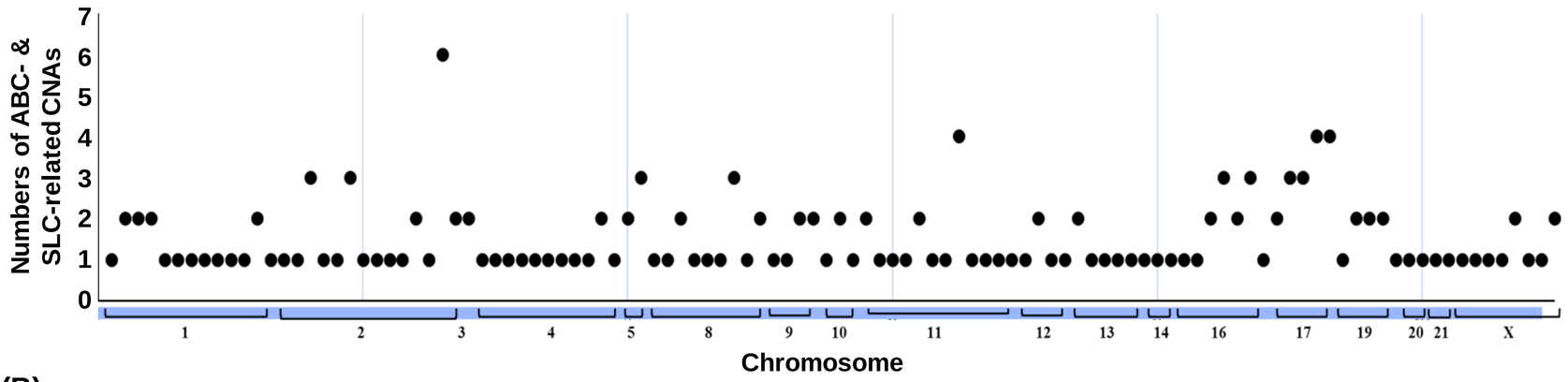
Supplementary Information Contents:

Additional file: Supplementary Figures 1-4

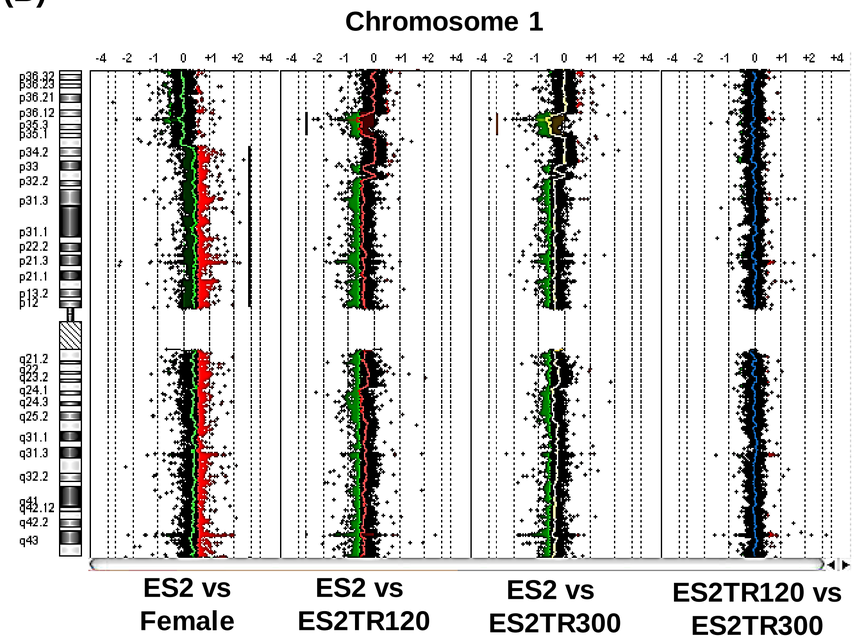
Manuscript:

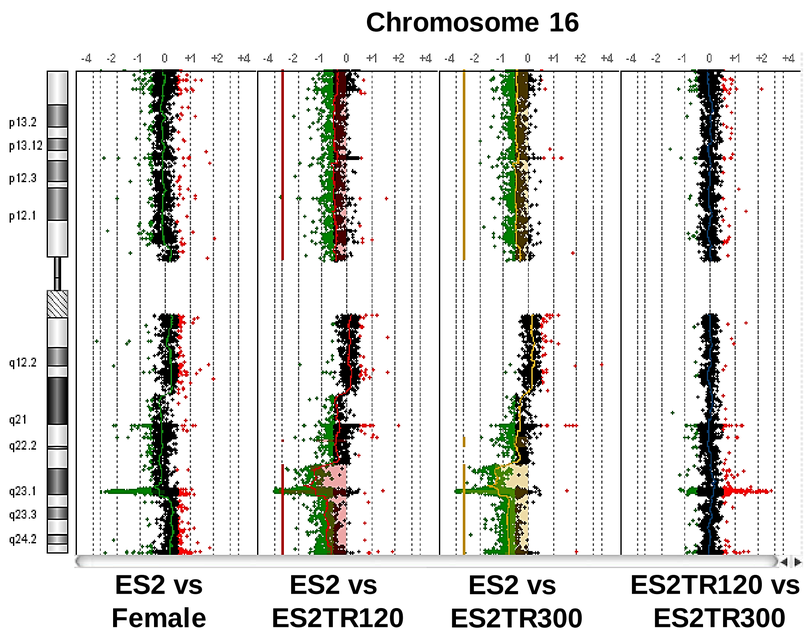
Paclitaxel resistance of ovarian clear cell carcinoma reveals the *ABC* and *SLC* transporter genes to mediate glycolytic metabolism

(A)

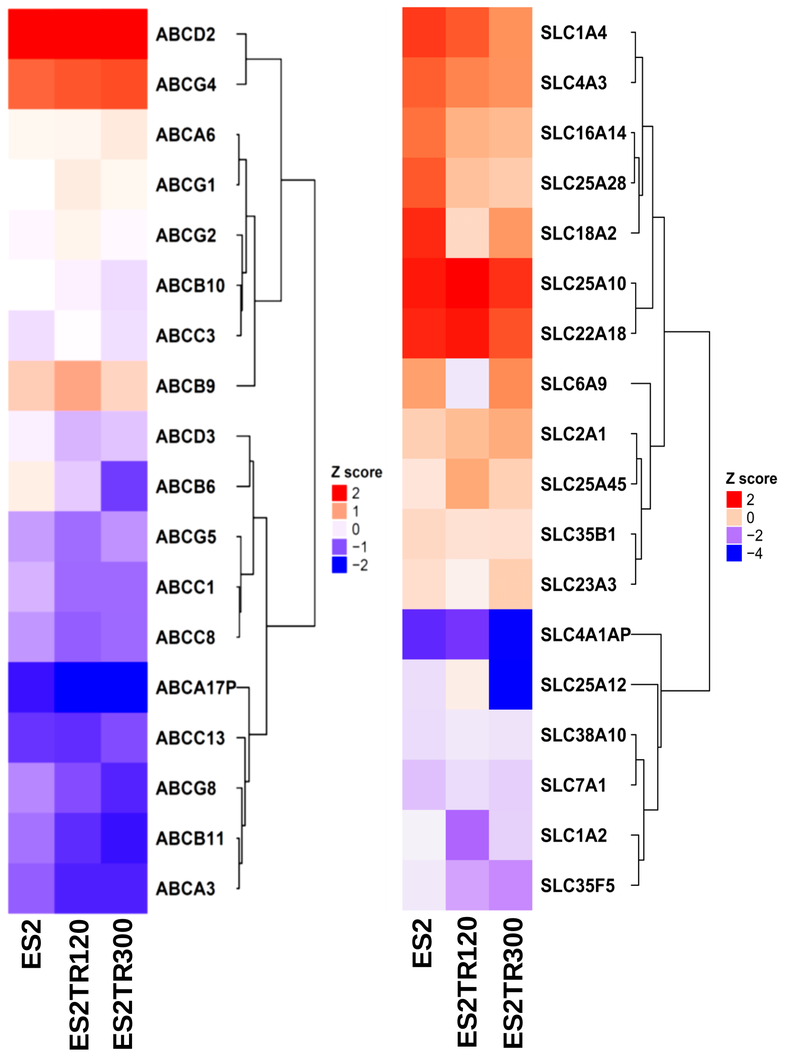

Numbers of ABC- & SLC-related CNAs
0
1
2
3
4
5
6
7
1
2
3
4
5
8
9
10
11
12
13
14
16
17
19
20
21
X
Chromosome

(B)


Chromosome 1
ES2 vs Female
ES2 vs ES2TR120
ES2 vs ES2TR300
ES2TR120 vs ES2TR300


Chromosome 16
ES2 vs Female
ES2 vs ES2TR120
ES2 vs ES2TR300
ES2TR120 vs ES2TR300

(C)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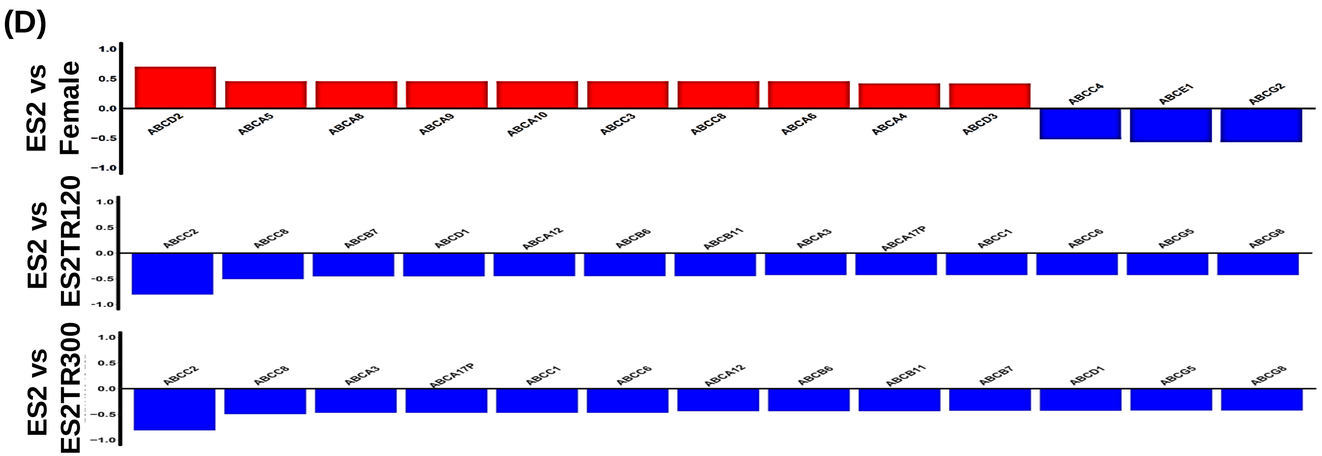
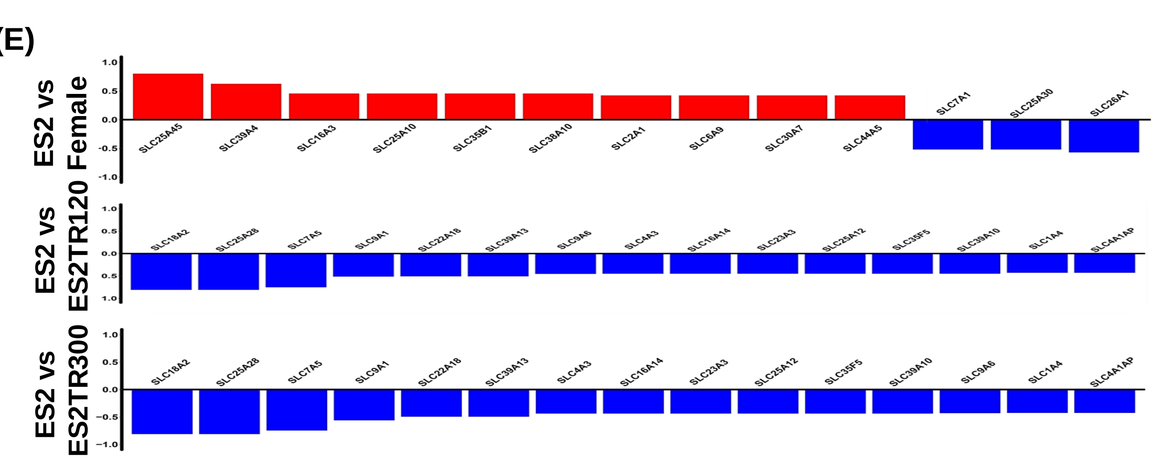
ABCA6
ABCG1
ABCG2
ABCB10
ABCC3
ABCB9
ABCD3
ABCB6
ABCG5
ABCC1
ABCC8
ABCA17P
ABCC13
ABCG8
ABCB11
ABCA3
ES2
ES2TR120
ES2TR300
Z score
SLC1A4
SLC4A3
SLC16A14
SLC25A28
SLC18A2
SLC25A10
SLC22A18
SLC6A9
SLC2A1
SLC25A45
SLC35B1
SLC23A3
SLC4A1AP
SLC25A12
SLC38A10
SLC7A1
SLC1A2
SLC35F5

(D)


ES2 vs Female
ABCD2
ABCA5
ABCA8
ABCA9
ABCA10
ABCC3
ABCC8
ABCA6
ABCA4
ABCD3
ABCC4
ABCE1
ABCG2
ES2 vs ES2TR120
ABCC2
ABCC8
ABCB7
ABCD1
ABCA12
ABCB6
ABCB11
ABCA3
ABCA17P
ABCC1
ABCC6
ABCG5
ABCG8
ES2 vs ES2TR300
ABCC2
ABCC8
ABCA3
ABCA17P
ABCC1
ABCC6
ABCA12
ABCB6
ABCB11
ABCB7
ABCD1
ABCG5
ABCG8

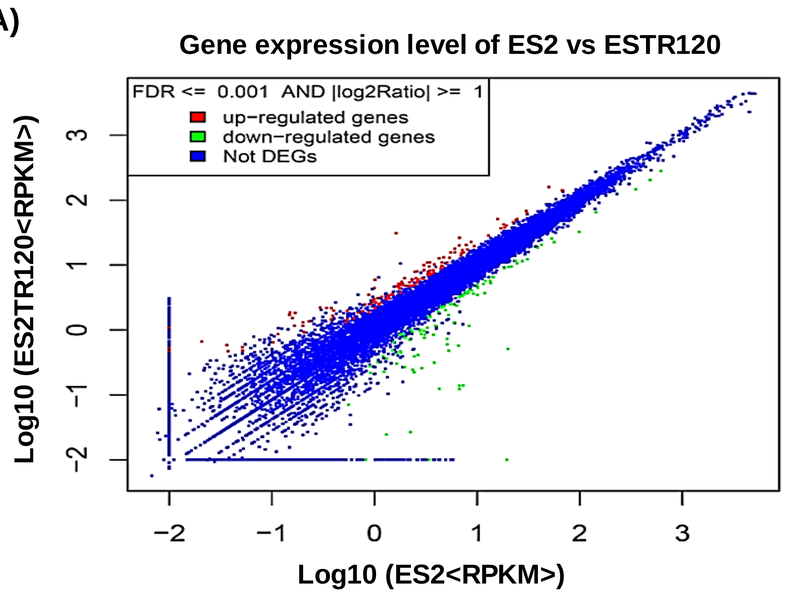
(E)


ES2 vs Female
SLC25A45
SLC39A4
SLC16A3
SLC25A10
SLC35B1
SLC38A10
SLC2A1
SLC6A9
SLC30A7
SLC44A5
SLC7A1
SLC25A30
SLC25A1
ES2 vs ES2TR120
SLC18A2
SLC25A28
SLC7A5
SLC9A1
SLC22A18
SLC39A13
SLC9A6
SLC4A3
SLC16A14
SLC2A3
SLC25A12
SLC35F5
SLC39A10
SLC1A4
SLC4A1AP
ES2 vs ES2TR300
SLC18A2
SLC25A28
SLC7A5
SLC9A1
SLC22A18
SLC39A13
SLC4A3
SLC16A14
SLC2A3
SLC25A12
SLC35F5
SLC39A10
SLC9A6
SLC1A4
SLC4A1AP

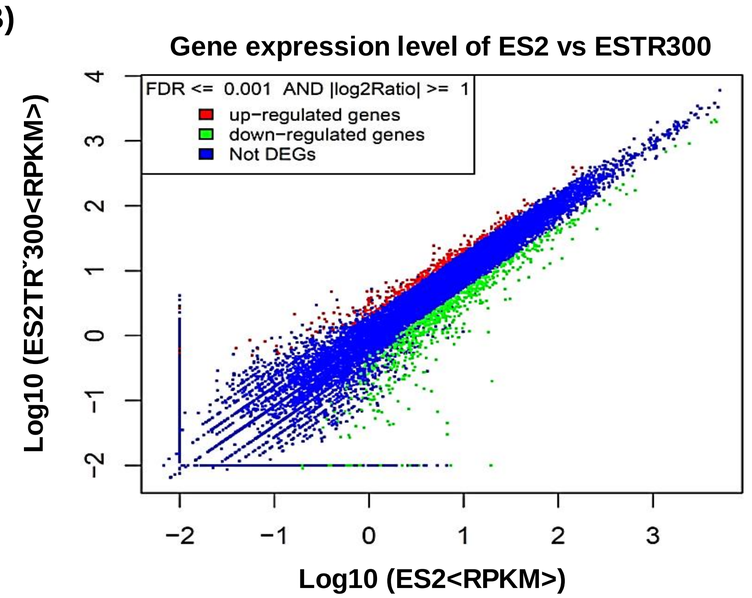
Supplemental Figure 1.

ABC- and SLC- transporter gene-related copy number alterations (CNAs) correlated with paclitaxel-resistance of ES2 cells. **(A)** Hits of ABC- and SLC-tr transporter genes-related CNAs across chromosomes (each dot indicates the number of CNAs within a particular cytogenetic locus within the indicated chromosome. **(B)** Representative maps of CNAs on chromosomes 1 and 16 of CGH analysis from comparison of ES2 vs. normal female genome, ES2 vs. ES2TR120 or ES2TR300 genomes, and ES2TR120 vs. ES2TR300 genomes were analyzed. **(C)** The heatmap clustering plot showed copy number alternations of ABC- (left) and SLC-(right) transporter genes in ES2, ES2TR120, and ES2TR300 cells. The signal intensity of the genome of ES2, ES2TR120, and ES2TR300 was renormalized to that averaged from 53 normal genomes in a public database, and the renormalized CGH data was combined with available segmentation results of CNAs in ovarian cancer cell lines in Cancer Cell Line Encyclopedia (CCLE), and to correct background signal, following by segmentation with Circular Binary Segmentation (CBS) algorithm. Differences in copy number are expressed as gain with log2(2.5/2 or loss with log2(1.5/2), and the FDR-adjusted p-value is ≤ 0.05. **(D, E)** Copy number alteration of DNA region containing indicated ABC-transporter genes **(D)** and SLC-transporter genes **(E)** compared between ES2 vs. normal female genomes (top), ES2TR120 vs. ES2 (middle) and ES2TR300 vs. ES2 genomes (bottom). The Log_2Ratio of each DNA region is shown as the value > 0 indicating amplification (marked in the red bar) and the value <0 representing the loss of copy number (blue bar).

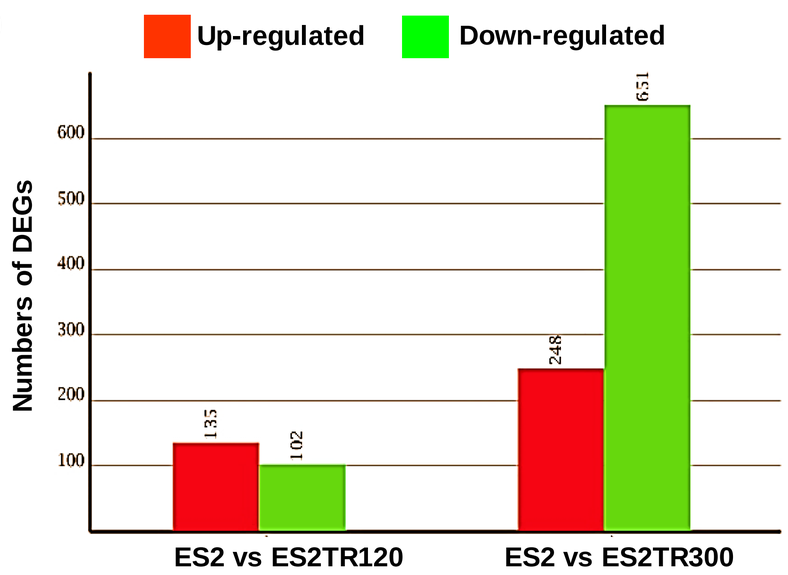
(A)



(B)



(C)



(D)

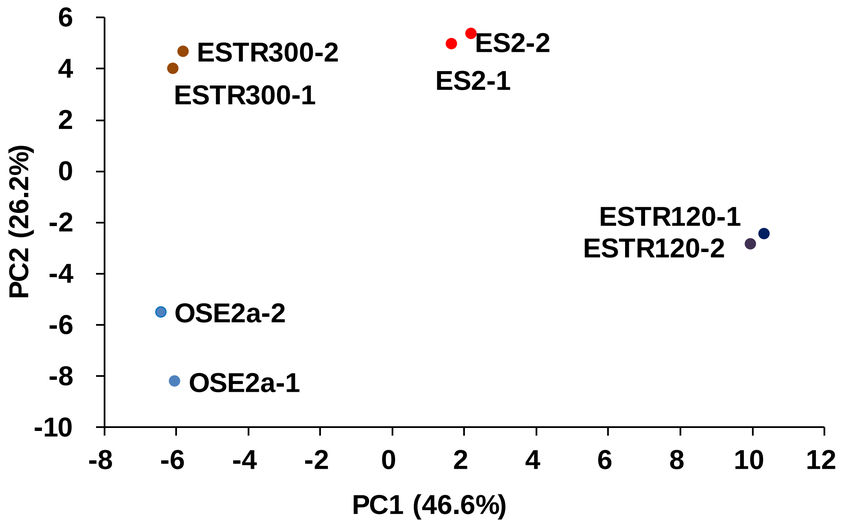
IPA analysis	Top 5 Associated Networks	Score
Analysis with genes up-regulated in both ES2TR cells compared to ES2	Cellular Development, Cellular Growth and Proliferation, Cancer	22
	Cell Cycle, Cellular Development, Cell Death and Survival	19
	Cancer, Cardiac Fibrosis, Cardiac Proliferation	2
	Connective Tissue Disorders, Immunological Disease, Inflammatory Disease	2
	Lipid Metabolism, Molecular Transport, Small Molecule Biochemistry	2
Analysis with genes down-regulated in both ES2TR cells compared to ES2	Carbohydrate Metabolism, Drug Metabolism, Small Molecule Biochemistry	47
	Cellular Movement, Organismal Injury and Abnormalities, Inflammatory Response	18
	Cellular Development, Cellular Growth and Proliferation, Cellular Movement	18
	Cellular Movement, Organismal Injury and Abnormalities, Reproductive System Disease	18
	Cell Morphology, Cell-To-Cell Signaling and Interaction, Developmental Disorder	2

Top Disease and Function (Molecular and Cellular Functions)	Name	p-value	Number of Molecules
Analysis with genes up-regulated in both ES2TR cells compared to ES2	Lipid Metabolism	1.86E-02 - 1.27E-05	3
	Molecular Transport	1.86E-02 - 1.27E-05	3
	Small Molecule Biochemistry	1.86E-02 - 1.27E-05	4
	Amino Acid Metabolism	2.09E-03 - 2.09E-03	1
	Carbohydrate Metabolism	2.68E-02 - 2.09E-03	2
Analysis with genes down-regulated in both ES2TR cells compared to ES2	Carbohydrate Metabolism	2.27E-02 - 9.33E-08	8
	Drug Metabolism	2.27E-02 - 9.33E-08	5
	Small Molecule Biochemistry	2.72E-02 - 9.33E-08	11
	Cellular Movement	2.72E-02 - 1.00E-05	22
	Cell-To-Cell Signaling and Interaction	2.72E-02 - 1.86E-05	14

Supplemental Figure 2.

RNA sequencing and differential gene expression (DEG) analysis applied to Ingenuity pathway analysis (IPA) in ES2, ES2TR120, and ES2TR300 cells. **(A-C)** RPKM scattered plots of differentially expressed **(C)** Chart showing differentially expressed genes. High expression is shown in red (positive values), while low expression is shown in green (negative values). **(D)** IPA analysis showed op 5 significant Molecular and Cellular Functions and Associated networks associated with DEGs in both ES2TR120 and ES2TR300 compared to the parental ES2 cells genes in ES2TR120 and ES2TR300 compared to the parental ES2 cells.

(A)

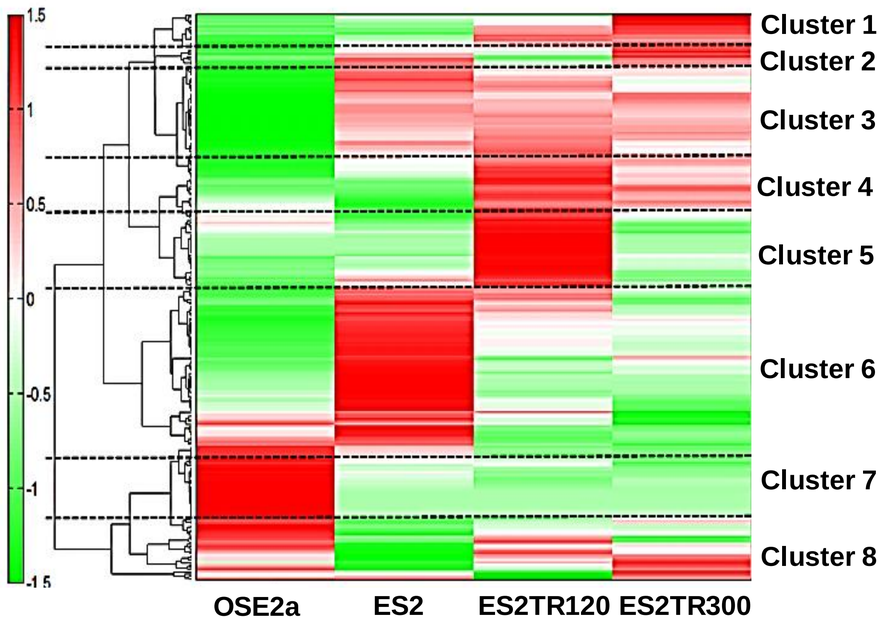


(B)

Top 20 metabolites with largest positive factor loadings (PC1)	Top 20 metabolites with largest positive factor loadings (PC2)
Gln	α-Ketoglutaric acid
Creatine	Malic acid
Asn	Fumaric acid
IMP	N-Carbamoylaspartic acid
GDP	PRPP
Glycerol 3-phosphate	Succinic acid
Hydroxyproline	Malonyl CoA
Xylulose 5-phosphate	Carnitine
Adenylosuccinic acid	N-Acetylglutamic acid
γ-Aminobutyric acid	Isocitric acid
ADP	Citric acid
NADH	2-Hydroxyglutaric acid
Ribulose 5-phosphate	Cystathionine
Carnosine	CoA
Folic acid	Galactose 1-phosphate
Fructose 1,6-diphosphate	Argininosuccinic acid
S-Adenosylhomocysteine	β-Ala
Ribose 5-phosphate	Ribose 1-phosphate
Uric acid	Glu
Inosine	Pyruvic acid

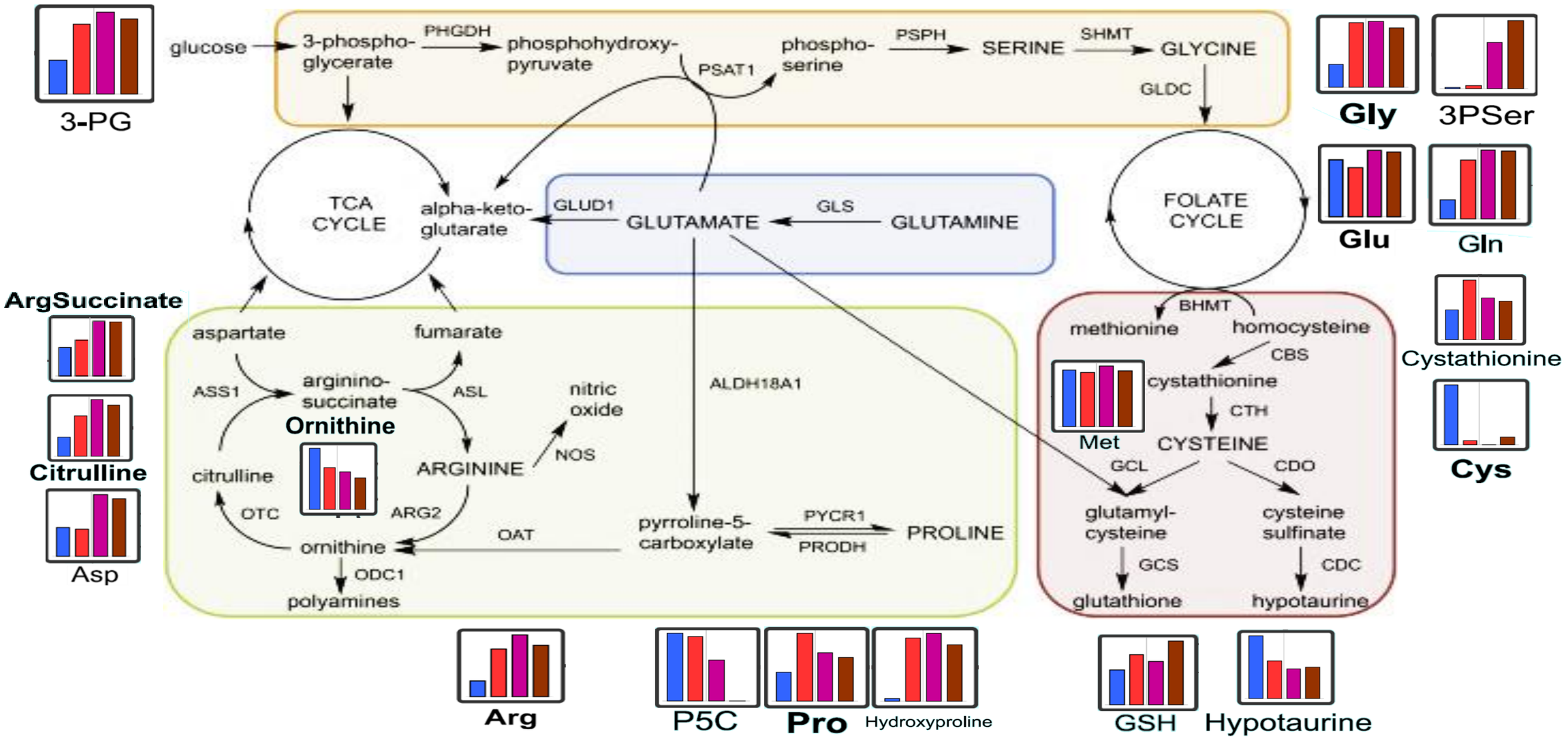
Top 20 metabolites with largest negative factor loadings (PC1)	Top 20 metabolites with largest negative factor loadings (PC2)
$NADP^+$	Leu
ATP	Ile
Homoserine	Citrulline
Thr	Ser
2-Phosphoglyceric acid	His
3-Phosphoglyceric acid	Trp
Phosphoenolpyruvic acid	Gly
2-Oxoisovaleric acid	Phe
Betaine	Val
2,3-Diphosphoglyceric acid	Met
Sarcosine	Cys
Pyruvic acid	N,N-Dimethylglycine
GTP	Tyr
Tyr	Phosphocreatine
Val	Fructose 6-phosphate
Phe	Sarcosine
Cys	2-Oxoisovaleric acid
PRPP	Ala
Fumaric acid	Xanthine
6-Phosphogluconic acid	Thr

(C)



Supplemental Figure 3.

The HMT detected metabolites determined by capillary electrophoresis time of flight mass spectrometer (CE-TOF/MS) and capillary electrophoresis-triple quadrupole mass spectrometry (CE-QqQMS) and analysis by PCA and HCA plot. **(A)** Result of principal component analysis (PCA) based on all 116 metabolites in OSE2a, ES2, ES2TR120, and ES2TR300 cells detected and annotated from CE-QqQMS measurement. PC1 and PC2 show the first principal component and the second principal component, respectively. The number in parentheses is the contribution rate. **(B)** List of top 20 metabolites with the largest positive and negative factor loading in PC1 and PC2 populations. **(C)** Hierarchical cluster analysis (HCA) plot of all metabolites in OSE2a, ES2, ESTR120, and ESTR300 cells detected and annotated from CE-QqQMS measurement (HMT analysis). The horizontal axis and the vertical axis of sample names and peak of individual metabolite. The distances between peaks are displayed in tree diagrams. Metabolites can be separated into 8 clusters based on their differential amount detected in each cell.


3-PG
glucose
3-phospho-glycerate
PHGDH
phosphohydroxy-pyruvate
PSAT1
phospho-serine
PSPH
SERINE
SHMT
GLYCINE
GLDC
Gly
3PSer
TCA CYCLE
alpha-keto-glutarate
GLUD1
GLUTAMATE
GLS
GLUTAMINE
FOLATE CYCLE
Glu
Gln
ArgSuccinate
aspartate
fumarate
ASS1
arginino-succinate
ASL
Ornithine
nitric oxide
NOS
ARGININE
citrulline
OTC
ARG2
ornithine
ODC1
polyamines
ALDH18A1
pyrroline-5-carboxylate
PYCR1
PRODH
PROLINE
OAT
BHMT
methionine
homocysteine
CBS
cystathionine
CTH
Met
CYSTEINE
GCL
CDO
glutamyl-cysteine
cysteine sulfinate
GCS
CDC
glutathione
hypotaurine
Cystathionine
Cys
Citrulline
Asp
Arg
P5C
Pro
Hydroxyproline
GSH
Hypotaurine

Supplemental Figure 4.

Metabolic pathways of selected cancer-related nonessential amino acids, including serine–glycine metabolism. The detected metabolites in our HMT analysis were shown in a bar graph with OSE2a in the blue bar, ES2 in the red bar, ES2TR120 in the purple bar, and ES2TR300 in the brown bar.