**Supplementary Table1 Four kinds of primers of present 13 studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author** | **Year** | **Forward （bp）** | **Reverse (bp)** | **Island(bp)** |
| Dong et al (2007, Korea) | 2007 | chr16:82,660,749-82,660,767 | chr16:82,660,652-82,660,673 | chr16:82660651-82661813 |
| Feng et al (2008, USA) | 2008 | chr16:82,660,749-82,660,767 | chr16:82,660,652-82,660,673 | chr16:82660651-82661813 |
| Hanabata et al (2004, Japan) | 2004 | chr16:82,660,749-82,660,767 | chr16:82,660,652-82,660,673 | chr16:82660651-82661813 |
| Hsu et al (2007, Taiwan) | 2007 | chr16:82,660,749-82,660,767 | chr16:82,660,652-82,660,673 | chr16:82660651-82661813 |
| Jin et al (2009, Japan) | 2009 | chr16:82,627,104-82,627,124 | chr16:82,627,187-82,627,206 | chr16:82660651-82661813 |
| Nikolaidis et al (2012, UK) | 2012 | chr16:82,660,654-82,660,671 | chr16:82,660,705-82,660,726 | chr16:82660651-82661813 |
| Toyooka et al (2001, USA) | 2001 | chr16:82,660,749-82,660,767 | chr16:82,660,652-82,660,673 | chr16:82660651-82661813 |
| Toyooka et al (2003, USA) | 2003 | chr16:82,660,749-82,660,767 | chr16:82,660,652-82,660,673 | chr16:82660651-82661813 |
| Tsou et al (2007, USA) | 2007 | chr16:82,660,709-82,660,729 | chr16:82,660,792-82,660,811 | chr16:82660651-82661813 |
| Ulivi et al (2006, Italy) | 2006 | chr16:82,660,749-82,660,767 | chr16:82,660,652-82,660,673 | chr16:82660651-82661813 |
| Wang et al (2008, China) | 2008 | NA | NA | chr16:82660651-82661813 |
| Zhai et al (2014, China) | 2014 | chr16:82,660,749-82,660,767 | chr16:82,660,652-82,660,673 | chr16:82660651-82661813 |
| Zhang et al (2011, China) | 2011 | chr16:82,660,749-82,660,767 | chr16:82,660,652-82,660,673 | chr16:82660651-82661813 |

NA: not found in the article.

**Supplementary Table 2 Differential FHIT methylation, odds ratio between adenocarcinoma, squamous cell carcinoma and their counterparts from GSE39279 & GSE52401 dataset**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type** | **Position** | **CpG site** | **McaM** | **McoM** | **∆β** | **p-value** | **p-value\_lr** | **OR** | **95%CI** |
| **LUAD** | chr16:82660670 | cg08747377 | 0.32658 | 0.1609 | 0.16568 | 1.11E-51 | 4.43E-28 | 0.08069 | 0.05056-0.123 |
| chr16:82660727 | cg05374412 | 0.23438 | 0.04392 | 0.19046 | 9.02E-77 | 1.29E-22 | 0.00074 | 0.00016-0.00285 |
| chr16:82661421 | cg08856946 | 0.2117 | 0.07414 | 0.13756 | 2.63E-68 | 1.21E-24 | 0.00467 | 0.00157-0.01214 |
| chr16:82661521 | cg13759328 | 0.28992 | 0.17442 | 0.11549 | 9.78E-61 | 1.29E-28 | 0.03326 | 0.01777-0.0582 |
| chr16:82661638 | cg09189772 | 0.28967 | 0.1819 | 0.10778 | 2.63E-49 | 9.12E-26 | 0.05385 | 0.03036-0.0899 |
| chr16:82661725 | cg19369556 | 0.27121 | 0.22947 | 0.04173 | 6.98E-09 | 6.44E-09 | 0.49284 | 0.38397-0.61876 |
|  |  |  |  |  |  |  |  |  |  |
| **LUSC** | chr16:82660670 | cg08747377 | 0.23598 | 0.1609 | 0.07507 | 8.92E-12 | 1.61E-10 | 0.36883 | 0.2681-0.49264 |
| chr16:82660727 | cg05374412 | 0.12757 | 0.04392 | 0.08365 | 3.65E-33 | 6.34E-14 | 0.04592 | 0.01977-0.09746 |
| chr16:82661421 | cg08856946 | 0.14118 | 0.07414 | 0.06704 | 3.55E-30 | 6.01E-17 | 0.0987 | 0.05594-0.16309 |
| chr16:82661521 | cg13759328 | 0.24259 | 0.17442 | 0.06817 | 2.59E-26 | 1.71E-17 | 0.17253 | 0.11345-0.25063 |
| chr16:82661638 | cg09189772 | 0.23064 | 0.1819 | 0.04875 | 9.62E-10 | 1.51E-10 | 0.33444 | 0.23537-0.45848 |
| chr16:82661725 | cg19369556 | 0.22208 | 0.22947 | 0.00739 | 0.005638311 | 0.145187084 | 1.18579 | 0.949-1.49855 |

McaM and McoM represent the mean of case methylation (Beta) and mean of control methylation (Beta). Methylation levels are calculated with formula: Beta = (M/M + U).

Position represents the chromosome position of each CpG site according to GRCh37/hg19.

P-valuesa are calculated from Wilcoxon rank sum test after false discovery rate(FDR adjustment).

P-valueb and ORb and 95%CIb are from logistic regression analysis with P-valueb were also after false discovery rate(FDR adjustment).

**Supplementary Table 3 Differential FHIT methylation, odds ratio between adenocarcinoma, squamous cell carcinoma and their counterparts from GSE56044 dataset**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type** | **CpG site** | **Position** | **McaM** | **McoM** | **∆β** | **p-value\_1** | **p-value\_lr** | **OR** | **95%CI** |
| **LUAD** | cg08747377 | chr16:82660670 | 0.3087 | 0.07175 | 0.23695 | 3.73E-05 | 0.009417688 | 0.02157 | 0.00081-0.16484 |
| cg05374412 | chr16:82660727 | 0.26302 | 0.02108 | 0.24194 | 1.98E-05 | 0.025807621 | 0.00059 | 0-0.04564 |
| cg00806490 | chr16:82660873 | 0.25434 | 0.0695 | 0.18484 | 1.20E-05 | 0.009417688 | 0.00456 | 0.00005-0.07634 |
| cg08856946 | chr16:82661421 | 0.18157 | 0.05058 | 0.13098 | 0.00038 | 0.02071135 | 0.01757 | 0.00042-0.21396 |
| cg13759328 | chr16:82661521 | 0.21981 | 0.10433 | 0.11547 | 0.00038 | 0.01137716 | 0.05811 | 0.0055-0.30289 |
| cg09189772 | chr16:82661638 | 0.24442 | 0.124 | 0.12042 | 0.001575 | 0.015071414 | 0.17491 | 0.03959-0.51628 |
| cg19369556 | chr16:82661725 | 0.19886 | 0.17308 | 0.02577 | 0.849679 | 0.520063591 | 0.75592 | 0.33854-1.41905 |
|  |  |  |  |  |  |  |  |  |  |
| **LUSC** | cg08747377 | chr16:82660670 | 0.16813 | 0.07175 | 0.09638 | 0.014318 | 0.081109893 | 0.12052 | 0.01519-0.5117 |
| cg05374412 | chr16:82660727 | 0.10174 | 0.02108 | 0.08066 | 0.167182 | 0.2151398 | 0.06249 | 0.0009-0.76577 |
| cg00806490 | chr16:82660873 | 0.1513 | 0.0695 | 0.0818 | 0.003025 | 0.081109893 | 0.04065 | 0.0021-0.31227 |
| cg08856946 | chr16:82661421 | 0.10843 | 0.05058 | 0.05785 | 0.136409 | 0.169328611 | 0.15071 | 0.01181-0.81974 |
| cg13759328 | chr16:82661521 | 0.18917 | 0.10433 | 0.08484 | 0.007995 | 0.081109893 | 0.06399 | 0.00442-0.40179 |
| cg09189772 | chr16:82661638 | 0.17848 | 0.124 | 0.05448 | 0.235086 | 0.266391756 | 0.39507 | 0.07427-1.08178 |
| cg19369556 | chr16:82661725 | 0.15178 | 0.17308 | 0.0213 | 0.148399 | 0.502066325 | 1.37405 | 0.67412-3.01339 |

McaM and McoM represent the mean of case methylation (Beta) and mean of control methylation (Beta). Methylation levels are calculated with formula: Beta = (M/M + U).

Position represents the chromosome position of each CpG site according to GRCh37/hg19.

P-valuesa are calculated from Wilcoxon rank sum test after false discovery rate (FDR adjustment).

P-valueb and ORb and 95%CIb are from logistic regression analysis with P-valueb were also after false discovery rate (FDR adjustment).

**Supplementary Figure 1 Funnel plot to diagnosis of the publication bias**

**Supplementary Figure 2 Combined estimates for the association between FHIT methylation and NSCLC after trim-fill treatment.**

**Supplementary Figure 3 Sensitivity analyses of the overall effect by omitting a single study.**

**Supplementary Figure 4 CpG sites on the Illumina Infinium HumanMethylation450 Beadchip array across FHIT gene region from GSE39279 & GSE52401 datasets.**

the x-axis shows the different CpG sites in FHIT genes and the y-axis shows the beta value of each CpG site to represent the methylation level of each CpG site.

**Supplementary Figure 5 CpG sites on the Illumina Infinium HumanMethylation450 Beadchip array across FHIT gene region from GSE56044 dataset.**

the x-axis shows the different CpG sites in FHIT genes and the y-axis shows the beta value of each CpG site to represent the methylation level of each CpG site.