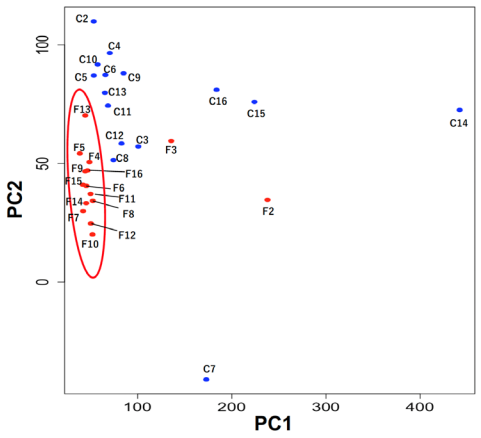

Figure S1 PCA analysis of the gene expression profile of high-grade fetal adenocarcinoma (H-FLAC) and the common adenocarcinoma counterpart of the lung. Each H-FLAC case (F2-16) is indicated by a red dot, whereas the common adenocarcinoma cases (C1-16) are shown by the blue dots with case identification numbers (see text). Cases of H-FLAC located close to each other are encircled in red, indicating a close group of 13 out of 15 H-FLAC cases examined. PCA, principal component analysis.

Table S1 Predicted pathways by IPA with P-value less than 0.05, corresponding to -log (P-value) greater than 1.3

Pathways	–log (P-value)	Ratio	z-score	molecules encoded by the DEGs involved in the constituents of the pathway
Role of BRCA1 in DNA Damage Response	5.02E+00	1.75E–01	–1.89	ACTB, ARID1A, ARID2, ATR, BLM, CHEK2, FANCD2, FANCM, MRE11, MSH2, NBN, RFC1, SMARCC1, STAT1
Complement System	4.71E+00	2.50E–01	–0.378	C1R, C1S, C3, C5, C6, CD55, CFI, ITGB2, SERPING1
Hereditary Breast Cancer Signaling	3.87E+00	1.22E–01	NaN	ACTB, ARID1A, ARID2, ATR, BLM, CHEK2, FANCD2, FANCM, MRE11, MSH2, NBN, PIK3R3, PIK3R4, POLR2B, RFC1, SMARCC1, UBC
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	3.53E+00	1.80E–01	0.378	ATR, CHEK2, MDM2, SKP1, TOP2A, TRIP12, YWHAE, YWHAG, YWHAQ
RhoA Signaling	3.51E+00	1.23E–01	–2.496	ABL2, ACTB, ACTR2, ARHGAP35, ARHGEF12, ARPC1A, CFL2, NEDD4, NGEF, NRP2, PIP5K1B, PTK2, RAPGEF2, RDX, RHPN2
Serotonin and Melatonin Biosynthesis	3.10E+00	6.00E–01	NaN	ASMT, TPH1, TPH2
Clathrin-mediated Endocytosis Signaling	3.06E+00	9.90E–02	NaN	ACTB, ACTR2, AP3B1, AP3M1, APOB, ARPC1A, CBL, CLTA, DAB2, EGF, HSPA8, ITGB1, ITGB2, MDM2, PIK3R3, PIK3R4, SYNJ1, TSG101, UBC
Mitotic Roles of Polo-Like Kinase	2.77E+00	1.43E–01	–2.449	ANAPC1, ANAPC4, CDC16, CDC23, CHEK2, PLK4, PPP2CB, PPP2R5C, SLK
DNA Double-Strand Break Repair by Homologous Recombination	2.58E+00	2.86E–01	NaN	ATRX, GEN1, MRE11, NBN
ATM Signaling	2.48E+00	1.15E–01	–1	ATR, BLM, CHEK2, FANCD2, MAPK8, MDM2, MRE11, NBN, PPP2CB, PPP2R5C, SMC2
Role of CHK Proteins in Cell Cycle Checkpoint Control	2.47E+00	1.40E–01	–2.646	ATR, CHEK2, MRE11, NBN, PPP2CB, PPP2R5C, RAD1, RFC1
HIPPO signaling	2.42E+00	1.19E–01	1.414	DLG5, ITCH, PPP2CB, PPP2R5C, SKP1, STK3, STK4, YWHAE, YWHAG, YWHAQ
Rac Signaling	2.12E+00	9.49E–02	–3.464	ACTR2, ARPC1A, CFL2, CYBB, IQGAP1, ITGB1, ITGB2, MAPK8, NCKAP1, PIK3R3, PIK3R4, PIP5K1B, PTK2
MSP-RON Signaling In Cancer Cells Pathway	2.12E+00	9.49E–02	–2.887	BRAF, ELF1, HNF1A, ITGB1, PIK3R3, PIK3R4, PTK2, RPS6KA3, SOS2, TCF4, YWHAE, YWHAG, YWHAQ
Protein Ubiquitination Pathway	2.06E+00	7.78E–02	NaN	ANAPC1, ANAPC4, CBL, CDC23, DNAJC21, DNAJC8, HSPA8, MDM2, NEDD4, PSMA3, PSMC6, PSMD9, SKP1, TRAF6, UBC, UBE2Q1, UBE3A, UBR1, USO1, USP36, USP9Y
Actin Cytoskeleton Signaling	1.99E+00	7.92E–02	–2.5	ACTB, ACTR2, ARHGAP35, ARHGEF12, ARPC1A, CFL2, EGF, IQGAP1, ITGB1, ITGB2, NCKAP1, PIK3R3, PIK3R4, PIP5K1B, PTK2, RDX, SOS2, TLN1, TRIO
EGF Signaling	1.99E+00	1.27E–01	–2.646	EGF, ITPR2, MAPK8, PIK3R3, PIK3R4, SOS2, STAT1
p53 Signaling	1.95E+00	1.02E–01	0.378	ATR, CCNG1, CHEK2, MAPK8, MDM2, PIK3R3, PIK3R4, ST13, STAG1, TRIM29
EIF2 Signaling	1.89E+00	8.02E–02	–1.897	ACTB, EIF2AK3, EIF3E, EIF3H, EIF4G3, PIK3R3, PIK3R4, RPL23, RPL32, RPL34, RPL37, RPLP0, RPS24, RPS3, RPS4Y1, SOS2, WARS1
ERK/MAPK Signaling	1.87E+00	7.98E–02	–1.941	BRAF, ELF1, ITGB1, ITGB2, KSR1, LAMTOR3, MKNK2, PIK3R3, PIK3R4, PPP2CB, PPP2R5C, PTK2, SOS2, STAT1, TLN1, YWHAG, YWHAQ
Signaling by Rho Family GTPases	1.86E+00	7.55E–02	–4	ACTB, ACTR2, ARHGEF12, ARPC1A, CDH12, CDH9, CFL2, CLIP1, CYBB, GNAZ, IQGAP1, ITGB1, ITGB2, MAPK8, NEDD4, PIK3R3, PIK3R4, PIP5K1B, PTK2, RDX

Table S1 *(continued)*

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Table S1 *(continued)*

Pathways	–log (P-value)	Ratio	z-score	molecules encoded by the DEGs involved in the constituents of the pathway
UDP-N-acetyl-D-galactosamine Biosynthesis II	1.86E+00	2.50E–01	NaN	GNPDA2, GNPNAT1, GPI
Acute Phase Response Signaling	1.79E+00	8.15E–02	–1.897	C1R, C1S, C3, C5, ELP1, HNF1A, IL18, IL6ST, MAPK8, PIK3R3, SERPING1, SOD2, SOS2, TCF4, TRAF6
IGF-1 Signaling	1.78E+00	9.62E–02	–2.236	IGFBP4, MAPK8, NEDD4, PIK3R3, PIK3R4, PTK2, SOS2, YWHAE, YWHAG, YWHAQ
Ephrin A Signaling	1.78E+00	1.28E–01	NaN	ADAM10, CFL2, NGEF, PIK3R3, PIK3R4, PTK2
IL-15 Production	1.77E+00	9.17E–02	–2.714	ABL2, KDR, LMTK2, MERTK, PTK2, ROR2, ROS1, STAT1, TNK2, TWF1, TXK
TCA Cycle II (Eukaryotic)	1.71E+00	1.67E–01	–2	OGDH, SDHA, SLC35G3, SUCLG1
Leukocyte Extravasation Signaling	1.69E+00	7.94E–02	–2.887	ACTB, ARHGAP35, CLDN14, CYBB, F11R, ITGB1, ITGB2, MAPK8, MMP10, PIK3R3, PIK3R4, PTK2, RDX, SELPLG, TXK
GP6 Signaling Pathway	1.67E+00	8.87E–02	–2.714	ADAM10, COL1A2, COL3A1, COL6A5, COL9A1, LAMA1, LAMC1, PIK3R3, PIK3R4, PTK2, TLN1
Zymosterol Biosynthesis	1.59E+00	3.33E–01	NaN	CYP51A1, LBR
PI3K/AKT Signaling	1.55E+00	7.61E–02	–1.155	ELP1, GYS2, IL6ST, ITGB1, ITGB2, MDM2, PIK3R3, PPP2CB, PPP2R5C, RHEB, SOS2, SYNJ1, YWHAE, YWHAG, YWHAQ
3-phosphoinositide Biosynthesis	1.53E+00	7.58E–02	–3.606	FIG4, PIK3R3, PIK3R4, PIP5K1B, PP2D1, PPP2CB, PPP2R5C, PTPN1, PTPN13, PTPN22, PTPRC, PTPRJ, SYNJ1, TPTE2, UBLCP1
Lymphotoxin b Receptor Signaling	1.51E+00	1.11E–01	–2.449	CYCS, ELP1, PIK3R3, PIK3R4, TRAF5, TRAF6
FAK Signaling	1.49E+00	8.62E–02	NaN	ACTB, ARHGAP26, EGF, ITGB1, ITGB2, PIK3R3, PIK3R4, PTK2, SOS2, TLN1
CNTF Signaling	1.44E+00	1.07E–01	–2.449	IL6ST, PIK3R3, PIK3R4, RPS6KA3, RPS6KA6, STAT1
Senescence Pathway	1.43E+00	6.80E–02	–2.84	ANAPC1, ANAPC4, ATR, BRAF, CACNA2D1, CDC16, CDC23, CHEK2, ELF1, EP400, ITPR2, MDM2, MRE11, NBN, PIK3R3, PIK3R4, PPP2CB, PPP2R5C, SOD2, TRAF6
ERK5 Signaling	1.41E+00	9.72E–02	–2.646	EGF, IL6ST, RPS6KA3, RPS6KA6, YWHAE, YWHAG, YWHAQ
Virus Entry via Endocytic Pathways	1.40E+00	8.65E–02	NaN	ACTB, AP3B1, AP3M1, CD55, CLTA, ITGB1, ITGB2, PIK3R3, PIK3R4
Regulation of Cellular Mechanics by Calpain Protease	1.40E+00	9.09E–02	NaN	CNGA3, CNGB1, CNGB3, EGF, ITGB1, ITGB2, PTK2, TLN1
RANK Signaling in Osteoclasts	1.37E+00	8.99E–02	–2.646	CBL, ELP1, MAPK8, MITF, PIK3R3, PIK3R4, TRAF5, TRAF6
Superpathway of Inositol Phosphate Compounds	1.35E+00	7.05E–02	–3.742	FIG4, PIK3R3, PIK3R4, PIP5K1B, PP2D1, PPIP5K2, PPP2CB, PPP2R5C, PTPN1, PTPN13, PTPN22, PTPRC, PTPRJ, SYNJ1, TPTE2, UBLCP1
Paxillin Signaling	1.35E+00	8.49E–02	–2.828	ACTB, ITGB1, ITGB2, MAPK8, PIK3R3, PIK3R4, PTK2, SOS2, TLN1
Ceramide Signaling	1.35E+00	8.89E–02	–1.134	CYCS, KSR1, MAPK8, NSMAF, PIK3R3, PIK3R4, PPP2CB, PPP2R5C
NRF2-mediated Oxidative Stress Response	1.33E+00	7.11E–02	–2.449	ABCC2, ACTB, AKR7A2, AOX1, DNAJC21, DNAJC8, EIF2AK3, FKBP5, GCLC, HACD3, MAPK8, MGST2, PIK3R3, PIK3R4, SOD2
Regulation of eIF4 and p70S6K Signaling	1.33E+00	7.43E–02	–0.816	EIF3E, EIF3H, EIF4G3, ITGB1, ITGB2, PIK3R3, PIK3R4, PPP2CB, PPP2R5C, RPS24, RPS3, RPS4Y1, SOS2
Inhibition of ARE-Mediated mRNA Degradation Pathway	1.31E+00	7.55E–02	–0.333	DDX6, PPP2CB, PPP2R5C, PSMA3, PSMC6, PSMD9, PSME4, TNFSF10, XRN1, YWHAE, YWHAG, YWHAQ

Identified IPA pathways are listed in descending order of the -log (P-value). Ratio, numbers of DEGs in the pathway was divided by that of genes included the pathway; z-score, negative z-scores indicates inactivation and vice versa. NaN means ineligible for analysis to assign the score.

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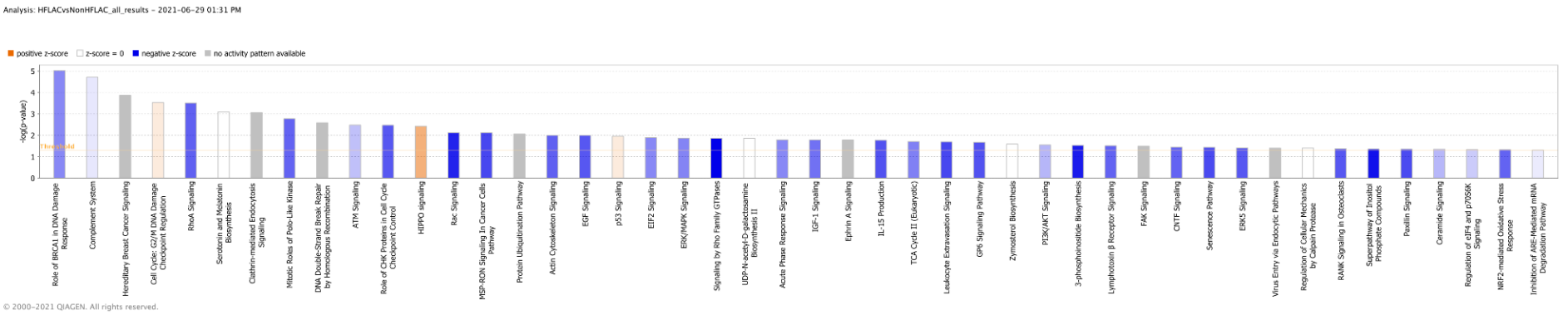

Figure S2 All 46 IPA pathways with a significant association with DEGs in high-grade fetal adenocarcinoma and common adenocarcinoma. The drawing was made through the IPA analysis, provided by the Ingenuity systems, QIAGEN. IPA, ingenuity pathway analysis; DEGs, differentially expressed genes.

A

19 DEGs
Gene Symbol
AGAP11
BEND3
C21orf91
CATSPER3
CNNM2
CSMD1
DGCR6
FIBIN
GRB10
KRT6C
MTPAP
MUC2
MUC3A
NTSR1
PLEKHA7
TBC1D26
VCX3B
DKFZP434K028
LOC728888

B

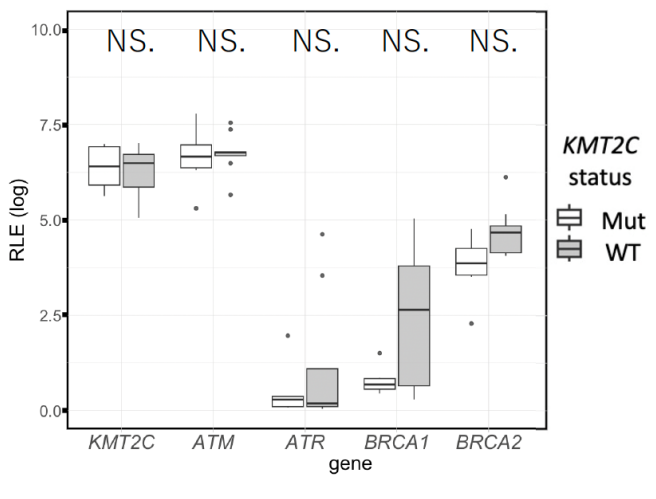

Figure S3 Comparison between high-grade fetal adenocarcinomas (H-FLACs) with and without *KMT2C* mutation. Gene expression obtained by RNA sequencing of six H-FLACs with *KMT2C* mutation was compared with ones without the mutations. (A) Symbols of 19 genes identified as DEGs. (B) Comparison of expression of *KMT2C*, *ATM*, *ATR*, *BRCA1*, and *BRCA2*. Boxplots were provided just as the ones in *Figure 3*. NS, non-significant; Mut, *KMT2C* mutation; WT, *KMT2C* wild type; DEGs, differentially expressed genes.

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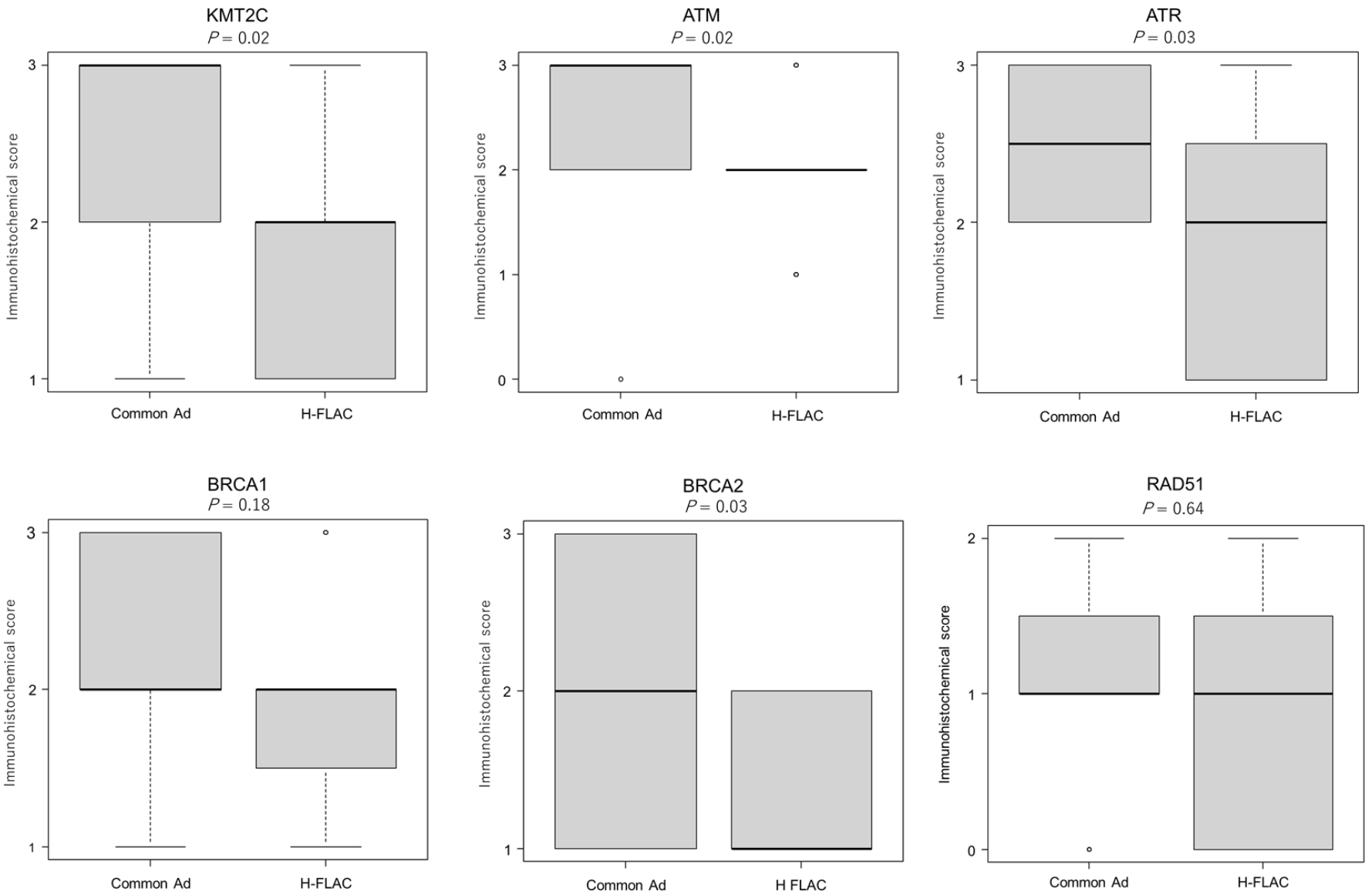

Figure S4 Boxplots of immunohistochemical expressions of KMT2C and HRR factors. Boxes indicate the first and the third quartile counts, lines in boxes indicate median values, and ends of whiskers indicate minimum and maximum values respectively. Dots demonstrate outliers. Common Ad, common adenocarcinoma; H-FLAC, high-grade fetal adenocarcinoma; HRR, homologous recombination repair.

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