A novel mutation panel for predicting etoposide resistance in small-cell lung cancer

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Purpose: Platinum-based chemotherapy, consisting of etoposide and cisplatin (EP), has been the cornerstone of therapy for extensive-stage small-cell lung cancer (ES-SCLC) for decades. Despite the marked initial sensitivity of SCLC to chemotherapy, EP regimens cannot avoid the emergence of drug resistance in clinical practice. With the rise of new chemotherapy regimens in recent years and the primary resistance or insensitivity of ES-SCLC to EP regimens, it is desirable to be able to identify patients with resistant or insensitive ES-SCLC.

Methods: The sequencing and drug sensitivity data of SCLC cell lines were provided by The Genomics of Drug Sensitivity in Cancer Project (GDSC). The data regarding sensitivity to etoposide of 54 SCLC cell lines were analyzed, and etoposide-sensitive cell lines and etoposide-resistant cell lines were differentiated according to the IC50 values defined by the GDSC. ROC curve analysis was performed on all mutations and combinations of mutations to select the optimal panel to predict resistance to etoposide.

Results: ROC analysis of etoposide resistance revealed that the most significant single gene mutation indicating resistance to etoposide was CSMD3, and the accuracy of predicting resistance to etoposide proved to be the highest when there was any mutation in CSMD3/PCLO/RYRI/EPB41L3, area under the curve =0.804 (95% confidence interval: 0.679–0.930, P<0.001).

Conclusion: This study found that a panel with four genes (CSMD3, EPB41L3, PCLO, and RYRI) can accurately predict sensitivity to etoposide. These findings provide new insights into the overall treatment for patients with ES-SCLC that is resistant or insensitive to etoposide.

Keywords: small-cell lung carcinoma, etoposide, EP regimens, IP regimens, gene mutation

Introduction

In recent years, humans have made significant progress in the early detection, early diagnosis, early treatment, and even prevention of cancer. However, lung cancer is the most commonly diagnosed cancer (11.6%) and the leading cause of cancer-related death (18.4%) worldwide.1 Currently, there are approximately 2.1 million lung cancer patients worldwide.1 Approximately 12–15% of new lung cancer patients are diagnosed with small-cell lung cancer (SCLC).2,3 According to the latest National Comprehensive Cancer Network (NCCN) Guidelines, an estimated 29,654 new cases of SCLC occurred in the United States in 2017.4,5 Studies have shown that the incidence of SCLC is attributable to cigarette smoking, and the smoking pack-years increases, so does the risk of SCLC. Ninety percent of patients with SCLC have been or are currently smokers, and smoking duration is positively associated with an increased risk of SCLC.6,7 In addition, SCLC is characterized by a high growth fraction, a high degree of malignancy, and the early development of
The 5-year survival rate in patients with SCLC is only 6.6%. Currently, SCLC is divided into limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC). Unfortunately, the 5-year survival rates are only 1.6% and 12.1% for patients with ES-SCLC (1/3) and ES-SCLC (2/3), respectively. In recent years, the chemotherapy for ES-SCLC has mainly been irinotecan, cisplatin (IP) and EP regimens. Despite the substantial initial sensitivity of SCLC to chemotherapy in the early stages of treatment, more than 90% of patients eventually develop clinical drug resistance and die as a result of relapse. At present, there is a great deal of controversy about the therapeutic effect and safety tolerance of IP and EP in the treatment of ES-SCLC.

In 2002, a randomized, multicenter, phase III trial (J9511) performed in Japan reported that patients with ES-SCLC who were treated with IP experienced a median survival of 12.8 months compared with 9.4 months for patients treated with EP ($P=0.002$). In addition, the 1-year survival rates were 58.4% vs 37.7% and the median progression-free survival (PFS) rates were 12.8 months vs 9.4 months in the IP and EP groups, respectively. Furthermore, Hermes et al studied 220 patients with ES-SCLC, and the results showed that the median overall survival (OS) was slightly higher in those receiving IP than in those receiving EP (8.5 months vs 7.1 months, $P=0.04$). However, it is surprising that there were no significant differences in the efficacy and survival of the IP and EP groups in 4 subsequent phase III trials. In a cohort study from Korea, the median OS and median PFS of patients with ES-SCLC treated with IP were 10.9 months and 6.5 months, respectively, whereas the median OS and PFS in the EP arm were 10.3 months ($P=0.120$) and 5.8 months ($P=0.115$), respectively. Similarly, no significant differences were observed in the 1- and 2-year survival rates in the IP versus EP groups. In the subgroup analysis, males, patients <65 years old and patients with Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1 were treated with IP or EP, and the two groups had significant therapeutic differences.

Currently, 4 to 6 cycles EP is the standard therapy widely used for a majority of SCLC in the clinic, with an ORR of 50%-80%. However, the median OS of patients with ES-SCLC is only 9 months, with only 2% of patients surviving after 5 years. Although SCLC usually responds well to chemotherapy regimens in the early stages of treatment, subsequent clinical drug resistance and disease recurrence occur in more than 90% of patients. This may be due to the existence of cancer stem cells that are relatively resistant to cytotoxic therapy. Chemotherapy cannot destroy residual tumor cells, leading to a high recurrence rate and a high drug resistance rate in SCLC. Primary resistance or acquired resistance to chemotherapy is a major factor in the poor prognosis of patients with lung cancer. In the drug sensitivity data from GDSC, we found that the IC50 of etoposide in the 54 SCLC cell lines ranged from 0.242 μM to 319 μM, and the drug resistance cut-off value provided by the website was 16 μM. In total, 65% of patients have SCLC that is sensitive to etoposide, which is close to the response rate for etoposide. Therefore, if we are able to select patients with ES-SCLC that is not sensitive to etoposide before treating them with standard chemotherapy, we could choose a different chemotherapy regimen to treat these patients, hopefully improving survival outcomes in those ES-SCLC patients. Survival time was significantly improved with the new chemotherapy compared with EP. However, there is currently no clinically relevant prediction factor and screening for appropriate means of insensitivity to etoposide.

To date, a growing number of studies have shown that the emergence of primary or acquired platinum and Topoisomerase Inhibitors resistance in EP is associated with certain gene expression changes or/and gene mutations. Chiu et al found that FBXL7 is a biomarker of poor prognosis in patients with ovarian cancer. A high expression level of FBXL7 is positively associated with a low survival rate in ovarian cancer patients, and the FBXL7 mRNA level and ovarian cancer cell line paclitaxel (PTX) IC50 values were positively correlated, leading to the speculation that the upregulation of FBXL7 expression results in resistant ovarian cancer cell lines. In addition, Chiu et al detected the transcriptional level of the shared gene in HCC38 (PTX-sensitive) and MDA-MB436 (PTX-resistant) TNBC cells posttreatment with paclitaxel. They found that the downregulation of miR-1180 may regulate OTUD7B, ultimately negatively regulating the NF-kB-Lin28 axis. This in turn triggers Let-7...
microRNA-mediated caspase-3 downregulation, ultimately leading to resistance to PTX. Based on these findings, the sensitivity and drug resistance of tumor cells to chemotherapy can be predicted by gene expression levels. Thus, patients with ES-SCLC that is sensitive or insensitive to chemotherapy can be further distinguished. We hope that the sensitivity of ES-SCLC to etoposide can be predicted by gene mutation panels, allowing the selection of patients with ES-SCLC that is insensitive to etoposide before standard chemotherapy is administered and the development of personalized, precise chemotherapy to extend patients’ OS and improve their quality of life (QOL).

To this end, we analyzed the sequencing and drug sensitivity data for a SCLC cell line through the GDSC database to determine whether mutations can predict the primary resistance to etoposide and try to explain the potential underlying mechanism to provide first-line treatment recommendations for patients with ES-SCLC.

Methods

Drug response, gene expression and mutation data
The natural logarithm half maximal inhibitory concentration (IC50) of all selected erlotinib-related cell lines were obtained from the GDSC (https://www.cancerrxgene.org/). Robust Multichip Average (RMA) normalized expression data from the Affymetrix Human Genome U219 array and gene mutation information found in cell lines by Illumina HiSeq 2000 whole-exome sequencing (WES) were downloaded from the GDSC.

Screening of mutated resistance genes
There were 54 SCLC cell lines in the GDSC with drug sensitivity data for etoposide. The GDSC site defined etoposide-resistant cell lines as those with IC50 values ≥16 μM and etoposide-sensitive cell lines as those with IC50 values <16 μM. ROC curve analysis was performed for all mutations, and the cell lines with areas under the curve (AUCs) >0.5 were selected and randomly combined; then, resistance to etoposide was predicted by the combined mutation panels. The Youden Index values obtained by various combined ROC analyses were sorted to select the best combination.

Statistical analysis
The IC50 distribution for etoposide in various cell lines was obtained with the GDSC web tool. ROC analysis and mapping were performed with SPSS 21.0 (IBM SPSS Statistics, IBM Corporation); mutation and gene expression data were analyzed and mapped with the maftools and limma packages in R. In the differential analysis of the gene expression profiles, \( P<0.05 \) and \( FC>1.5 \) or \( FC<2/3 \) were considered to indicate significant differences. The survival analysis was with the log-rank test after the Kaplan-Meier analysis to investigate the predictive ability of a mutation panel with regard to survival. Gene Ontology (GO) annotation analysis and KEGG pathway enrichment analysis of the differentially expressed genes (DEGs) in this study were performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID) (https://david.ncifcrf.gov/).

Results
The sensitivity of cancer cell lines to drugs is mainly expressed as the IC50 value, which refers to the concentration of drug that kills half of the tumor cells in vitro. Because the drug concentration is diluted to 1/10 or 1/100, we used lnIC50 values to distinguish between resistant or sensitive cell lines. Based on the GDCS 7.0 database (updated on March 20, 2018), there are 64 SCLC cell lines, but only 54 of them have etoposide susceptibility data (drug sensitivity data), WES mutation data and RNA Seq data.

Using the GDSC website tools, we obtained the IC50 distribution for etoposide by tissue type (Figure 1A). We found that most of the tumors are sensitive to etoposide, and the IC50 values of most cell SCLC lines indicate that they are sensitive to etoposide. By analyzing the IC50 values of the 54 SCLC cell lines shown in Figure 1B, we found that there are 35 cell lines that are sensitive to etoposide, accounting for 64.8% of the total, and their median and mean IC50 values were 2.06 μM (range: 0.242–15.2 μM) and 4.02±4.07 μM, respectively. In total, 19 strains were resistant to etoposide, accounting for 35.2% of the total, and their median and mean IC50 values were 50.0 μM (range: 16.4–319.0 μM) and 71.9 ±71.8 μM, respectively. The raw data for the IC50 values of all cell lines with regard to etoposide can be found in Table S1.

After sorting the IC50 values for etoposide, we found that in the mutation landscape of the 54 SCLC cell lines (Figure 2), the genes with the highest mutation frequencies were \( TP53 \) (91%), \( TTN \) (78%) and \( Rb1 \) (70%). Among them, \( TP53 \) and \( TTN \) mutations were mainly missense mutations, while the \( Rb1 \) mutations were mainly nonsense and splice mutations.
We performed an ROC analysis of to predict etoposide resistance using all mutated genes (see Table S2). From the ROC curves, we found that the most significant single gene mutation associated with resistance to etoposide was CSMD3, with an AUC of 0.697 (P=0.016) (Table 1). By experimenting with different combinations, we found that when any mutations occurred in CSMD3/PCLO/RYR1/EPB41L3, the accuracy of predicting resistance to etoposide was the highest (AUC=0.804, 95% CI: 0.679–0.930, P<0.001) (Table 1). The ROC curve results of the panel composed of CSMD3/PCLO/RYR1/EPB41L3 and the individual genes are shown in Figure 3A.

We performed a log-rank test with the Kaplan–Meier plots according to mutations and clinical follow-up data in 110 SCLCs published by George et al. In addition, we found a significantly lower average survival time in patients with CLC with no mutations in all four genes (35.6±5.3 months vs 76.7±12.1 months, P=0.040) (Figure 3B). By analyzing significantly enriched KEGG pathways of DEGs, we found that there was a significant association between both CSMD3 and RYR1 mutations and MAPK signaling pathway (P=0.015 and P=0.023, respectively) (Table 2).

Discussion

EP has been the most common therapy for ES-SCLC for decades. As a standard treatment, it can inhibit tumor proliferation, relieve clinical symptoms, and achieve ideal results. We found that 19 (35.2%) of the 54 SCLC cell lines were insensitive to etoposide according to the data from the GDSC. Currently, the clinically accepted ORR of EP is 50–80%. Based on the above findings, the majority of patients with SCLC do not receive survival benefits from EP, indicating that screening for patients with primary resistance to etoposide is necessary. Therefore, this study further analyzed the mutation, gene expression and etoposide sensitivity data of 54 ES-SCLC cell lines obtained from the GDSC. We identified four genes, namely, CSMD3, EPB41L3, PCLO, and RYR1; mutations in these genes predict resistance to etoposide. The predictive sensitivity this four-gene panel for resistance to etoposide is as high as 85%, with 77.8% accuracy when screening for patients with primary etoposide resistance. In addition, the ROC showed an AUC of 0.804 (95% CI 0.679–0.930), and the model was considered to have a high degree of confidence.

Recently, a small phase III trial performed in Japan compared the efficacy of IP and EP in patients with ES-SCLC. The trial results showed a higher median OS (12.8 months vs 9.4 months), 1-year survival rate (58.4% vs 37.7%) and 2-year survival rate (19.5% vs 5.2%) after IP than after EP. In addition, Hermes et al studied 220 patients with ES-SCLC, and the results showed a longer median OS resulting from the IP regimen compared with the EP regimen (8.5 months vs 7.1 months, P=0.04).

We analyzed the data and found that mutations in both CSMD3 and RYR1 can cause the activation of the downstream MAPK signaling pathway (Figure 4). In addition, Liu et al found that etoposide activates the MAPK/ERK signaling pathway, inhibits p53 expression and enhances c-Myc expression.
Figure 2 Mutation landscape of 54 SCLC cell lines.
Abbreviation: SCLC, small-cell lung cancer.

Table 1 Receiver operator characteristic curve analysis for four-gene panel and four genes separately to etoposide resistance status in small-cell lung cancer cell lines

| Gene       | Area under curve | 95% confidence interval | Sensitivity | Specificity | Youden index | P-value |
|------------|------------------|-------------------------|-------------|-------------|--------------|---------|
| CSMD3      | 0.697            | 0.546–0.848             | 0.600       | 0.794       | 0.394        | 0.016   |
| PCLO       | 0.591            | 0.429–0.754             | 0.300       | 0.882       | 0.182        | 0.267   |
| RYR1       | 0.631            | 0.469–0.792             | 0.350       | 0.912       | 0.262        | 0.111   |
| EPB41L3    | 0.610            | 0.447–0.774             | 0.250       | 0.971       | 0.221        | 0.179   |
| Panel      | 0.804            | 0.679–0.930             | 0.850       | 0.706       | 0.556        | <0.001  |
**Table 2** Significantly enriched KEGG pathways of DEGs

| Mutation | Term                                      | Count | P-value |
|----------|-------------------------------------------|-------|---------|
| **CSMD3**| hsa04142: Lysosome                        | 8     | 0.002   |
|          | hsa04010: MAPK signaling pathway          | 10    | 0.015   |
|          | hsa05230: Central carbon metabolism in cancer | 5     | 0.016   |
|          | hsa04610: Complement and coagulation cascades  | 5     | 0.021   |
|          | hsa01130: Biosynthesis of antibiotics      | 8     | 0.044   |
| **EPB41L3**| hsa01200: Carbon metabolism               | 8     | 0.003   |
|          | hsa01130: Biosynthesis of antibiotics      | 11    | 0.004   |
|          | hsa01100: Metabolic pathways              | 33    | 0.010   |
|          | hsa00020: Citrate cycle (TCA cycle)       | 4     | 0.015   |
|          | hsa04730: Long-term depression            | 5     | 0.020   |
|          | hsa04130: SNARE interactions in vesicular transport | 4     | 0.021   |
|          | hsa04720: Long-term potentiation          | 5     | 0.028   |
|          | hsa03022: Basal transcription factors     | 4     | 0.044   |
|          | hsa04726: Serotonergic synapse            | 6     | 0.045   |
| **PCLO** | hsa0410: Regulation of actin cytoskeleton | 11    | <0.001  |
|          | hsa04151: PI3K-Akt signaling pathway      | 12    | 0.005   |
|          | hsa04510: Focal adhesion                  | 9     | 0.005   |
|          | hsa04512: ECM-receptor interaction        | 6     | 0.005   |
|          | hsa03320: PPAR signaling pathway          | 5     | 0.011   |
|          | hsa05205: Proteoglycans in cancer         | 8     | 0.016   |
|          | hsa05160: Hepatitis C                     | 6     | 0.031   |
|          | hsa05231: Choline metabolism in cancer    | 5     | 0.044   |
| **RYR1** | hsa04810: Starch and sucrose metabolism   | 3     | 0.019   |
|          | hsa04010: MAPK signaling pathway          | 6     | 0.023   |
|          | hsa04960: Aldosterone-regulated sodium reabsorption | 3     | 0.026   |
|          | hsa00280: Valine, leucine and isoleucine degradation | 3     | 0.037   |
|          | hsa01130: Biosynthesis of antibiotics      | 5     | 0.048   |

**Abbreviations:** MAPK, mitogen activated kinase-like protein; TCA, tricarboxylic acid; SNARE, small NF90 (ILF3) associated RNA E; PI3K-Akt: phosphoinositide-3-kinase/serine threonine kinase; ECM, extracellular matrix; PPAR, peroxisome proliferators-activated receptors.
to decrease the sensitivity of gastric cancer cells to chemotherapy in. Therefore, we hypothesized that mutations in the CSMD3 and RYR1 genes may cause a significant resistance to etoposide in ES-SCLC via the downstream MAPK signaling pathway. It is well known that etoposide induces DNA double-strand breakage (DSB) and triggers the DNA damage response by activating the ataxia telangiectasia-mutated gene (ATM). DNA repair is a process of energy dissipation, and ATP-dependent chromatin remodeling complexes participate in DSB repair. In aerobic conditions, tumor cells preferentially perform glycolysis rather than providing energy for cell growth through the more efficient oxidative phosphorylation pathway and are therefore characterized by high glucose uptake, glycolysis activity levels and lactic acid content in the metabolites. Glycolysis consumes more glucose but produces less ATP. The PI3K/AKT signaling pathway promotes aerobic glycolysis by upregulating cell surface glucose transporters and glycolytic enzymes in tumor cells. Surprisingly, we found that the mutation of the EPB41L3 gene caused increased activity of the glucose metabolism pathway in tumor cells. Therefore, we speculate that mutations in EPB41L3 may reduce sensitivity to etoposide through DNA repair in tumor cells. In addition, AKT is involved in the repair of DNA damage caused by genotoxicity, mainly by the action of DNA-dependent protein kinase (DNA-PK), the kinase ATM/ATM and nonhomologous end joining (NHEJ) to repair DSB. Makinoshima et al found that PI3K/AKT/mTOR signaling inhibitors can effectively inhibit the expression of GLUT1 on the cell membrane. They used RNAi to interfere with the expression of GLUT1, ultimately reducing the aerobic glycolysis process and cell proliferation rate. Furthermore, our results suggest that PCLO mutations cause activation of the PI3K-Akt pathway, so we hypothesized that PCLO mutations may enhance glucose metabolism by activating the PI3K/Akt pathway, thereby enhance the ability of the tumor cell to repair DNA.
## Table 3 Completed/ongoing clinical trials of alternative treatment of etoposide in SCLC patients

| Drug name               | Clinical phase | Comments | NCT No.                        | Treatment                                    | Pathway/target                                                   |
|-------------------------|----------------|----------|--------------------------------|----------------------------------------------|------------------------------------------------------------------|
| Irinotecan              | 3              |          | NCT00168896                    | Carboplatin+Irinotecan                       | Topoisomerase 1                                                  |
|                         | 2              |          | NCT01441349                    |                                              |                                                                  |
|                         | 2              |          | NCT00695292                    |                                              |                                                                  |
|                         | 1              |          | NCT00045604                    | Carboplatin+Irinotecan+Imatinib              |                                                                  |
|                         | 1              |          | NCT0052494                     |                                              |                                                                  |
|                         | 2              |          | NCT0248482                     |                                              |                                                                  |
|                         | 2              |          | NCT00597612                    | Carboplatin+Irinotecan                       |                                                                  |
|                         | 1              |          | NCT01441349                    |                                              |                                                                  |
|                         | 2              |          | NCT00695292                    |                                              |                                                                  |
|                         | 2              |          | NCT01441349                    | Carboplatin+Sunitinib+Irinotecan             |                                                                  |
|                         | 2              |          | NCT00695292                    |                                              |                                                                  |
|                         | 1              |          | NCT00695292                    |                                              |                                                                  |
| Bevacizumab             | 2              |          | NCT00118235                    | Cisplatin+Irinotecan+Bevacizumab             | VEGF                                                            |
| Pemetrexed              | 2              |          | NCT00051506                    | Carboplatin+Pemetrexed                       | TS, DHFR,GARFT                                                   |
|                         | 2              |          | NCT00494026                    |                                              |                                                                  |
|                         | 2              |          | NCT00051506                    | Carboplatin+Pemetrexed                       |                                                                  |
|                         | 2              |          | NCT00475657                    |                                              |                                                                  |
| Dimethylxanthenone Acetic Acid (DMXAA) | 2          |          | NCT01057342                    | Carboplatin+Dimethylxanthenone Acetic Acid (DMXAA)+Paclitaxel | DT-diaphorase                                                   |
| Paclitaxel              | 2              |          | NCT01057342                    | Carboplatin+Dimethylxanthenone Acetic Acid (DMXAA)+Paclitaxel |                                                                  |
|                         | 2              |          | NCT00454324                    | Carboplatin+Paclitaxel                       | Mitosis;Microtubule stabiliser                                  |
|                         | 1              |          | NCT02069158                    | Carboplatin+Paclitaxel+PF-05212384           |                                                                  |
| PF-05212384             | 1              |          | NCT02069158                    | Carboplatin+Paclitaxel+PF-05212384           | PI3K/mTOR, PI3Kα, PI3Kγ,mTOR                                     |
| Gemcitabine             | 2              |          | NCT02722369                    | Carboplatin+Gemcitabine                     | DNA replication;Pyrimidine antimetabolite                        |
| Pegfilgrastim           | 2              |          | NCT01076504                    | Carboplatin+Pegfilgrastim+Amrubicin          | Granulocyte colony-stimulating factor receptor; Neutrophil elastase |
| Amrubicin               | 2              |          | NCT01076504                    | Carboplatin+Pegfilgrastim+Amrubicin          | Topoisomerase 2                                                  |
| Sunitinib               | 2              |          | NCT00695292                    | Carboplatin+Sunitinib+Irinotecan            | RTK signaling;PDGFR, KIT, VEGFR, FLT3, RET, CSFIR               |

(Continued)
### Table 3 (Continued)

| Drug name | Clinical phase | Comments | NCT No. | Treatment | Pathway/target |
|-----------|----------------|----------|---------|-----------|----------------|
| Topotecan | 2              |          | NCT00316186 | Carboplatin+Topotecan | DNA topoisomerases |
|           | 3              |          | NCT00043927 | Topotecan |                |
|           | 2              |          | NCT00028925 | Carboplatin+Topotecan+G-CSF |                |
| Belotecan | 3              |          | NCT00826644 | Carboplatin+Belotecan | HDAC |
| Imatinib  | 2              | c-kit positive | NCT00248482 | Cisplatin+Imatinib | RTK signaling: ABL, KIT, PDGFR |
|           | 1              |          | NCT00045604 | Cisplatin+Irinotecan+Imatinib |                |
|           | 1              | c-kit positive | NCT00052494 |                |                |
| Simvastatin | 2             |          | NCT01441349 | Cisplatin+Simvastatin+Irinotecan | HMG-CoA Reductase |
|           | 2              |          | NCT00452634 |                |                |
| Krestin    | 2              |          | NCT01441349 | Carboplatin+Irinotecan+Simvastatin | Apoptosis; p21 (WAF/Cip1) |
| Sagopilone | 2              |          | NCT00546130 | Cisplatin+Krestin+Irinotecan | Microtubule stabiliser |
|           | 2              |          | NCT00359359 | Cisplatin+Sagopilone |                |

**Notes:** TS, Thymidylate Synthetase; DHFR, Dihydrofolate Reductase; GARFT, Formylglycinamide Ribotide Amidotransferase; PI3K/mTOR, Phosphoinosomde-3-Kinase/The Mammalian Target of Rapamycin; HMG-CoA, Hydroxy Methylglutaryl Coenzyme A Reductase; RTK, Receptor Tyrosine Kinase; PDGFR, Platelet-Derived Growth Factor Receptors; Kit, KIT proto-oncogene, Receptor Tyrosine Kinase; VEGFR, Vascular Endothelial Growth Factor Receptor; FLT3, Fms Related Tyrosine Kinase; RET, Ret Proto-Oncogene; CSF1R, Colony Stimulating Factor 1 Receptor; HDAC, Histone Deacetylase; ABL, Abl Tyrosine Kinase; p21 (WAF/Cip1), Cyclin Dependent Kinase Inhibitor; G-CSF, granulocyte colony stimulating factor; SCLC, small-cell lung cancer.
Identifying outpatients with ES-SCLC that is not sensitive to etoposide and treating them with another combination therapy are important steps in improving the survival of patients with SCLC. Screening for the sensitivity to etoposide in patients with SCLC who are receiving chemotherapy for the first time allows clinicians to use a different combination chemotherapy regimen (Table 3) in these patients to avoid treatment failure due to primary resistance to etoposide. Currently, alternative treatment options that are commonly used in clinical practice include IP protocols, platinum-based drugs plus paclitaxel, and IP plus sunitinib. A phase II clinical trial (NCT00454324) on the use of a platinum-based compound plus paclitaxel in patients with ES-SCLC has shown good efficacy.44 In a phase II clinical trial (NCT00695292),45 sunitinib combined with IP for patients with ES-SCLC showed potential clinical efficacy and safety, with an ORR of 59%, a one-year survival rate of 54% and a median PFS of 7.6 months. In recent years, combinations of various chemotherapy regimens have been shown to provide excellent survival advantages in patients with ES-SCLC. It may be possible to classify patients by adding inclusion criteria and then use a more specific new chemotherapy regimen as a clinical treatment to achieve individualized and precise treatment of ES-SCLC patients, overcoming the treatment bottleneck for patients with ES-SCLC that is resistant to EP and ultimately prolonging their survival time and improving their QOL.

There were some limitations in this study. First, the most suitable alternative drug at present is irinotecan. GDSC does not provide data regarding the sensitivity to irinotecan, and the sensitivity of etoposide-resistant ES-SCLC to irinotecan is still unclear. Second, currently, there are no suitable large-sample clinical datasets that directly support our conclusions, and relevant clinical research needs to be further conducted to verify our hypothesis; moreover, we have initiated a clinical trial(NCT03162705) and hope this ongoing clinical trial could provide more direct evidence onm. Third, the accuracy of the model prediction is inadequate, and it may be necessary to expand the model to optimize it.

Conclusion
In conclusion, we analyzed the mutation and gene expression data from the GDSC of 54 ES-SCLC cell lines with regard to etoposide susceptibility and found that the panel including CSMD3, EPB41L3, PCLO, and RYR1 can likely predict the sensitivity of ES-SCLC to etoposide and, therefore, the clinical survival of patients with SCLC.

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Disclosure
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### Supplementary materials

#### Table S1 Etoposide IC50 values of 54 SCLC cell lines

| Cell line | IC50 (μM) | AUC  |
|-----------|-----------|------|
| LU-135    | 0.242     | 0.262|
| SBC-3     | 0.276     | 0.292|
| SBC-5     | 0.406     | 0.344|
| LU-134-A  | 0.407     | 0.363|
| NCI-H526  | 0.515     | 0.393|
| NCI-H1048 | 0.563     | 0.405|
| DMS-273   | 0.595     | 0.42 |
| NCI-H211  | 0.618     | 0.423|
| NCI-H187  | 0.758     | 0.458|
| NCI-H748  | 0.838     | 0.475|
| NCI-H209  | 0.97      | 0.495|
| IST-SL2   | 0.978     | 0.496|
| SW1271    | 1.29      | 0.537|
| COR-L279  | 1.39      | 0.555|
| NCI-H1694 | 1.52      | 0.566|
| LB647-SCLC| 1.77      | 0.585|
| COLO-668  | 2.01      | 0.61 |
| NCI-H1876 | 2.06      | 0.614|
| NCI-H1304 | 2.34      | 0.629|
| NCI-H1417 | 3.26      | 0.669|
| MS-1      | 3.62      | 0.709|
| NCI-H64   | 3.93      | 0.742|
| NCI-H2081 | 4.28      | 0.715|
| LU-139    | 4.7       | 0.71 |
| NCI-H69   | 5.35      | 0.74 |
| NCI-H1963 | 6.37      | 0.795|
| NCI-H510A | 6.78      | 0.795|
| NCI-H847  | 7.38      | 0.827|
| NCI-H2141 | 7.39      | 0.797|
| NCI-H2196 | 8.08      | 0.798|
| IST-SL1   | 10.5      | 0.83 |
| LU-165    | 10.9      | 0.821|
| NCI-H1688 | 11        | 0.825|
| NCI-H2029 | 12.3      | 0.867|
| NCI-H841  | 15.2      | 0.871|
| CPC-N     | 16.4      | 0.865|
| COR-L95   | 17.5      | 0.86 |
| DMS-79    | 21.4      | 0.877|
| COR-L88   | 22        | 0.876|
| NCI-H2171 | 23.8      | 0.933|
| SBC-1     | 33.3      | 0.935|
| NCI-H82   | 36        | 0.942|
| NCI-H1836 | 41.1      | 0.928|
| NCI-H446  | 45.6      | 0.936|
| NCI-H524  | 50        | 0.965|
| SHP-77    | 57.7      | 0.97 |
| NCI-H1092 | 65.2      | 0.96 |
| NCI-H2227 | 69.3      | 0.949|
| DMS-53    | 71.3      | 0.955|

(Continued)
| Test result variable(s) | Area | Standard error* | Asymptotic significance | Asymptotic 95% confidence interval |
|-------------------------|------|----------------|--------------------------|-----------------------------------|
| CSMD3                   | 0.697| 0.077          | 0.016                    | 0.546 0.848                       |
| USP34                   | 0.685| 0.099          | 0.053                    | 0.49 0.879                        |
| MYO1B                   | 0.679| 0.096          | 0.061                    | 0.491 0.867                       |
| ABCA13                  | 0.673| 0.093          | 0.07                     | 0.491 0.855                       |
| DNAH2                   | 0.673| 0.099          | 0.07                     | 0.479 0.866                       |
| LAMA5                   | 0.661| 0.099          | 0.092                    | 0.468 0.854                       |
| SCN4A                   | 0.655| 0.101          | 0.105                    | 0.457 0.853                       |
| ARAP2                   | 0.643| 0.101          | 0.134                    | 0.446 0.84                         |
| CNTRL                   | 0.643| 0.101          | 0.134                    | 0.446 0.84                         |
| ENSG00000250423         | 0.643| 0.101          | 0.134                    | 0.446 0.84                         |
| RYR1                    | 0.631| 0.082          | 0.111                    | 0.469 0.792                       |
| EYS                     | 0.631| 0.096          | 0.17                     | 0.443 0.818                       |
| HSPG2                   | 0.631| 0.1            | 0.17                     | 0.435 0.827                       |
| NLRP5                   | 0.631| 0.1            | 0.17                     | 0.435 0.827                       |
| UNCI13C                 | 0.631| 0.1            | 0.17                     | 0.435 0.827                       |
| DDX12                   | 0.619| 0.1            | 0.212                    | 0.424 0.814                       |
| XIRP2                   | 0.619| 0.096          | 0.212                    | 0.432 0.806                       |
| EPB4I13                 | 0.61 | 0.083          | 0.179                    | 0.447 0.774                       |
| COL3A1                  | 0.607| 0.099          | 0.261                    | 0.413 0.802                       |
| NIPBL                   | 0.607| 0.099          | 0.261                    | 0.413 0.802                       |
| NLRP3                   | 0.607| 0.099          | 0.261                    | 0.413 0.802                       |
| POLQ                    | 0.607| 0.099          | 0.261                    | 0.413 0.802                       |
| GRM5                    | 0.601| 0.101          | 0.289                    | 0.404 0.798                       |
| PKD1L1                  | 0.601| 0.097          | 0.289                    | 0.411 0.792                       |
| REG3G                   | 0.601| 0.101          | 0.289                    | 0.404 0.798                       |
| AHNK                    | 0.595| 0.099          | 0.318                    | 0.402 0.789                       |
| PCLO                    | 0.591| 0.083          | 0.267                    | 0.429 0.754                       |
| ACO27369_8              | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| BRIP1                   | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| COL6A3                  | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| ERBB4                   | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| FAM135B                 | 0.589| 0.097          | 0.349                    | 0.399 0.779                       |
| FBN1                    | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| FREM1                   | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| HFM1                    | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| KDR                     | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| MYH1                    | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| NDST4                   | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| PPP1R9A                 | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| SMARCA4                 | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| THSD7B                  | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| UBQLN3                  | 0.589| 0.1            | 0.349                    | 0.393 0.785                       |
| NAV3                    | 0.583| 0.098          | 0.382                    | 0.391 0.776                       |
| ADAMTS16                | 0.577| 0.099          | 0.417                    | 0.383 0.772                       |
| AKAP13                  | 0.577| 0.099          | 0.417                    | 0.383 0.772                       |
| ALPK2                   | 0.577| 0.099          | 0.417                    | 0.383 0.772                       |
| COL14A1                 | 0.577| 0.099          | 0.417                    | 0.383 0.772                       |
| DPP10                   | 0.577| 0.099          | 0.417                    | 0.383 0.772                       |
| EML5                    | 0.577| 0.099          | 0.417                    | 0.383 0.772                       |
| KIAA1109                | 0.577| 0.099          | 0.417                    | 0.383 0.772                       |

(Continued)
| Test result variable(s) | Area  | Standard error | Asymptotic significance | Asymptotic 95% confidence interval |
|------------------------|-------|----------------|-------------------------|-----------------------------------|
|                        |       |                |                         | Lower bound | Upper bound                    |
| LYST                   | 0.577 | 0.099          | 0.417                   | 0.383       | 0.772                          |
| MYH13                  | 0.577 | 0.099          | 0.417                   | 0.383       | 0.772                          |
| MYH7                   | 0.577 | 0.099          | 0.417                   | 0.383       | 0.772                          |
| PDGFRα                 | 0.577 | 0.099          | 0.417                   | 0.383       | 0.772                          |
| ZEB1                   | 0.577 | 0.099          | 0.417                   | 0.383       | 0.772                          |
| LRRK2                  | 0.571 | 0.098          | 0.454                   | 0.38        | 0.763                          |
| ACAN                   | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| ADAMTS11               | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| ADCY8                  | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| ALMS1                  | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| ANKS1B                 | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| CNTNAP4                | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| FRAS1                  | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| LAMA1                  | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| MORC1                  | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| MUC16                  | 0.565 | 0.092          | 0.492                   | 0.385       | 0.746                          |
| MUC5B                  | 0.565 | 0.097          | 0.492                   | 0.376       | 0.755                          |
| PTPR8                  | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| SIGLEC10               | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| STAB2                  | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| SYNE1                  | 0.565 | 0.097          | 0.492                   | 0.376       | 0.755                          |
| UBR4                   | 0.565 | 0.099          | 0.492                   | 0.372       | 0.759                          |
| DNAH8                  | 0.56  | 0.097          | 0.533                   | 0.368       | 0.751                          |
| RELN                   | 0.56  | 0.097          | 0.533                   | 0.368       | 0.751                          |
| TPS3                   | 0.56  | 0.089          | 0.533                   | 0.385       | 0.734                          |
| WDR72                  | 0.56  | 0.099          | 0.533                   | 0.365       | 0.754                          |
| ZNF831                 | 0.56  | 0.099          | 0.533                   | 0.365       | 0.754                          |
| ADAMTS12               | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| ADG8                   | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| FB2                    | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| GPR112                 | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| ITGAD                  | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| KALRN                  | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| KIF2B                  | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| PKHD1L1                | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| TG                     | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| WDR87                  | 0.554 | 0.098          | 0.574                   | 0.361       | 0.746                          |
| ANKRD11                | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741                          |
| CNTN5                  | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741                          |
| COL12A1                | 0.548 | 0.097          | 0.618                   | 0.357       | 0.738                          |
| COL17A1                | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741                          |
| CPS1                   | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741                          |
| DAPK1                  | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741                          |
| DNAH6                  | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741                          |
| FCGBP                  | 0.548 | 0.097          | 0.618                   | 0.357       | 0.738                          |
| GLI3                   | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741                          |
| GRIN2B                 | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741                          |
| HECL1                  | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741                          |
| HYDIN                  | 0.548 | 0.095          | 0.618                   | 0.361       | 0.735                          |

(Continued)
| Test result variable(s) | Area  | Standard error | Asymptotic significance | Asymptotic 95% confidence interval |
|-------------------------|-------|----------------|-------------------------|-----------------------------------|
|                         |       |                |                         | Lower bound | Upper bound |
| IGSF3                   | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741       |
| KIAA1409                | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741       |
| LINGO2                  | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741       |
| LRRQI                   | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741       |
| MADD                    | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741       |
| MCF2                    | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741       |
| PLXNA4                  | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741       |
| RYR2                    | 0.548 | 0.095          | 0.618                   | 0.361       | 0.735       |
| SORCS3                  | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741       |
| UNC80                   | 0.548 | 0.097          | 0.618                   | 0.357       | 0.738       |
| WDR17                   | 0.548 | 0.099          | 0.618                   | 0.354       | 0.741       |
| CUBN                    | 0.542 | 0.098          | 0.622                   | 0.351       | 0.733       |
| DSCAML1                 | 0.542 | 0.098          | 0.622                   | 0.351       | 0.733       |
| ENSG00000121031         | 0.542 | 0.098          | 0.622                   | 0.351       | 0.733       |
| ENSG00000188219         | 0.542 | 0.098          | 0.622                   | 0.351       | 0.733       |
| FAT3                    | 0.542 | 0.096          | 0.622                   | 0.353       | 0.73        |
| LAMA2                   | 0.542 | 0.098          | 0.622                   | 0.351       | 0.733       |
| SYNE2                   | 0.542 | 0.098          | 0.622                   | 0.351       | 0.733       |
| TAF1L                   | 0.542 | 0.098          | 0.622                   | 0.351       | 0.733       |
| TNN                     | 0.542 | 0.098          | 0.622                   | 0.351       | 0.733       |
| ZNF99                   | 0.542 | 0.098          | 0.622                   | 0.351       | 0.733       |
| ACSM2B                  | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| ASPM                    | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| ATP10D                  | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| BCLAF1                  | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| C12orf35                | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| C6                      | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| CACNA1H                 | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| CDH19                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| COL19A1                 | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| COL24A1                 | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| CREBBP                  | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| DCHS2                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| DNAH17                  | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| DOCK7                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| EP400                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| IGF2R                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| LTBPI                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| MUC17                   | 0.536 | 0.097          | 0.708                   | 0.346       | 0.725       |
| MYH11                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| NOTCH1                  | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| OTOF                    | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| PIK3CG                  | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| POM121L12               | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| POTEC                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| POTEG                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| PTEN                    | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| ROBO4                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |
| SCN1A                   | 0.536 | 0.098          | 0.708                   | 0.344       | 0.727       |

(Continued)
Table S2 (Continued)

| Test result variable(s) | Area  | Standard error | Asymptotic significance | Asymptotic 95% confidence interval |
|-------------------------|-------|----------------|-------------------------|-----------------------------------|
|                         |       |                |                         | Lower bound        | Upper bound        |
|                         |       |                |                         |                     |                    |
| SLC5A10                 | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| SLIT3                   | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| SRCA1                   | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| TRHD1                   | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| TTN                     | 0.536 | 0.093          | 0.708                   | 0.354              | 0.718              |
| VWA3B                   | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| W8SCR17                 | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| WNK3                    | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| ZNF208                  | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| ZNF804B                 | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| ZSCAN20                 | 0.536 | 0.098          | 0.708                   | 0.344              | 0.727              |
| DOCK11                  | 0.53  | 0.097          | 0.755                   | 0.34               | 0.72               |
| PKHD1                   | 0.53  | 0.097          | 0.755                   | 0.34               | 0.72               |
| SPTA1                   | 0.53  | 0.097          | 0.755                   | 0.34               | 0.72               |
| ZFHX4                   | 0.53  | 0.096          | 0.755                   | 0.342              | 0.718              |
| ZNF536                  | 0.53  | 0.097          | 0.755                   | 0.34               | 0.72               |
| ABCA12                  | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| ABCB1                   | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| AC007731.1              | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| ANKRD30B                | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| C20orf26                | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| C7orf58                 | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| CACNA1C                 | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| DMD                     | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| DPP6                    | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| FLG2                    | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| GRM1                    | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| HMCN1                   | 0.524 | 0.096          | 0.803                   | 0.335              | 0.712              |
| MAGEC1                  | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| MDN1                    | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| MGAM                    | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| MIK67                   | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| MUC12                   | 0.524 | 0.096          | 0.803                   | 0.335              | 0.712              |
| MUC2                    | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| NID2                    | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| OR8K1                   | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| PAPPA                   | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| PTPN13                  | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| SAMD9                   | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| SI                      | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| SPHKAP                  | 0.524 | 0.096          | 0.803                   | 0.335              | 0.712              |
| TPO                     | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| USP32                   | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| VCAN                    | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| WRN                     | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| ZEB2                    | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| ZNF479                  | 0.524 | 0.097          | 0.803                   | 0.334              | 0.714              |
| DNAH1I                  | 0.518 | 0.096          | 0.851                   | 0.329              | 0.707              |
| DNAH14                  | 0.518 | 0.096          | 0.851                   | 0.329              | 0.707              |

(Continued)
| Test result variable(s) | Area | Standard error* | Asymptotic significance | Asymptotic 95% confidence interval |
|------------------------|------|-----------------|------------------------|-----------------------------------|
|                        |      |                 |                        | Lower bound                       |
|                        |      |                 |                        | Upper bound                       |
| GABRA5                 | 0.518| 0.097           | 0.851                  | 0.328                             |
| VPS13B                 | 0.518| 0.096           | 0.851                  | 0.329                             |
| ABC31                  | 0.512| 0.096           | 0.901                  | 0.323                             |
| CDC141                 | 0.512| 0.096           | 0.901                  | 0.323                             |
| CDH10                  | 0.512| 0.096           | 0.901                  | 0.323                             |
| CDH8                   | 0.512| 0.096           | 0.901                  | 0.323                             |
| CEP350                 | 0.512| 0.096           | 0.901                  | 0.323                             |
| COL1I A2               | 0.512| 0.096           | 0.901                  | 0.323                             |
| CRB1                   | 0.512| 0.096           | 0.901                  | 0.323                             |
| DOCK2                  | 0.512| 0.096           | 0.901                  | 0.323                             |
| LAMA3                  | 0.512| 0.096           | 0.901                  | 0.323                             |
| POTEH                  | 0.512| 0.096           | 0.901                  | 0.323                             |
| PXDNL                  | 0.512| 0.096           | 0.901                  | 0.323                             |
| SAMD9L                 | 0.512| 0.096           | 0.901                  | 0.323                             |
| SPAG17                 | 0.512| 0.096           | 0.901                  | 0.323                             |
| TACE                   | 0.512| 0.096           | 0.901                  | 0.323                             |
| CACNA1E                | 0.506| 0.096           | 0.95                   | 0.318                             |
| FAM5B                  | 0.506| 0.096           | 0.95                   | 0.318                             |
| FAT4                   | 0.506| 0.096           | 0.95                   | 0.318                             |
| HNR                     | 0.506| 0.096           | 0.95                   | 0.318                             |
| MGD2                   | 0.506| 0.096           | 0.95                   | 0.318                             |
| MYCBP2                 | 0.506| 0.096           | 0.95                   | 0.318                             |
| NBP16F                 | 0.506| 0.096           | 0.95                   | 0.318                             |
| OR10J                  | 0.506| 0.096           | 0.95                   | 0.318                             |
| TNXB                   | 0.506| 0.096           | 0.95                   | 0.318                             |
| TRPA1                  | 0.506| 0.096           | 0.95                   | 0.318                             |
| ZIC1                   | 0.506| 0.096           | 0.95                   | 0.318                             |
| ABCA9                  | 0.5  | 0.095           | 1                      | 0.313                             |
| DNAH3                  | 0.5  | 0.095           | 1                      | 0.313                             |
| FAM5D4                 | 0.5  | 0.095           | 1                      | 0.313                             |
| FMN2                   | 0.5  | 0.095           | 1                      | 0.313                             |
| KIAA0947               | 0.5  | 0.095           | 1                      | 0.313                             |
| MUS52                  | 0.5  | 0.095           | 1                      | 0.313                             |
| MYH4                   | 0.5  | 0.095           | 1                      | 0.313                             |
| NEB                    | 0.5  | 0.095           | 1                      | 0.313                             |
| OR14K1                 | 0.5  | 0.095           | 1                      | 0.313                             |
| SLC8A3                 | 0.5  | 0.095           | 1                      | 0.313                             |
| TEP1                   | 0.5  | 0.095           | 1                      | 0.313                             |
| THSD7A                 | 0.5  | 0.095           | 1                      | 0.313                             |
| USH2A                  | 0.5  | 0.095           | 1                      | 0.313                             |
| C15orf2                | 0.494| 0.095           | 0.95                   | 0.308                             |
| CDH20                  | 0.494| 0.095           | 0.95                   | 0.308                             |
| COL1 I A1              | 0.494| 0.095           | 0.95                   | 0.308                             |
| COL5A2                 | 0.494| 0.095           | 0.95                   | 0.308                             |
| DNAH9                  | 0.494| 0.095           | 0.95                   | 0.308                             |
| FSTL5                  | 0.494| 0.095           | 0.95                   | 0.308                             |
| GRIP1                  | 0.494| 0.095           | 0.95                   | 0.308                             |
| KIF21A                 | 0.494| 0.095           | 0.95                   | 0.308                             |
| MYO7A                  | 0.494| 0.095           | 0.95                   | 0.308                             |

(Continued)
| Test result variable(s) | Area  | Standard error* | Asymptotic significance | Asymptotic 95% confidence interval |
|-------------------------|-------|-----------------|--------------------------|-----------------------------------|
|                         |       |                 |                          | Lower bound                       |
|                         |       |                 |                          | Upper bound                       |
| MYPN                    | 0.494 | 0.095           | 0.95                     | 0.308                             |
| NALCN                   | 0.494 | 0.095           | 0.95                     | 0.308                             |
| PHKB                    | 0.494 | 0.095           | 0.95                     | 0.308                             |
| PRUNE2                  | 0.494 | 0.095           | 0.95                     | 0.308                             |
| SCN7A                   | 0.494 | 0.095           | 0.95                     | 0.308                             |
| SPEG                    | 0.494 | 0.095           | 0.95                     | 0.308                             |
| TFPAP2D                 | 0.494 | 0.095           | 0.95                     | 0.308                             |
| ZPFM2                   | 0.494 | 0.095           | 0.95                     | 0.308                             |
| ZNF142                  | 0.494 | 0.095           | 0.95                     | 0.308                             |
| AHNAK2                  | 0.488 | 0.095           | 0.901                    | 0.303                             |
| DNAH7                   | 0.488 | 0.095           | 0.901                    | 0.303                             |
| HCN1                    | 0.488 | 0.095           | 0.901                    | 0.303                             |
| PCDH11S                 | 0.488 | 0.095           | 0.901                    | 0.303                             |
| ZNF729                  | 0.488 | 0.095           | 0.901                    | 0.303                             |
| BSN                     | 0.482 | 0.094           | 0.851                    | 0.298                             |
| CENPF                   | 0.482 | 0.094           | 0.851                    | 0.298                             |
| CLSTN2                  | 0.482 | 0.094           | 0.851                    | 0.298                             |
| FLNC                    | 0.482 | 0.094           | 0.851                    | 0.298                             |
| HEATR1                  | 0.482 | 0.094           | 0.851                    | 0.298                             |
| KIAA1239                | 0.482 | 0.094           | 0.851                    | 0.298                             |
| LCT                     | 0.482 | 0.094           | 0.851                    | 0.298                             |
| LPHN3                   | 0.482 | 0.094           | 0.851                    | 0.298                             |
| MLL2                    | 0.482 | 0.094           | 0.851                    | 0.297                             |
| ODZ2                    | 0.482 | 0.094           | 0.851                    | 0.298                             |
| OST1                    | 0.482 | 0.094           | 0.851                    | 0.298                             |
| OR6Y1                   | 0.482 | 0.094           | 0.851                    | 0.298                             |
| PCDH11X                 | 0.482 | 0.094           | 0.851                    | 0.298                             |
| PCDHB7                  | 0.482 | 0.094           | 0.851                    | 0.298                             |
| PKD1L2                  | 0.482 | 0.094           | 0.851                    | 0.298                             |
| PLCH1                   | 0.482 | 0.094           | 0.851                    | 0.298                             |
| PTPRD                   | 0.482 | 0.094           | 0.851                    | 0.298                             |
| RGD3                    | 0.482 | 0.094           | 0.851                    | 0.298                             |
| SELP                    | 0.482 | 0.094           | 0.851                    | 0.298                             |
| SYTL2                   | 0.482 | 0.094           | 0.851                    | 0.298                             |
| TKT1L2                  | 0.482 | 0.094           | 0.851                    | 0.298                             |
| TFR                     | 0.482 | 0.094           | 0.851                    | 0.298                             |
| UTP20                   | 0.482 | 0.094           | 0.851                    | 0.298                             |
| VWF                     | 0.482 | 0.094           | 0.851                    | 0.298                             |
| APOB                    | 0.476 | 0.094           | 0.803                    | 0.293                             |
| CNTNAP5                 | 0.476 | 0.094           | 0.803                    | 0.293                             |
| EP300                   | 0.476 | 0.094           | 0.803                    | 0.293                             |
| HEATR7B2                | 0.476 | 0.094           | 0.803                    | 0.293                             |
| ROS1                    | 0.476 | 0.094           | 0.803                    | 0.293                             |
| ZIM2                    | 0.476 | 0.094           | 0.803                    | 0.293                             |
| ABCA8                   | 0.47  | 0.093           | 0.755                    | 0.288                             |
| ABCG12                  | 0.47  | 0.093           | 0.755                    | 0.288                             |
| ACSM5                   | 0.47  | 0.093           | 0.755                    | 0.288                             |
| ADAM2                   | 0.47  | 0.093           | 0.755                    | 0.288                             |
| ANKRDS5                 | 0.47  | 0.093           | 0.755                    | 0.288                             |

(Continued)
| Test result variable(s) | Area | Standard error | Asymptotic significance | Asymptotic 95% confidence interval |
|------------------------|------|----------------|------------------------|-----------------------------------|
|                        |      |                |                        | Lower bound    | Upper bound   |
| ATP1A2                 | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| C10orf112              | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| C12orf51               | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| CMYA5                  | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| CSMD1                  | 0.47 | 0.094          | 0.755                  | 0.286          | 0.654         |
| CYP11B1                | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| DCHS1                  | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| DSEL                   | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| DYFS                   | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| FAT1                   | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| HERC2                  | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| KCNJ1                  | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| LRPIB                  | 0.47 | 0.095          | 0.755                  | 0.284          | 0.656         |
| MSH4                   | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| MYH15                  | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| MYH2                   | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| MYO9A                  | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| NLRP4                  | 0.47 | 0.093          | 0.755                  | 0.286          | 0.654         |
| OBSCN                  | 0.47 | 0.094          | 0.755                  | 0.288          | 0.652         |
| PRDM9                  | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| PTPRU                  | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| S1T2                   | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| TNR                    | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| TRPM2                  | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| UTRN                   | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| ZNF462                 | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| ZNF534                 | 0.47 | 0.093          | 0.755                  | 0.288          | 0.652         |
| ANK2                   | 0.464| 0.093          | 0.708                  | 0.282          | 0.646         |
| COL22A1                | 0.464| 0.093          | 0.708                  | 0.282          | 0.646         |
| DST                    | 0.464| 0.093          | 0.708                  | 0.282          | 0.646         |
| GRIN2A                 | 0.464| 0.092          | 0.708                  | 0.285          | 0.644         |
| RYR3                   | 0.464| 0.093          | 0.708                  | 0.282          | 0.646         |
| SLCO1B1                | 0.464| 0.092          | 0.708                  | 0.285          | 0.644         |
| ABCB5                  | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| BAI3                   | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| CSorf42                | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| CD163                  | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| DCC                    | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| MYO7B                  | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| NLRP12                 | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| ODZ1                   | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| ODZ3                   | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| OR8H3                  | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| PDE4DIP                | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| RIMS2                  | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| SAC5                   | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| SVEP1                  | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| TCHH                   | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| ZNF521                 | 0.458| 0.092          | 0.662                  | 0.279          | 0.638         |
| Test result variable(s) | Area | Standard error* | Asymptotic significance | Asymptotic 95% confidence interval |
|-------------------------|------|-----------------|-------------------------|----------------------------------|
|                         |      |                 |                         | Lower bound | Upper bound |
| C1orf173                | 0.452| 0.092           | 0.618                   | 0.272   | 0.633 |
| DOCK4                   | 0.452| 0.09            | 0.618                   | 0.275   | 0.629 |
| GPR98                   | 0.452| 0.092           | 0.618                   | 0.272   | 0.633 |
| KIAA1549                | 0.452| 0.09            | 0.618                   | 0.275   | 0.629 |
| MACF1                   | 0.452| 0.092           | 0.618                   | 0.272   | 0.633 |
| CDH18                   | 0.446| 0.091           | 0.574                   | 0.269   | 0.624 |
| CTNNA2                  | 0.446| 0.091           | 0.574                   | 0.269   | 0.624 |
| DNAH5                   | 0.446| 0.091           | 0.574                   | 0.269   | 0.624 |
| FAM5C                   | 0.446| 0.091           | 0.574                   | 0.269   | 0.624 |
| TRRAP                   | 0.446| 0.091           | 0.574                   | 0.269   | 0.624 |
| BRWD3                   | 0.44  | 0.089           | 0.533                   | 0.266   | 0.615 |
| CACHD1                  | 0.44  | 0.089           | 0.533                   | 0.266   | 0.615 |
| CDH7                    | 0.44  | 0.089           | 0.533                   | 0.266   | 0.615 |
| DSCAM                   | 0.44  | 0.089           | 0.533                   | 0.266   | 0.615 |
| LRP2                    | 0.44  | 0.091           | 0.533                   | 0.262   | 0.619 |
| MUC19                   | 0.44  | 0.091           | 0.533                   | 0.262   | 0.619 |
| OR1I1H12                | 0.44  | 0.089           | 0.533                   | 0.266   | 0.615 |
| OR52R1                  | 0.44  | 0.089           | 0.533                   | 0.266   | 0.615 |
| SIGLEC8                 | 0.44  | 0.089           | 0.533                   | 0.266   | 0.615 |
| TMEM132D                | 0.44  | 0.091           | 0.533                   | 0.262   | 0.619 |
| MUC4                    | 0.435 | 0.094           | 0.492                   | 0.25    | 0.619 |
| AIM1                    | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| CARD11                  | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| COLS3                   | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| CSMD2                   | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| EYA4                    | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| FREM3                   | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| KIAA0240                | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| KIAA1211                | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| LAMC3                   | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| LPA                     | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| LRNF5                   | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| NAV2                    | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| NCAM2                   | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| SDK1                    | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| SETD2                   | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| SHROOM3                 | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| SPTB                    | 0.429 | 0.088           | 0.454                   | 0.257   | 0.6    |
| ANKRD30A                | 0.423 | 0.089           | 0.417                   | 0.249   | 0.596 |
| OTOR                    | 0.423 | 0.089           | 0.417                   | 0.249   | 0.596 |
| PAPPA2                  | 0.423 | 0.089           | 0.417                   | 0.249   | 0.596 |
| C10orf71                | 0.417 | 0.086           | 0.382                   | 0.247   | 0.586 |
| COL6A6                  | 0.417 | 0.086           | 0.382                   | 0.247   | 0.586 |
| FLG                     | 0.417 | 0.09            | 0.382                   | 0.241   | 0.592 |
| FSCB                    | 0.417 | 0.086           | 0.382                   | 0.247   | 0.586 |
| PCNX                    | 0.417 | 0.086           | 0.382                   | 0.247   | 0.586 |
| XDH                     | 0.417 | 0.086           | 0.382                   | 0.247   | 0.586 |
| BODIL                   | 0.405 | 0.085           | 0.318                   | 0.238   | 0.571 |
| LRRC7                   | 0.405 | 0.085           | 0.318                   | 0.238   | 0.571 |

(Continued)
Table S2 (Continued)

| Test result variable(s) | Area  | Standard error* | Asymptotic significance | Asymptotic 95% confidence interval |
|-------------------------|-------|------------------|--------------------------|-----------------------------------|
|                         |       |                  |                          | Lower bound | Upper bound |
| RP1L1                   | 0.405 | 0.085            | 0.318                    | 0.238       | 0.571       |
| ADAMTS20                | 0.399 | 0.086            | 0.289                    | 0.23        | 0.568       |
| MLL3                    | 0.393 | 0.084            | 0.261                    | 0.229       | 0.537       |
| DNAH10                  | 0.369 | 0.081            | 0.17                     | 0.21        | 0.528       |
| RB1                     | 0.369 | 0.096            | 0.17                     | 0.182       | 0.557       |

Note: *Under the nonparametric assumption.

Abbreviation: ROC, receiver operating characteristic.