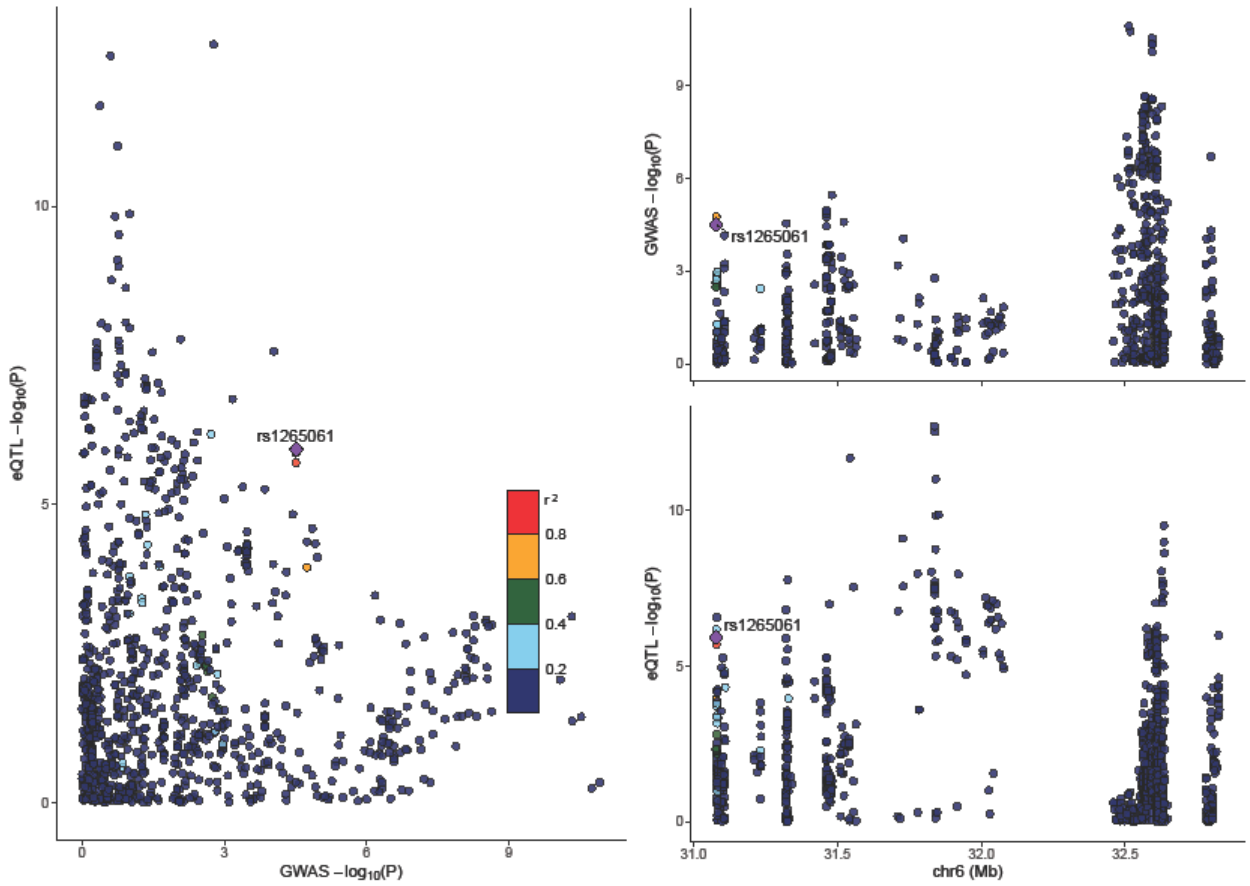
	RSSobs	P value
LC	14.57079	0.409
BC	21.0186	0.195
CC	21.98918	0.125
CRC	7.342303	0.589
EC	30.68657	0.017
PC	10.43617	0.822
GC	0.004564	0.645

Table 6: The MR-PRESSO global test did not detect potential horizontal pleiotropy.

Out-come	Tar-get	egger_ intercept	se	pval	Q	Q_ df	Q_pval
CRC	NEU1	-0.01875	0.022068	0.417621	4.116792	9	0.903559
					4.838461	10	0.901704
LC	NEU1	-0.00202	0.028113	0.94383	24.04698	13	0.050701
					24.05652	14	0.045107
GC	NEU1	-0.03663	0.054346	0.512062	39.78387	13	1.50E-04
					41.37351	14	1.55E-04
PC	NEU1	0.000794	0.055971	0.988894	9.105273	13	0.764947
					9.105475	14	0.824235
EC	NEU1	-0.01878	0.026061	0.48384	9.45304	13	0.737932
					9.496439	14	0.797996
CC	NEU1	-0.08864	0.084945	0.315712	31.08048	13	0.063281
					33.68406	14	0.052293
BC	NEU1	0.014114	0.008473	0.119662	26.53494	13	0.714397
					32.1986	14	0.053754

Table 7: GWAS related to rheumatoid arthritis was used to reselect NEU1 instrumental variables, and repeating the aforementioned approach indicates stable results can be obtained.

Supplementary Figure



Supplementary Figure: To verify the impact of each SNP on the overall causal estimates, we performed a leave-one-out analysis.

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