**Supplementary**

**Figure S1** Six base substitution type spectra of mutations in 16 high-grade fetal adenocarcinomas (H-FLACs) and The Cancer Genome Atlas (TCGA) lung adenocarcinomas (LUADs). Six base substitution type spectra of mutations of H-FLACs were compared with those of the TCGA LUADs.

**Figure S2** Heatmap of cosine similarity with the 30 mutational signatures of the 514 The Cancer Genome Atlas (TCGA) lung adenocarcinomas. The black-boxed cases resemble the common adenocarcinoma-like cluster of high-grade fetal adenocarcinomas.
Table S1 Depth of whole-exome sequencing in this study

| Case | Tumor/normal | Mapped bases | Total reads | Mapped reads | Average depth |
|------|--------------|--------------|-------------|--------------|---------------|
| 1    | Normal       | 14,207,250,876 | 145,588,534 | 145,567,663  | 173.4         |
|      | Tumor        | 10,549,991,287 | 108,989,542 | 108,978,966  | 120.3         |
| 2    | Normal       | 10,298,302,219 | 107,095,830 | 106,331,339  | 118.8         |
|      | Tumor        | 9,516,642,628  | 98,964,910  | 98,264,021   | 125.8         |
| 3    | Normal       | 12,682,724,915 | 130,077,950 | 130,044,402  | 176.2         |
|      | Tumor        | 17,464,278,431 | 179,188,518 | 179,147,506  | 249.4         |
| 4    | Normal       | 20,852,408,890 | 213,940,710 | 213,918,518  | 236.6         |
|      | Tumor        | 16,681,722,588 | 170,866,769 | 170,866,769  | 176.0         |
| 5    | Normal       | 16,012,910,291 | 163,047,551 | 163,047,551  | 197.3         |
|      | Tumor        | 9,201,544,823  | 93,851,652  | 93,851,652   | 129.6         |
| 6    | Normal       | 9,406,739,344  | 96,386,977  | 96,386,977   | 132.5         |
|      | Tumor        | 14,296,561,905 | 146,577,527 | 146,577,527  | 207.3         |
| 7    | Normal       | 6,794,952,150  | 69,220,129  | 69,220,129   | 196.2         |
|      | Tumor        | 7,765,555,835  | 79,409,065  | 79,409,065   | 109.3         |
| 8    | Normal       | 7,030,664,437  | 72,222,492  | 72,222,492   | 227.3         |
|      | Tumor        | 10,286,952,074 | 106,153,003 | 106,153,003  | 129.1         |
| 9    | Normal       | 5,273,558,726  | 53,628,956  | 53,628,956   | 176.0         |
|      | Tumor        | 3,922,298,094  | 39,907,336  | 39,907,336   | 162.4         |
| 10   | Normal       | 22,138,805,708 | 227,164,600 | 227,164,600  | 309.9         |
|      | Tumor        | 14,965,894,854 | 153,087,820 | 153,087,820  | 209.0         |
| 11   | Normal       | 3,741,774,558  | 38,018,030  | 38,018,030   | 140.8         |
|      | Tumor        | 7,912,218,220  | 80,481,374  | 80,481,374   | 169.2         |
| 12   | Normal       | 10,561,042,636 | 107,387,426 | 107,387,426  | 147.4         |
|      | Tumor        | 10,745,806,494 | 109,516,062 | 109,516,062  | 154.2         |
| 13   | Normal       | 5,732,584,430  | 58,231,333  | 58,231,333   | 149.1         |
|      | Tumor        | 8,346,102,076  | 84,706,190  | 84,706,190   | 116.9         |
| 14   | Normal       | 7,562,510,568  | 78,982,023  | 78,982,023   | 100.5         |
|      | Tumor        | 10,458,370,047 | 106,360,625 | 106,360,625  | 120.8         |
| 15   | Normal       | 7,334,071,274  | 74,399,424  | 74,399,424   | 190.9         |
|      | Tumor        | 10,418,159,370 | 106,533,342 | 106,533,342  | 133.8         |
| 16   | Normal       | 8,269,812,792  | 84,592,882  | 84,592,882   | 149.5         |
|      | Tumor        | 6,502,322,511  | 66,478,559  | 66,478,559   | 155.3         |
Table S2 Summary of nonsynonymous somatic mutations of high-grade fetal adenocarcinomas

| Gene        | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|-------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| KMT2C       |    |    |    | C391X | Y512C | K339N | C391X | Multiple* | D2703E |    |    |    |    |    |    |
| TP53        |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| KRAS        |    |    |    | G12D | G12C | G12D | G12D |    |    |    |    |    |    |    |    |    |
| STK11       |    |    |    | Q37X |    |    |    |    |    |    |    |    |    |    |    |    |
| SMAD4       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| RB1         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| NF1         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| MET         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| CTNNB1      |    | D32Y | D32V |    |    |    |    |    |    |    |    |    |    |    |    |    |
| CDKN2A      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| BRAF        |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| STX2        |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SMARCA4     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SLC4A5      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| PIK3CA      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| MAP2K1      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| KEAP1       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| FAT1        |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ERBB2       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| EGFR        |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| CDK12       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ARID1A      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ARHGAP35    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| APC         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| PTEN        |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| COBL        |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ACVR1B      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SHROOM1     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| NKX2-1      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SFTPC       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

*, patients with severe emphysema; †, patients with UIP. KMT2C multiple*: E5X, G568C and S2350Y; NF1 multiple*: S521C and A1453fX. UIP, usual interstitial pneumonia.