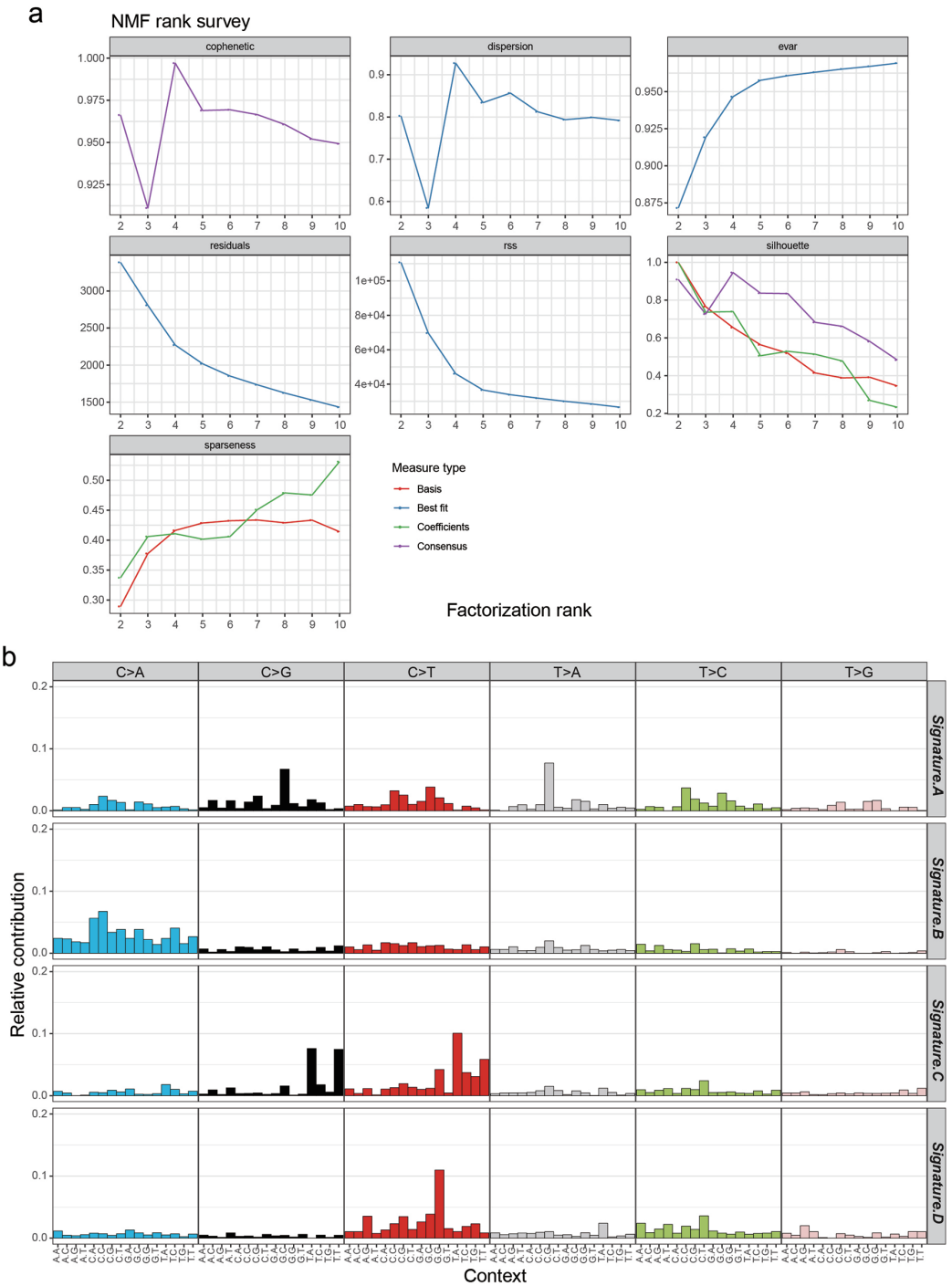


**Figure S1** The extraction and patterns of substitutions for *de novo* signatures. (A) *De novo* mutational signature extraction using NMF. NMF rank survey was used to find the optimal factorization rank using the NMF package. The most common approach is to choose the smallest rank for which cophenetic correlation coefficient starts decreasing. Another approach is to choose the rank for which the plot of the RSS between the input matrix and its estimate shows an inflection point. According to the cophenetic plot, we determined to use a rank of 4. (B) Patterns of substitutions for signatures A–D. Each signature is displayed according to the 96 substitution classifications defined by the substitution class and sequence context immediately 50 and 30 to the mutated base. The vertical axis represents mutation fractions of each substitution classification. RSS, residual sum of squares.


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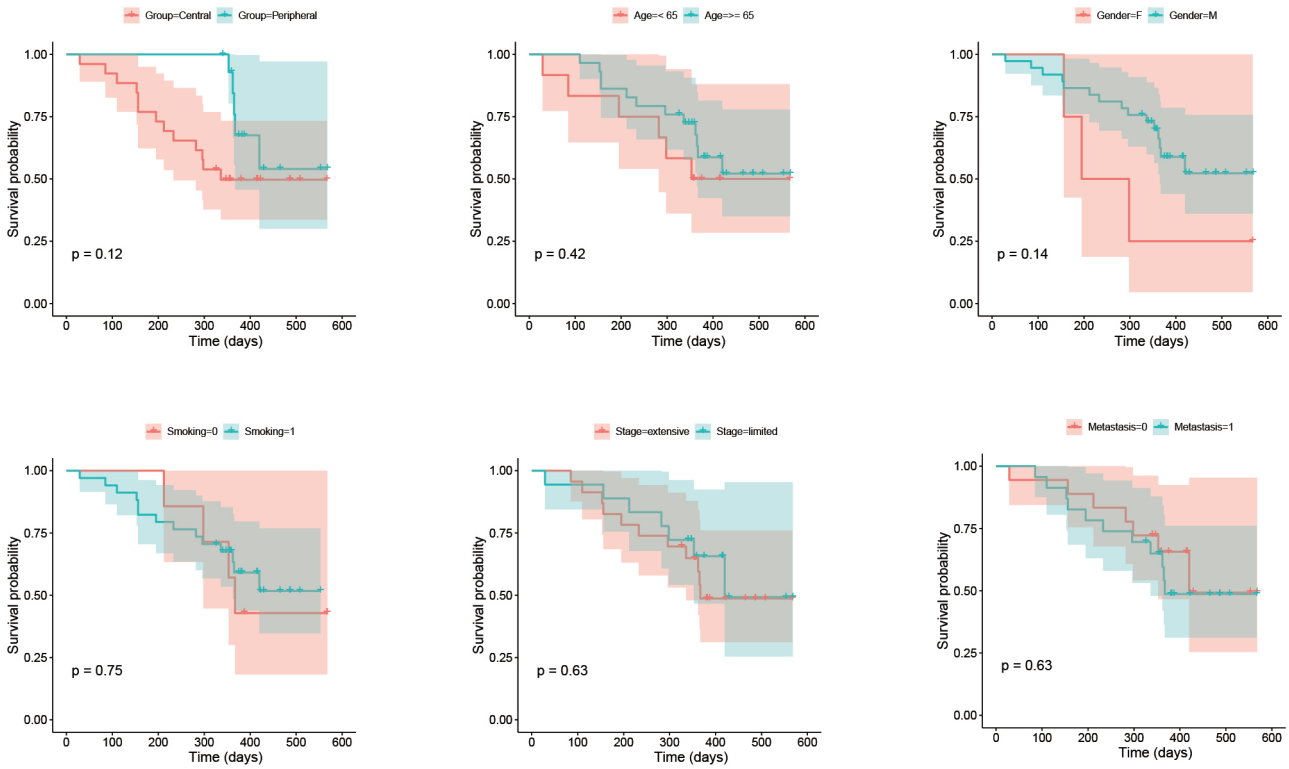


**Figure S2** The association between clinical characteristics and OS in SCLCs. No significant correlation was found. OS, overall survival; SCLC, small-cell lung cancer.


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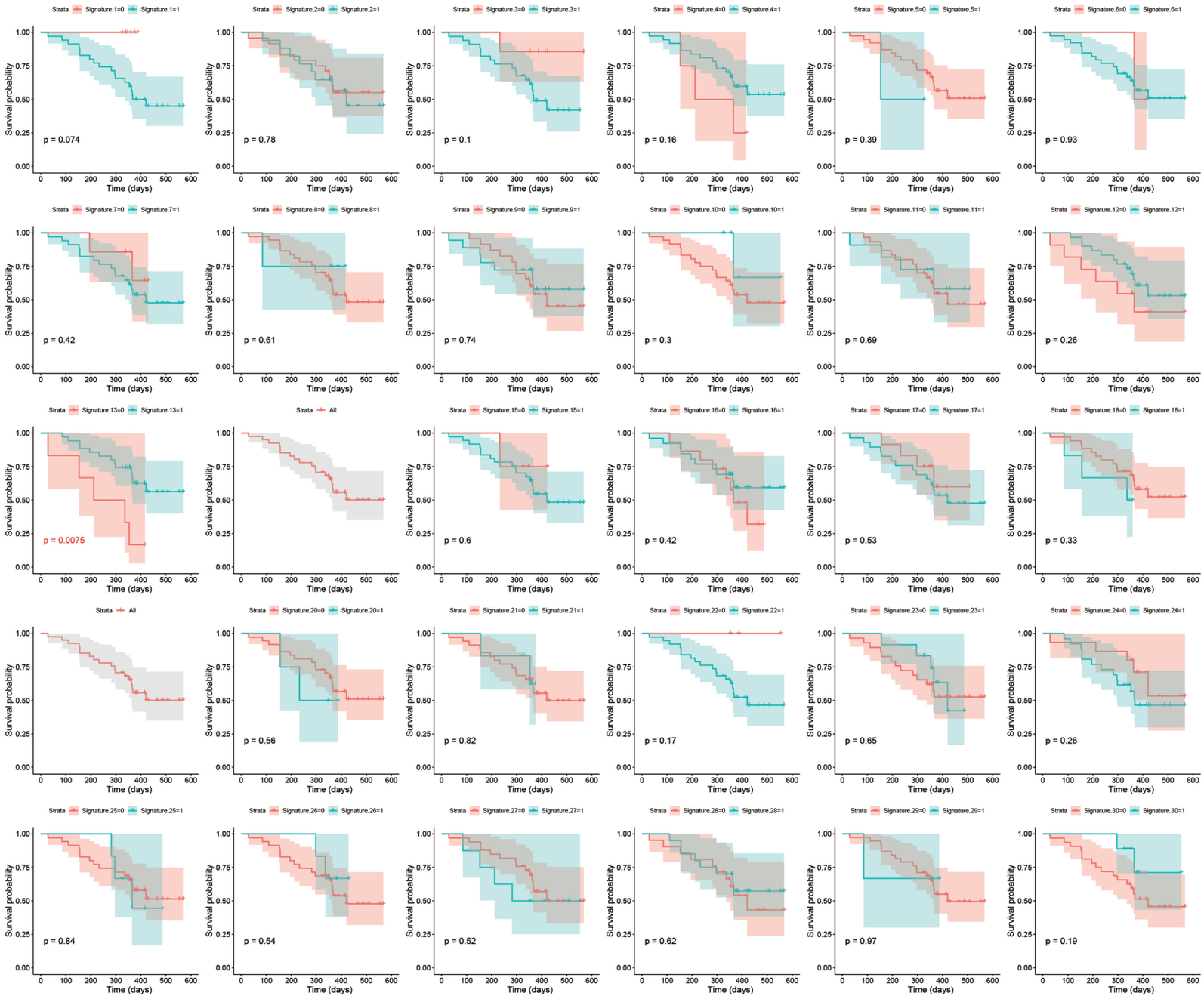


**Figure S3** The association between COSMIC signatures and OS in SCLCs. Signature 13 was significant negatively correlated with OS in SCLCs. OS, overall survival; SCLC, small-cell lung cancer.


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**Table S1** MutsigCV results of the two types of SCLCs

| Group | Gene | P | q |
|---|---|---|---|
| Central | *TP53* | 2.22045E–16 | 4.18821E–12 |
| | *RB1* | 1.33227E–15 | 1.25646E–11 |
| | *APOC1* | 3.84152E–05 | 0.1635742 |
| | *ZPBP2* | 4.29258E–05 | 0.1635742 |
| | *XCL1* | 4.33608E–05 | 0.1635742 |
| Peripheral | *TP53* | 5.55112E–16 | 1.04705E–11 |
| | *RB1* | 6.60028E–13 | 6.22472E–09 |
| | *C1QB* | 4.30911E–05 | 0.270928 |
| | *BTN2A1* | 0.00022215 | 0.6256373 |
| | *IGLL5* | 0.000223274 | 0.6256373 |

A report of significant mutations, listed in descending order from most significant to least significant. MutsigCV analyzed lists of mutations discovered in WES, to identify genes that were mutated more often than expected by chance given background mutation processes. The P value are calculated for each gene, as well as the false discovery rate (q value). Genes exceeding a chosen threshold were reported as significantly mutated. SCLC, small-cell lung cancer; WES, whole-exome sequencing.


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**Table S2** Comparisons of the absolute contributions of de novo signatures between central and peripheral-type SCLCs

| Signatures | Characteristics | Stratification | P value | Significance | P.adj |
|---|---|---|---|---|---|
| Signature.A | Combined | | 0.03 | * | 0.03 |
| | Metastasis | 0 | 0.094 | NS | 0.19 |
| | | 1 | 0.354 | NS | 0.35 |
| | Age | ≥65 | 0.3698 | NS | 0.37 |
| | | <65 | 0.0091 | ** | 0.018 |
| | Gender | M | 0.022 | * | 0.022 |
| | Smoking | 1 | 0.077 | NS | 0.15 |
| | | 0 | 0.400 | NS | 0.4 |
| Signature.B | Combined | | 0.86 | NS | 0.86 |
| | Metastasis | 0 | 0.55 | NS | 1 |
| | | 1 | 1.00 | NS | 1 |
| | Age | <65 | 1.00 | NS | 1 |
| | | ≥65 | 0.56 | NS | 1 |
| | Gender | M | 0.53 | NS | 0.53 |
| | Smoking | 0 | 0.63 | NS | 1 |
| | | 1 | 0.66 | NS | 1 |
| Signature.C | Combined | | 0.28 | NS | 0.28 |
| | Metastasis | 1 | 0.47 | NS | 0.47 |
| | | 0 | 0.22 | NS | 0.43 |
| | Age | ≥65 | 0.50 | NS | 0.96 |
| | | <65 | 0.48 | NS | 0.96 |
| | Gender | M | 0.47 | NS | 0.47 |
| | Smoking | 1 | 0.29 | NS | 0.46 |
| | | 0 | 0.23 | NS | 0.46 |
| Signature.D | Combined | | 0.55 | NS | 0.55 |
| | Metastasis | 1 | 0.26 | NS | 0.51 |
| | | 0 | 0.60 | NS | 0.6 |
| | Age | <65 | 0.73 | NS | 0.94 |
| | | ≥65 | 0.47 | NS | 0.94 |
| | Gender | M | 0.66 | NS | 0.66 |
| | Smoking | 1 | 0.36 | NS | 0.73 |
| | | 0 | 0.40 | NS | 0.73 |

FDR algorithm was applied during multiple comparisons when stratification was performed. *, P<0.05; **, P<0.01. SCLC, small-cell lung cancer; P.adj, adjusted P value.


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