

# **A Comprehensive Analysis of Metabolomics and Transcriptomics in Cervical Cancer**

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## Strategy of metabolite identification

First, peak lists and annotation results obtained by R package XCMS<sup>1</sup> and CAMERA<sup>2</sup> were analyzed to find quasi-molecular ions and determine the corresponding molecular weights.

Second, the exact molecular weights of the monoisotopic ions were used to search the online databases, such as HMDB<sup>3</sup> (<http://www.hmdb.ca/>), METLIN<sup>4</sup> (<http://metlin.scripps.edu/>) and MassBank<sup>5</sup> (<http://www.massbank.jp/>). The mass tolerance between the measured m/z values and the exact mass of the components of interest was set within 10 ppm.

Third, a Q-TOF mass analyzer (6520, Agilent) was used to produce fragmentation patterns and structure information for biomarker candidates in the MS/MS experiments. The MS/MS fragmentation patterns of the biomarkers were compared to the spectral data of metabolites that had the same m/z in HMDB, METLIN or MassBank.

Finally, if available, confirmation with standards was performed by comparison of retention time, isotopic distribution, and fragments of reference standards (Sigma-Aldrich) with those obtained in real samples.

Metabolite identification was classed into 4 levels based on the Metabolomics Standard Initiative<sup>6</sup>.

The first level (level 1): Metabolites are verified by reference standards.

The second level (level 2): Metabolites are identified based on accurate mass data, retention time, experimental MS/MS spectra, and library MS/MS spectra.

The third level (level 3): Metabolites are identified based on accurate mass data, retention time, experimental MS/MS spectra, and knowledge of characteristic MS/MS ions spectra.

The fourth level (level 4): Metabolites are speculated based on accurate mass data, retention time, and biological relevance. Metabolites in this level would be further validated in the future with the improvement of library spectra and availability of reference standards

## References

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**Supplementary Table S1: The detailed statistical and database information of metabolites in this study.**

No.	mode	m/z	RT(min)	PPM	Metabolite	HMDB/METLIN	PubChem	Level <sup>#</sup>	l <sub>f</sub> dr	VIP	FC	AUC
1	ESI+	146.1167	4.43	5.90	4-Trimethylammonio-butanoic acid	HMDB01161	134	3	5.01E-04	1.06	0.70	0.69
2	ESI+	147.1143	1.55	9.95	L-Lysine	HMDB00182	5962	1	4.66E-06	1.18	0.53	0.75
3	ESI+	169.0355	2.13	0.60	Uric acid	HMDB00289	1175	1	1.43E-03	1.02	0.77	0.51
4	ESI+	180.0654	5.62	0.72	Hippuric acid	HMDB00714	464	1	6.18E-05	1.09	0.40	0.65
5	ESI+	229.2159	12.79	1.21	Myristic acid	HMDB00806	11005	3	1.42E-07	1.31	0.64	0.76
6	ESI+	263.2369	13.31	8.87	Palmitaldehyde	HMDB01551	984	3	7.70E-06	1.39	0.71	0.75
7	ESI+	274.2742	6.69	0.19	Hexadecasphinganine	392316*	656816	3	4.76E-08	1.53	0.68	0.79
8	ESI+	277.2151	11.65	4.64	palmitoleic acid	HMDB03229	445638	3	2.80E-05	1.29	0.59	0.77
9	ESI+	302.3051	7.49	0.97	Sphinganine	HMDB00269	91486	4	4.66E-06	1.29	0.72	0.73
10	ESI+	328.3188	13.76	6.75	N,N-Dimethyl-sphingosine	HMDB13645	5282309	4	2.14E-14	1.91	0.60	0.90
11	ESI+	329.2476	12.88	0.14	Docosahexaenoic acid	HMDB02183	445580	3	1.79E-08	1.63	0.57	0.79
12	ESI+	353.2658	13.39	7.81	MG(0:0/18:3/0:0)	HMDB11539	11646044	4	3.43E-04	1.17	0.66	0.71
13	ESI+	357.241	11.88	2.81	Tetrahydrodeoxy-corticosterone	HMDB00879	101771	4	2.11E-10	1.77	0.54	0.76

14	ESI+	361.1999	6.38	2.97	Aldosterone	HMDB00037	24758425	4	4.66E-06	1.56	1.32	0.73
15	ESI+	384.3076	6.73	8.45	N-oleoyl threonine	75490*	52922063	3	1.77E-10	1.74	0.51	0.85
16	ESI+	466.315	6.49	2.80	Glycocholic Acid	HMDB00138	23617285	1	2.03E-05	1.04	2.38	0.69
17	ESI+	468.3085	8.09	0.11	LysoPC(14:0)	HMDB10379	460604	3	1.69E-14	1.81	0.45	0.86
18	ESI+	472.302	7.00	2.81	Chenodeoxy-glycocholic acid	HMDB06898	53477907	2	1.79E-08	1.34	2.45	0.76
19	ESI+	480.3428	10.31	4.20	LysoPC(P-16:0)	HMDB10407	10917802	3	1.06E-16	2.09	0.59	0.92
20	ESI+	482.3241	8.87	0.02	LysoPC(15:0)	HMDB10381	24779458	3	1.06E-16	2.12	0.49	0.92
21	ESI+	496.3407	9.80	1.84	LysoPC(16:0)	HMDB10382	460602	1	7.89E-20	2.33	0.68	0.94
22	ESI+	506.3587	10.77	3.62	CerP(d18:1/8:0)	83734*	10864091	3	3.38E-18	2.22	0.51	0.94
23	ESI+	510.3557	10.81	0.62	LysoPC(17:0)	HMDB12108	24779463	3	3.38E-18	2.18	0.51	0.94
24	ESI+	518.3242	8.17	0.11	LysoPC(18:3)	HMDB10387	52924045	3	7.25E-10	1.47	0.61	0.83
25	ESI+	522.3567	10.25	2.52	LysoPC(18:1)	HMDB02815	16081932	3	1.06E-13	1.92	0.67	0.88
26	ESI+	524.372	11.88	1.80	LysoPC(18:0)	HMDB10384	497299	1	6.33E-18	2.23	0.60	0.94
27	ESI+	536.3714	11.19	0.59	LysoPE(22:1)	HMDB11491	53480940	3	1.06E-17	2.15	0.54	0.93

28	ESI+	544.3375	10.23	4.07	LysoPC(20:4)	HMDB10395	24779476	3	2.16E-07	1.39	0.68	0.79
29	ESI+	546.3543	11.88	2.05	LysoPC(20:3)	HMDB10393	53480467	3	3.88E-09	1.55	0.64	0.83
30	ESI+	562.4223	12.92	1.45	CerP(d18:1/12:0)	HMDB10699	5283580	3	1.09E-12	1.79	0.56	0.88
31	ESI+	568.3401	8.93	0.57	LysoPC(22:6)	HMDB10404	10415542	3	4.66E-06	1.41	0.75	0.83
32	ESI+	570.3553	9.38	0.18	LysoPC(22:5)	HMDB10402	53480473	3	1.85E-03	1.21	0.78	0.82
33	ESI+	585.2709	6.35	0.26	Bilirubin	HMDB00054	5280352	1	1.94E-12	1.67	0.37	0.88
34	ESI+	777.6875	6.38	8.32	L-Thyroxine	HMDB00248	5819	1	1.33E-02	1.1	1.23	0.68
35	ESI-	87.0091	1.87	3.84	Pyruvate	HMDB00243	1060	2	5.43E-15	1.73	0.41	0.83
36	ESI-	105.0194	1.82	1.11	L-Glyceric acid	HMDB06372	6326776	3	2.68E-08	1.51	0.59	0.77
37	ESI-	133.0144	1.82	1.01	L-Malic acid	HMDB00156	222656	1	1.30E-03	1.10	0.48	0.60
38	ESI-	145.0134	1.88	5.64	Oxoglutaric acid	HMDB00208	51	2	2.21E-09	1.46	0.49	0.81
39	ESI-	154.0619	1.64	1.76	L-Histidine	HMDB00177	6274	1	4.62E-04	1.03	0.71	0.54
40	ESI-	174.0884	1.68	0.20	Citrulline	HMDB00904	9750	2	9.53E-05	1.12	0.67	0.62
41	ESI-	187.1338	6.97	0.66	3-Hydroxycapric acid	HMDB02203	26612	3	1.99E-05	1.14	0.65	0.71

42	ESI-	215.1635	1.68	8.39	12-Hydroxy-dodecanoic acid	HMDB02059	79034	3	1.47E-09	1.36	1.72	0.92
43	ESI-	249.0891	4.69	9.43	Threonyl-Methionine	HMDB29067	7020165	2	9.09E-06	1.23	1.68	0.77
44	ESI-	255.2335	13.97	2.30	Palmitic acid	HMDB00220	985	3	6.54E-05	1.01	0.55	0.69
45	ESI-	263.129	6.58	0.45	$\gamma$ -CEHC	44822*	15887183	2	9.09E-06	1.21	0.66	0.56
46	ESI-	275.2013	11.66	1.41	Stearidonic Acid	HMDB06547	5312508	3	5.26E-08	1.34	0.47	0.82
47	ESI-	277.2178	12.5	1.92	$\alpha$ -Linolenic Acid	HMDB01388	5280934	2	1.04E-06	1.14	0.57	0.75
48	ESI-	279.2341	13.33	4.26	Linoleic acid	HMDB00673	5280450	3	3.67E-06	1.11	0.61	0.72
49	ESI-	281.2496	14.05	3.57	Oleic Acid	HMDB00207	445639	3	2.83E-05	1.08	0.57	0.69
50	ESI-	297.2437	12.49	0.64	3-Oxooctadecanoic acid	HMDB10736	5283005	3	5.77E-07	1.29	0.69	0.77
51	ESI-	299.259	13.94	0.58	3R-hydroxy-octadecanoic acid	HMDB10737	5312838	3	1.20E-04	1.04	0.67	0.66
52	ESI-	321.2051	13.04	3.77	N1,N12-Diacetylspermine	HMDB02172	132680	4	2.26E-05	1.04	0.66	0.68
53	ESI-	329.249	13.32	1.11	Docosapentaenoic acid	HMDB06528	5497182	3	8.59E-06	1.23	0.54	0.71
54	ESI-	345.2051	12.5	5.87	21-Deoxycortisol	HMDB04030	222803	4	2.11E-07	1.33	0.64	0.76
55	ESI-	355.2648	13.6	1.52	Tetracosahexaenoic acid	HMDB02007	11792612	3	1.04E-11	1.52	0.35	0.82

56	ESI-	448.3073	7.00	1.10	Glycoursodeoxycholic acid	HMDB00708	12310288	2	1.81E-09	1.20	2.68	0.74
57	ESI-	480.3088	9.82	1.60	LysoPE(18:0)	HMDB11129	53480667	3	5.43E-15	1.42	0.75	0.88
58	ESI-	506.3255	10.28	0.60	LysoPE(20:1)	HMDB11482	53480931	3	3.67E-13	1.70	0.70	0.90
59	ESI-	566.5492	10.28	4.51	Cer(d18:0/18:0)	HMDB11761	5283573	3	1.39E-13	1.80	0.58	0.92
60	ESI-	588.5372	9.04	1.85	Cer(d18:2/20:1)	83726*	52931121	3	4.62E-04	1.03	0.70	0.82
61	ESI-	590.5532	9.69	2.40	Cer(d18:2/20:0)	83725*	52931120	3	9.09E-06	1.13	0.64	0.77
62	ESI-	608.3571	9.05	0.33	PGPC	45374*	46907872	3	9.09E-06	1.13	0.70	0.63

\*Referred database: METLIN ID.

# Metabolite identification was classed into 4 levels based on the Metabolomics Standard Initiative: 1. Metabolites are verified by reference standards. 2. Metabolites are identified based on accurate mass data, retention time, experimental MS/MS spectra, and library MS/MS spectra. 3. Metabolites are identified based on accurate mass data, retention time, experimental MS/MS spectra, and knowledge of characteristic MS/MS ions spectra. 4. Metabolites are speculated based on accurate mass data, retention time, and biological relevance.



**Supplementary Table S2: Metabolic pathway of metabolites in this study.**

<b>Pathway</b>	<b>Metabolites</b>	<b>biofunction</b>
Citrate cycle	Pyruvate, Oxoglutaric acid, L-Malic acid	Energy source,  Pyruvate metabolism, amino acid metabolism
Glycerophospholipid metabolism	LysoPC(14:0), LysoPC(15:0), LysoPC(16:0), LysoPC(P-16:0), LysoPC(17:0), LysoPC(18:0), LysoPC(18:1), LysoPC(18:3), LysoPC(20:3), LysoPC(20:4), LysoPC(22:5), LysoPC(22:6)	Cell signaling,  membrane integrity
Lysophospholipid metabolism	LysoPE(18:0), LysoPE(20:1) LysoPE(22:1)	Cell signaling,  membrane integrity
Sphingolipid metabolism	Sphinganine, Hexadecasphinganine, N,N-Dimethylsphingosine, Cer(d18:0/18:0), Cer(d18:2/20:0), Cer(d18:2/20:1), CerP(d18:1/12:0), CerP(d18:1/8:0)	Cell signaling,  membrane integrity
Steroid hormone biosynthesis	21-Deoxycortisol, Aldosterone, Tetrahydrodeoxycorticosterone	Cell signaling
Bile acid biosynthesis	Glycocholic Acid, Glycoursodeoxycholic acid, Chenodeoxyglycocholic acid	Cell signaling, fuel and energy source
Lysine metabolism	L-Lysine, 4-Trimethylammoniobutanoic acid	Aminoacyl-tRNA biosynthesis , amino acid metabolism
Phenylalanine metabolism	Hippuric acid	Aminoacyl-tRNA biosynthesis, amino acid metabolism
Tyrosine metabolism	L-Thyroxine	Oxidative

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		phosphorylation
Histidine metabolism	L-Histidine	Aminoacyl-tRNA biosynthesis, amino acid metabolism
Arginine biosynthesis	Citrulline	amino acid metabolism
Glycine, serine and threonine metabolism	L-Glyceric acid	Protein synthesis, amino acid metabolism
Protein catabolism	Threoninyl-Methionine, N-oleoyl threonine	Not Available
Vitamin E metabolism	$\gamma$ -CEHC	Antioxidant activity, Natriuresis
Purine metabolism	Uric acid	Not Available
Porphyrin and chlorophyll metabolism	Bilirubin	Heme degradation
Glutathione metabolism	12-Hydroxydodecanoic acid	Cell signaling, membrane integrity, fuel and energy source
Fatty acid degradation	3-Hydroxycapric acid, Palmitaldehyde	Cell signaling, membrane integrity, fuel and energy source
Fatty acid metabolism	3-Oxo-octadecanoic acid, Tetracosahexanoic acid	Cell signaling, membrane integrity, fuel and energy source
Fatty acid biosynthesis	3R-hydroxy-octadecanoic acid, palmitoleic acid, Myristic acid	Cell signaling, membrane integrity, fuel

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		and energy source
Biosynthesis of unsaturated fatty acids	Oleic Acid, Palmitic acid, Docosahexaenoic acid, docosapentaenoic acid, Linoleic acid	Cell signaling, membrane integrity, fuel and energy source
alpha-Linolenic acid metabolism	Stearidonic Acid, $\alpha$ -Linolenic Acid	Cell signaling, membrane integrity, fuel and energy source
Other	N1,N12-Diacetylspermine, MG(0:0/18:3/0:0), PGPC	

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**Supplementary Table S3: the clustering results of all metabolites based on their metabolic profiling.**

<b>Cluster</b>	<b>Metabolites</b>
Cluster1	3R-hydroxy-octadecanoic acid, L-Histidine, L-Lysine, 4-Trimethylammoniobutanoic acid, L-Glyceric acid, Hippuric acid, Citrulline, L-Malic acid, Oxoglutaric acid, $\gamma$ -CEHC, Bilirubin, PGPC
Cluster2	$\alpha$ -Linolenic Acid, Docosapentaenoic acid, Docosahexaenoic acid, Linoleic acid, Palmitic acid, Oleic Acid, Myristic acid, Tetracosahexaenoic acid, 3-Oxo-octadecanoic acid, Palmitaldehyde, 3-Hydroxycapric acid, 21-Deoxycortisol, N1,N12-Diacetylspermine
Cluster3	Stearidonic Acid, palmitoleic acid, LysoPC(14:0), LysoPC(15:0), LysoPC(16:0), LysoPC(P-16:0), LysoPC(17:0), LysoPC(18:0), LysoPC(18:1), LysoPC(18:3), LysoPC(22:6), LysoPC(22:5), LysoPE(18:0), LysoPE(20:1), LysoPE(22:1), CerP(d18:1/8:0), CerP(d18:1/12:0), Cer(d18:0/18:0), Cer(d18:2/20:0), Cer(d18:2/20:1), N,N-Dimethylsphingosine, Sphinganine, C16 Sphinganine
Cluster4	LysoPC(20:3), LysoPC(20:4), Tetrahydrodeoxycorticosterone, N-oleoyl threonine, Pyruvate, Uric acid, MG(0:0/18:3/0:0)
Cluster5	Glycocholic Acid, Chenodeoxyglycocholic acid, Glycoursodeoxycholic acid, Aldosterone, L-Thyroxine, Threoninyl-Methionine, 12-Hydroxydodecanoic acid

**Supplementary Table S4: Result from pathway analysis of the 62 metabolites conducted in metaboAnalyst.**

<b>Pathway</b>	<b>Total</b>	<b>Hits</b>	<b>Raw P</b>	<b>FDR</b>	<b>Impact</b>
Fatty acid biosynthesis	49	4	0.0019	0.1509	0
Glyoxylate and dicarboxylate metabolism	50	3	0.0174	0.5422	0.0571
Citrate cycle (TCA cycle)	20	2	0.0203	0.5422	0.1294
Lysine biosynthesis	32	2	0.0489	0.9354	0.0999
Histidine metabolism	44	2	0.0859	0.9354	0.1399
Lysine degradation	47	2	0.0962	0.9354	0.1523
Steroid hormone biosynthesis	99	3	0.0968	0.9354	0.0284
Fatty acid metabolism	50	2	0.1069	0.9354	0.0448
D-Glutamine and D-glutamate metabolism	11	1	0.1169	0.9354	0
Biotin metabolism	11	1	0.1169	0.9354	0
Linoleic acid metabolism	15	1	0.1561	1	0.6563
Aminoacyl-tRNA biosynthesis	75	2	0.2048	1	0.0563
Alanine, aspartate and glutamate metabolism	24	1	0.2382	1	0
Sphingolipid metabolism	25	1	0.2468	1	0.1402
Fatty acid elongation in mitochondria	27	1	0.2638	1	0
beta-Alanine metabolism	28	1	0.2722	1	0
alpha-Linolenic acid metabolism	29	1	0.2804	1	0.2034
Pyruvate metabolism	32	1	0.3047	1	0
Vitamin B6 metabolism	32	1	0.3047	1	0.0191
Glycerolipid metabolism	32	1	0.3047	1	0.0206

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Pentose phosphate pathway	32	1	0.3047	1	0.0218
Nitrogen metabolism	39	1	0.3582	1	0
Glycerophospholipid metabolism	39	1	0.3582	1	0.0032
Butanoate metabolism	40	1	0.3655	1	0
Ascorbate and aldarate metabolism	45	1	0.4009	1	0
Phenylalanine metabolism	45	1	0.4009	1	0.0315
Primary bile acid biosynthesis	47	1	0.4145	1	0.0085
Glycine, serine and threonine metabolism	48	1	0.4212	1	0.0005
Tyrosine metabolism	76	1	0.5815	1	0
Arginine and proline metabolism	77	1	0.5863	1	0.02
Purine metabolism	92	1	0.6529	1	0.0097

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**Supplementary Table S5: The detailed statistical information of differentially expressed genes in this study.**

Gene	lfd	FC	Gene	lfd	FC	Gene	lfd	FC
HNMT	3.94E-09	0.80	COMT	4.50E-04	0.90	DLST	7.00E-03	1.22
CYP3A4	1.34E-08	0.79	COLGALT1	4.50E-04	1.09	SULT1E1	7.00E-03	0.78
UGT2B28	2.38E-08	0.66	AKR1C4	9.07E-04	1.03	UGT2A3	7.00E-03	0.97
WHSC1	8.48E-08	1.18	ALDH3B1	9.07E-04	0.85	GLYCTK	7.09E-03	0.84
DDC	1.17E-07	0.90	HSD17B8	9.07E-04	0.90	GRHPR	1.06E-02	0.97
BBOX1	1.17E-07	0.53	SHMT2	9.07E-04	1.06	IDH3G	1.06E-02	0.93
HSD11B1	1.17E-07	1.75	HSD17B1	9.07E-04	0.90	HSD17B2	1.06E-02	0.71
UGT2B15	2.76E-07	0.63	ACSL4	1.14E-03	0.80	ACSBG1	1.06E-02	0.98
SDHB	2.76E-07	1.25	GCDH	1.14E-03	0.86	HAL	1.06E-02	0.56
STS	1.11E-06	0.93	MDH2	1.14E-03	0.90	PCCA	1.06E-02	0.97
SULT2B1	1.39E-06	0.66	GLUL	1.14E-03	0.81	KMT2B	1.06E-02	0.97
KMT2A	1.39E-06	0.93	ALDH3B2	1.30E-03	0.78	CYP11B1	1.22E-02	0.98
SUV39H2	2.58E-06	1.28	ALDH1B1	1.30E-03	0.85	SUCLG1	1.22E-02	0.97
CYP19A1	2.58E-06	0.95	ACLY	1.30E-03	1.39	UGT2B4	1.28E-02	0.98
CYP11A1	2.58E-06	0.86	AKR1C3	1.31E-03	0.74	SDHD	1.35E-02	0.99
CYP3A5	2.58E-06	0.61	HSD17B12	1.61E-03	0.96	OGDH	1.74E-02	0.90
UGT2A1	2.58E-06	0.75	ALDH2	1.61E-03	0.92	ACSL1	1.74E-02	0.95
UGT2A2	2.58E-06	0.75	SRD5A1	1.61E-03	0.92	HSD3B1	1.74E-02	0.98
HYKK	1.28E-05	0.89	UGT2B17	1.61E-03	0.65	ALDH7A1	1.74E-02	0.92
CYP1A2	2.63E-05	0.84	DOT1L	1.61E-03	1.25	IDH2	1.74E-02	0.93

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SUV39H1	3.45E-05	1.16	UGT1A10	2.72E-03	1.05	FASN	1.74E-02	0.98
OLAH	3.45E-05	0.90	UGT1A3	2.72E-03	1.05	PGP	1.74E-02	1.10
COLGALT2	3.45E-05	0.88	UGT1A4	2.72E-03	1.05	CAMKMT	1.74E-02	1.11
PLOD2	3.46E-05	1.90	UGT1A5	2.72E-03	1.05	SETDB2	1.74E-02	1.10
EHMT2	3.46E-05	0.91	UGT1A7	2.72E-03	1.05	SETD7	1.74E-02	0.96
AKR1C2	3.46E-05	1.04	UGT1A8	2.72E-03	1.05	HSD17B6	1.74E-02	1.32
KMT2D	9.41E-05	0.87	UGT1A9	2.72E-03	1.05	CYP7A1	2.53E-02	0.98
ASH1L	9.41E-05	0.79	HOGA1	2.72E-03	1.05	PIPOX	2.53E-02	1.06
WHSC1L1	9.41E-05	1.13	SRD5A2	2.90E-03	1.08	KMT2E	2.53E-02	1.05
UGT1A6	9.41E-05	0.92	ACSL6	3.29E-03	0.97	SETD2	4.16E-02	0.87
ACAT1	1.83E-04	0.96	SRD5A3	3.29E-03	0.81	CNDP2	4.16E-02	0.98
FH	1.83E-04	0.83	SDHA	3.84E-03	1.10	CYP17A1	4.40E-02	0.95
CYP2E1	2.09E-04	1.31	NSD1	3.84E-03	1.25	GLDC	4.40E-02	1.40
ACACB	2.37E-04	0.98	MAOB	4.33E-03	0.83	PCK1	4.40E-02	1.02
AOC1	2.37E-04	0.69	MAOA	4.33E-03	0.86	DLAT	4.40E-02	1.09
FTCD	2.37E-04	0.93	ALDH9A1	4.73E-03	0.95	PCCB	4.40E-02	1.09
SETMAR	4.50E-04	1.17	CYP11B2	4.73E-03	1.06	HAO1	4.40E-02	0.98
CYP3A7	4.50E-04	0.98	PLOD3	7.00E-03	1.25	ACO1	4.40E-02	1.04
AGXT	4.50E-04	0.97	SETDB1	7.00E-03	1.10	SDHC	4.40E-02	1.09

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**Supplementary Table S6: . The detailed gene name and functional information of differentially expressed genes in this study.**

<b>Gene Symbol</b>	<b>Gene Name</b>	<b>PANTHER GO-Slim Molecular Function</b>
HNMT	Histamine N-methyltransferase	methyltransferase activity(GO:0003824)
CYP3A4	Cytochrome P450 3A4	oxidoreductase activity(GO:0003824)
DDC	Aromatic-L-amino-acid decarboxylase	carboxy-lyase activity(GO:0003824)
WHSC1	Histone-lysine N-methyltransferase NSD2	
UGT2B28	UDP-glucuronosyltransferase 2B28	transferase activity, transferring glycosyl groups(GO:0003824)
SUV39H2	Histone-lysine N-methyltransferase SUV39H2	
SULT2B1	Sulfotransferase family cytosolic 2B member 1	transferase activity(GO:0003824)
STS	Steryl-sulfatase	hydrolase activity(GO:0003824)
UGT2B15	UDP-glucuronosyltransferase 2B15	transferase activity, transferring glycosyl groups(GO:0003824)
SDHB	Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial	oxidoreductase activity(GO:0003824)
KMT2A	Histone-lysine N-methyltransferase 2A	
HSD11B1	Corticosteroid 11-beta-dehydrogenase isozyme 1	oxidoreductase activity(GO:0003824)
BBOX1	Gamma-butyrobetaine dioxygenase	oxidoreductase activity(GO:0003824)
CYP19A1	Aromatase	oxidoreductase activity(GO:0003824)
CYP11A1	Cholesterol side-chain cleavage enzyme, mitochondrial	oxidoreductase activity(GO:0003824)
CYP3A5	Cytochrome P450 3A5	oxidoreductase activity(GO:0003824)
UGT2A1	UDP-glucuronosyltransferase 2A1	transferase activity, transferring glycosyl groups(GO:0003824)
UGT2A2	UDP-glucuronosyltransferase 2A1	transferase activity, transferring glycosyl groups(GO:0003824)
HYKK	Hydroxylysine kinase	
CYP1A2	Cytochrome P450 1A2	oxidoreductase activity(GO:0003824)
SUV39H1	Histone-lysine N-methyltransferase SUV39H1	
OLAH	S-acyl fatty acid synthase thioesterase, medium chain	

COLGALT2	Procollagen galactosyltransferase 2	oxidoreductase activity(GO:0003824)
PLOD2	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	
EHMT2	Histone-lysine N-methyltransferase EHMT2	
AKR1C2	Aldo-keto reductase family 1 member C2	oxidoreductase activity(GO:0003824);transporter activity(GO:0016491)
KMT2D	Histone-lysine N-methyltransferase 2D	
ASH1L	Histone-lysine N-methyltransferase ASH1L	
WHSC1L1	Histone-lysine N-methyltransferase NSD3	
UGT1A6	UDP-glucuronosyltransferase 1-6	transferase activity, transferring glycosyl groups(GO:0003824)
ACAT1	Acetyl-CoA acetyltransferase, mitochondrial	acetyltransferase activity(GO:0003824)
FH	Fumarate hydratase, mitochondrial	
CYP2E1	Cytochrome P450 2E1	oxidoreductase activity(GO:0003824)
ACACB	Acetyl-CoA carboxylase 2	ligase activity(GO:0003824)
AOC1	Amiloride-sensitive amine oxidase [copper-containing]	
FTCD	Formimidoyltransferase-cyclodeaminase	deaminase activity(GO:0003824);hydrolase activity(GO:0019239);transferase activity(GO:0016787)
SETMAR	Histone-lysine N-methyltransferase SETMAR	
CYP3A7	Cytochrome P450 3A7	oxidoreductase activity(GO:0003824)
AGXT	Serine--pyruvate aminotransferase	transaminase activity(GO:0003824)
COMT	Catechol O-methyltransferase	methyltransferase activity(GO:0003824)
COLGALT1	Procollagen galactosyltransferase 1	oxidoreductase activity(GO:0003824)
AKR1C4	Aldo-keto reductase family 1 member C4	oxidoreductase activity(GO:0003824);transporter activity(GO:0016491)
ALDH3B1	Aldehyde dehydrogenase family 3 member B1	oxidoreductase activity(GO:0003824)
HSD17B8	Estradiol 17-beta-dehydrogenase 8	oxidoreductase activity(GO:0003824)

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SHMT2	Serine hydroxymethyltransferase, mitochondrial	methyltransferase activity(GO:0003824)
HSD17B1	Estradiol 17-beta-dehydrogenase 1	oxidoreductase activity(GO:0003824)
ACSL4	Long-chain-fatty-acid--CoA ligase 4	ligase activity(GO:0003824);transporter activity(GO:0016874)
GCDH	Glutaryl-CoA dehydrogenase, mitochondrial	nucleotide binding(GO:0005488);oxidoreductase activity(GO:0000166)
MDH2	Malate dehydrogenase, mitochondrial	oxidoreductase activity(GO:0003824)
GLUL	Glutamine synthetase	ligase activity(GO:0003824)
ALDH3B2	Aldehyde dehydrogenase family 3 member B2	oxidoreductase activity(GO:0003824)
ALDH1B1	Aldehyde dehydrogenase X, mitochondrial	oxidoreductase activity(GO:0003824)
ACLY	ATP-citrate synthase	ligase activity(GO:0003824);lyase activity(GO:0016874);transferase activity(GO:0016829)
AKR1C3	Aldo-keto reductase family 1 member C3	oxidoreductase activity(GO:0003824);transporter activity(GO:0016491)
HSD17B12	Very-long-chain 3-oxoacyl-CoA reductase	oxidoreductase activity(GO:0003824)
ALDH2	Aldehyde dehydrogenase, mitochondrial	oxidoreductase activity(GO:0003824)
SRD5A1	3-oxo-5-alpha-steroid 4-dehydrogenase 1	oxidoreductase activity(GO:0003824)
UGT2B17	UDP-glucuronosyltransferase 2B17	transferase activity, transferring glycosyl groups(GO:0003824)
DOT1L	Histone-lysine N-methyltransferase, H3 lysine-79 specific	methyltransferase activity(GO:0003824)
UGT1A10	UDP-glucuronosyltransferase 1-10	transferase activity, transferring glycosyl groups(GO:0003824)
UGT1A3	UDP-glucuronosyltransferase 1-3	transferase activity, transferring glycosyl groups(GO:0003824)
UGT1A4	UDP-glucuronosyltransferase 1-4	transferase activity, transferring glycosyl groups(GO:0003824)
UGT1A5	UDP-glucuronosyltransferase 1-5	transferase activity, transferring glycosyl groups(GO:0003824)
UGT1A7	UDP-glucuronosyltransferase 1-7	transferase activity, transferring glycosyl groups(GO:0003824)
UGT1A8	UDP-glucuronosyltransferase 1-8	transferase activity, transferring glycosyl groups(GO:0003824)
UGT1A9	UDP-glucuronosyltransferase 1-9	transferase activity, transferring glycosyl groups(GO:0003824)
HOGA1	4-hydroxy-2-oxoglutarate aldolase, mitochondrial	lyase activity(GO:0003824)

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SRD5A2	3-oxo-5-alpha-steroid 4-dehydrogenase 2	oxidoreductase activity(GO:0003824)
ACSL6	Long-chain-fatty-acid--CoA ligase 6	ligase activity(GO:0003824);transporter activity(GO:0016874)
SRD5A3	Polyprenol reductase	
SDHA	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial	oxidoreductase activity(GO:0003824)
NSD1	Histone-lysine N-methyltransferase, H3 lysine-36 and H4 lysine-20 specific	
MAOB	Amine oxidase [flavin-containing] B	DNA-methyltransferase activity(GO:0003824);nucleic acid binding(GO:0016740);oxidoreductase activity(GO:0008168)
MAOA	Amine oxidase [flavin-containing] A	DNA-methyltransferase activity(GO:0003824);nucleic acid binding(GO:0016740);oxidoreductase activity(GO:0008168)
ALDH9A1	4-trimethylaminobutyraldehyde dehydrogenase	oxidoreductase activity(GO:0003824)
CYP11B2	Cytochrome P450 11B2, mitochondrial	oxidoreductase activity(GO:0003824)
PLOD3	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 3	
SETDB1	Histone-lysine N-methyltransferase SETDB1	
DLST	Dihydrolipoyllysine-residue succinyltransferase component of 2-oxoglutarate dehydrogenase complex, mitochondrial	acetyltransferase activity(GO:0003824)
SULT1E1	Estrogen sulfotransferase	transferase activity(GO:0003824)
UGT2A3	UDP-glucuronosyltransferase 2A3	transferase activity, transferring glycosyl groups(GO:0003824)
GLYCTK	Glycerate kinase	kinase activity(GO:0003824)
GRHPR	Glyoxylate reductase/hydroxypyruvate reductase	oxidoreductase activity(GO:0003824)
IDH3G	Isocitrate dehydrogenase [NAD] subunit gamma, mitochondrial	oxidoreductase activity(GO:0003824)
HSD17B2	Estradiol 17-beta-dehydrogenase 2	oxidoreductase activity(GO:0003824)
ACSBG1	Long-chain-fatty-acid--CoA ligase ACSBG1	ligase activity(GO:0003824);transporter activity(GO:0016874)
HAL	Histidine ammonia-lyase	

PCCA	Propionyl-CoA carboxylase alpha chain, mitochondrial	ligase activity(GO:0003824)
KMT2B	Histone-lysine N-methyltransferase 2B	
CYP11B1	Cytochrome P450 11B1, mitochondrial	oxidoreductase activity(GO:0003824)
SUCLG1	Succinyl-CoA ligase [ADP/GDP-forming] subunit alpha, mitochondrial	ligase activity(GO:0003824)
UGT2B4	UDP-glucuronosyltransferase 2B4	transferase activity, transferring glycosyl groups(GO:0003824)
SDHD	Succinate dehydrogenase [ubiquinone] cytochrome b small subunit, mitochondrial	oxidoreductase activity(GO:0003824)
OGDH	2-oxoglutarate dehydrogenase, mitochondrial	oxidoreductase activity(GO:0003824)
ACSL1	Long-chain-fatty-acid--CoA ligase 1	ligase activity(GO:0003824);transporter activity(GO:0016874)
HSD3B1	3 beta-hydroxysteroid dehydrogenase/Delta 5--4-isomerase type 1	hydro-lyase activity(GO:0003824);oxidoreductase activity(GO:0016829);racemase and epimerase activity(GO:0016836)
ALDH7A1	Alpha-aminoadipic semialdehyde dehydrogenase	oxidoreductase activity(GO:0003824)
IDH2	Isocitrate dehydrogenase [NADP], mitochondrial	
FASN	Fatty acid synthase	hydrolase activity, acting on ester bonds(GO:0003824);ligase activity(GO:0016787);methyltransferase activity(GO:0016788);transferase activity, transferring acyl groups(GO:0016874)
PGP	Phosphoglycolate phosphatase	hydrolase activity(GO:0003824)
CAMKMT	Calmodulin-lysine N-methyltransferase	
SETDB2	Histone-lysine N-methyltransferase SETDB2	
SETD7	Histone-lysine N-methyltransferase SETD7	kinase activity(GO:0003824)
HSD17B6	17-beta-hydroxysteroid dehydrogenase type 6	oxidoreductase activity(GO:0003824)
CYP7A1	Cholesterol 7-alpha-monooxygenase	oxidoreductase activity(GO:0003824)

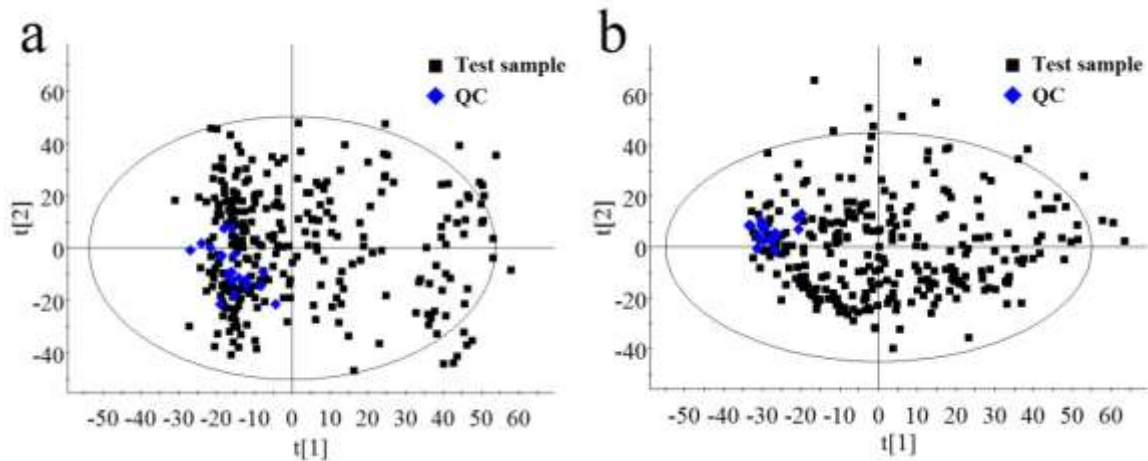
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PIPOX	Peroxisomal sarcosine oxidase	oxidoreductase activity(GO:0003824)
KMT2E	Histone-lysine N-methyltransferase 2E	
SETD2	Histone-lysine N-methyltransferase SETD2	
CNDP2	Cytosolic non-specific dipeptidase	deacetylase activity(GO:0003824);metallopeptidase activity(GO:0016787)
CYP17A1	Steroid 17-alpha-hydroxylase/17,20 lyase	
GLDC	Glycine dehydrogenase (decarboxylating), mitochondrial	binding(GO:0005488);oxidoreductase activity(GO:0003824)
PCK1	Phosphoenolpyruvate carboxykinase, cytosolic [GTP]	carboxy-lyase activity(GO:0003824)
DLAT	Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial	acetyltransferase activity(GO:0003824)
PCCB	Propionyl-CoA carboxylase beta chain, mitochondrial	ligase activity(GO:0003824)
HAO1	Hydroxyacid oxidase 1	isomerase activity(GO:0003824);ligase activity(GO:0016853);oxidoreductase activity(GO:0016874)
ACO1	Cytoplasmic aconitate hydratase	hydro-lyase activity(GO:0003824)
SDHC	Succinate dehydrogenase cytochrome b560 subunit, mitochondrial	

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**Supplementary Table S7: KEGG pathways of differentially expressed genes in this study.**

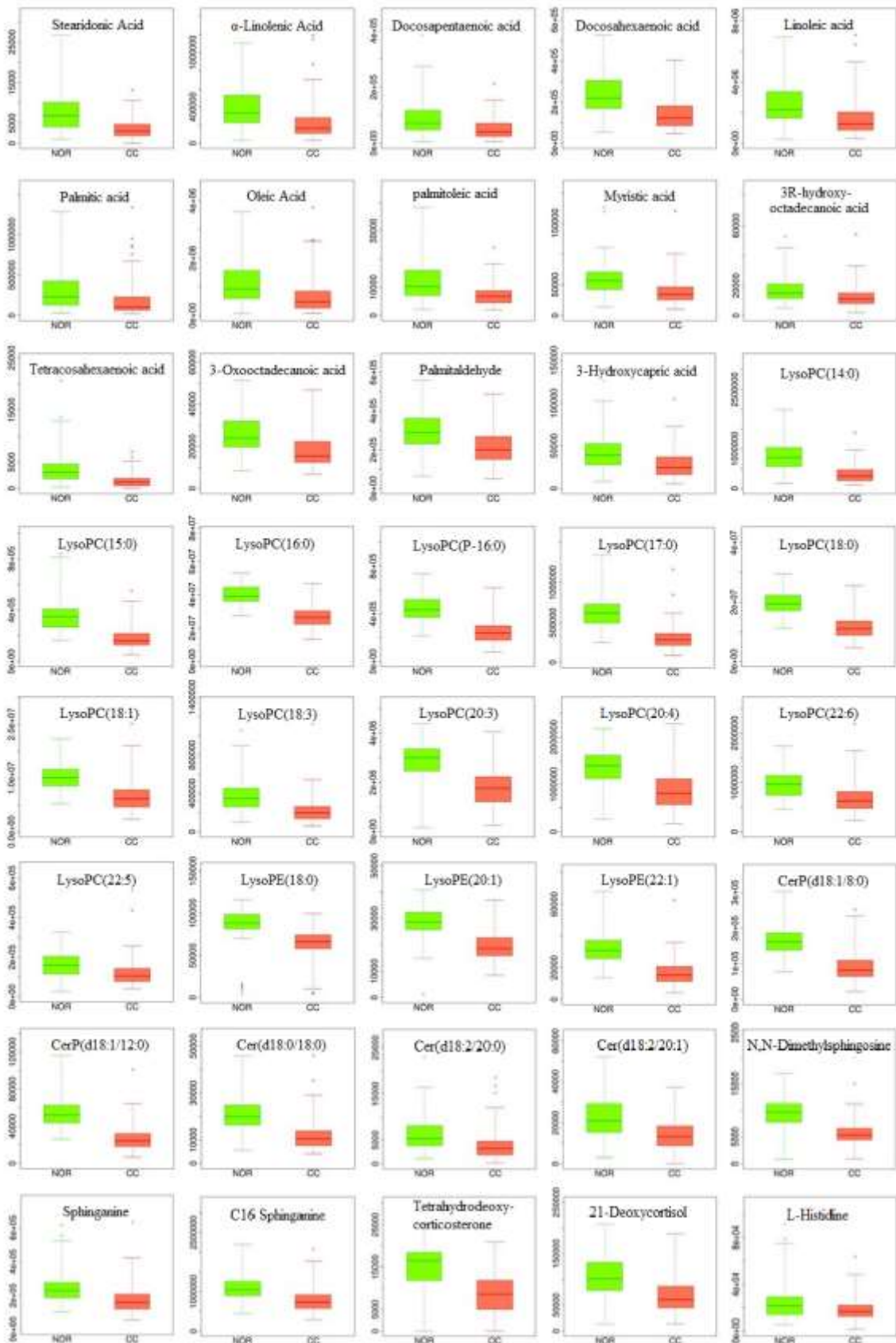
<b>Pathway</b>	<b>genes</b>
Fatty acid biosynthesis	ACACB, ACSBG1, ACSL1, ACSL4, ACSL6, FASN, OLAH
Glyoxylate and dicarboxylate metabolism	ACAT1, ACO1, AGXT, GLDC, GLUL, GLYCTK, GRHPR, HAO1, HOGA1, MDH2, PCCA, PCCB, PGP, SHMT2
Citrate cycle (TCA cycle)	ACLY, ACO1, DLAT, DLST, FH, IDH2, IDH3G, MDH2, OGDH, PCK1, SDHA, SDHB, SDHC, SDHD, SUCLG1
Lysine biosynthesis	ALDH7A1
Histidine metabolism	ALDH1B1, ALDH2, ALDH3B1, ALDH3B2, ALDH7A1, ALDH9A1, AOC1, CNDP2, DDC, FTCD, HAL, HNMT, MAOA, MAOB
Lysine degradation	ACAT1, ALDH1B1, ALDH2, ALDH7A1, ALDH9A1, ASH1L, BBOX1, CAMKMT, COLGALT1, COLGALT2, DLST, DOT1L, EHMT2, GCDH, HYKK, KMT2A, KMT2B, KMT2D, KMT2E, NSD1, OGDH, PIPOX, PLOD2, PLOD3, SETD2, SETD7, SETDB1, SETDB2, SETMAR, SUV39H1, SUV39H2, WHSC1, WHSC1L1
Steroid hormone biosynthesis	AKR1C2, AKR1C3, AKR1C4, COMT, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP1A2, CYP2E1, CYP3A4, CYP3A5, CYP3A7, CYP7A1, HSD11B1, HSD17B1, HSD17B12, HSD17B2, HSD17B6, HSD17B8, HSD3B1, SRD5A1, SRD5A2, SRD5A3, STS, SULT1E1, SULT2B1, UGT1A10, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT2A1, UGT2A2, UGT2A3, UGT2B15, UGT2B17, UGT2B28, UGT2B4

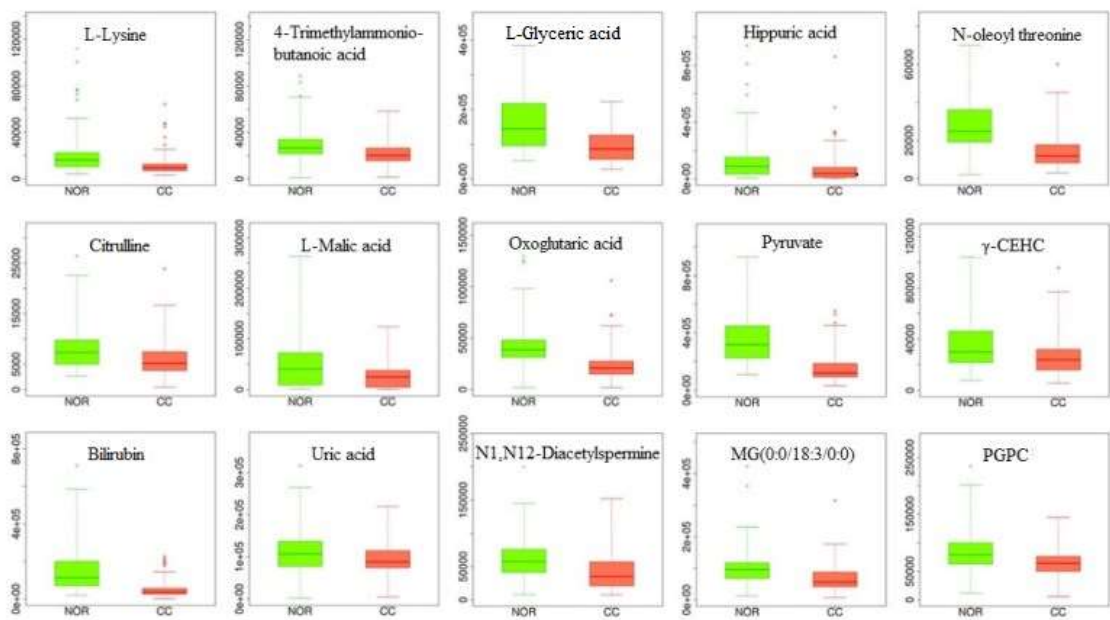


**Supplementary Figure S1:** (A)PCA score plot for test samples and QCs (quality control) in ESI+ mode. (B)PCA score plot for test samples and QCs (quality control) in ESI- mode.

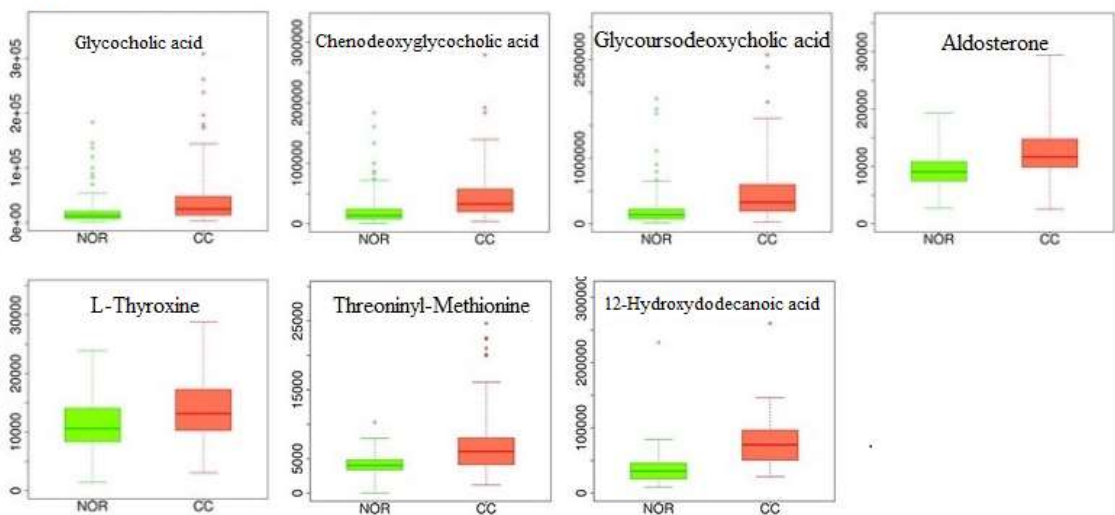


a

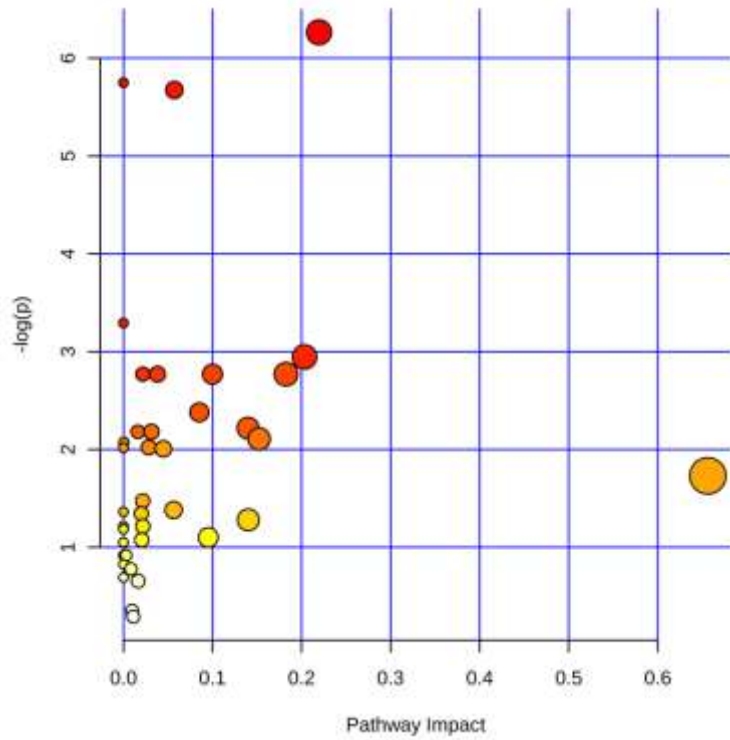




**b**



**Supplementary Figure S2:** (A) box plots for metabolites down-regulated in cervical cancer patients. (B).boxplot plots for metabolites up-regulated in cervical cancer patients.



**Supplementary Figure S3:** Summary of the pathway analysis.