Supplementary Figures Legends

Supplementary Figure 1. High glucose induces SULT1E1 expression in HepG2 3D culture and Huh7 cells. (A) HepG2 3D spheroids and (B) Huh7 cells were treated by low glucose and high glucose DMEM respectively for 48 hours, followed by measuring their *SULT1E1* mRNA expression levels. (D) HepG2 and Huh7 cell viabilities in response to low glucose and high glucose exposures for 48 hours were measured. The values (N = 3) represent means ± S.D. Mean difference is significant from low glucose treated group at ****, $p < 0.0001$; ***, $p < 0.0005$ (Student's *t*-test).

Supplementary Figure 2. HNF4α activates while RORα suppresses *SULT1E1* in Huh7 cells. (A - B) HNF4α was knocked down by siRNA in Huh7 cells, followed by low glucose and high glucose treatments respectively for 48 hours. *SULT1E1* and *HNF4α* mRNA expression levels of these treated cells were subsequently detected. (C - D) RORα was knocked down by siRNA in Huh7 cells, followed by low glucose and high glucose treatments respectively for 48 hours. *SULT1E1* and *RORα* gene expressions of these treated cells were subsequently detected. The values (N = 3) represent means ± S.D. Mean difference is significant from scramble siRNA transfected group ****, $p < 0.0001$; ***, $p < 0.0005$; *, $p < 0.05$ (Student's *t*-test).

Supplementary Figure 3. RORα S100D activates endogenous *SULT1E1* in HepG2 cells. (A) Flag-tagged RORα WT, RORα S100A or RORα S100D was transfected into HepG2 cells respectively for 24 hours, followed by measuring their *SULT1E1* mRNA expression levels. The values (N = 4) represent means ± S.D. Mean difference is significant from empty vector transfected group at ***, $p < 0.0005$ (One-way ANOVA). (B) The expression patterns of these

Flag-tagged RORαs in the nuclei of transfected HepG2 cells were detected by western blotting with an anti-Flag antibody. Nuclear protein HDAC1 was used as a loading control.

Supplementary Figure 4. RORα interacting with HNF4α binds to the *SULT1E1* gene. (A) *In vitro* translated Flag-tagged HNF4α, RORα WT, RORα S100A and RORα S100D were applied in the gel shift assays. The expression levels of these *in vitro* translated proteins were detected by western blotting with an anti-Flag antibody. (B) The radioactive labeled *SULT1E1* DR1_RORE probe was incubated with HNF4α, HNF4α/RORα WT mixture, HNF4α/RORα S100A mixture or HNF4α/RORα S100D mixture respectively. The formed complex (indicated by a solid arrow) was recognized by the antibodies against HNF4α and RORα respectively. Supershifted bands were indicated by a dashed arrow. A normal IgG was used as a control for the antibodies used in the assays. (C) Binding capacities of the *in vitro* translated RORα WT, RORα S100A and RORα S100D to a consensus RORE were tested by gel shift assays.

Supplementary Figure 5. Controls for 3C assays. (A) The 3C target was sequenced, from which the ligated point was displayed. (B) A non-coding region (from +7066 bp to +8570 bp) of the *SULT1E1* gene that has a similar size to the *SULT1E1* promoter was used as a negative control in the 3C assays. Primer set (TP3 and TP4, indicated by solid arrows) was used to amplify a 127 bp non-3C target from the glucose treated HepG2 cells. (C) The efficiency of the primer sets used in the 3C assays was validated by RT-PCR using purified fragments (3C target and Control) and synthesized DNA (Non-3C target) as templates.

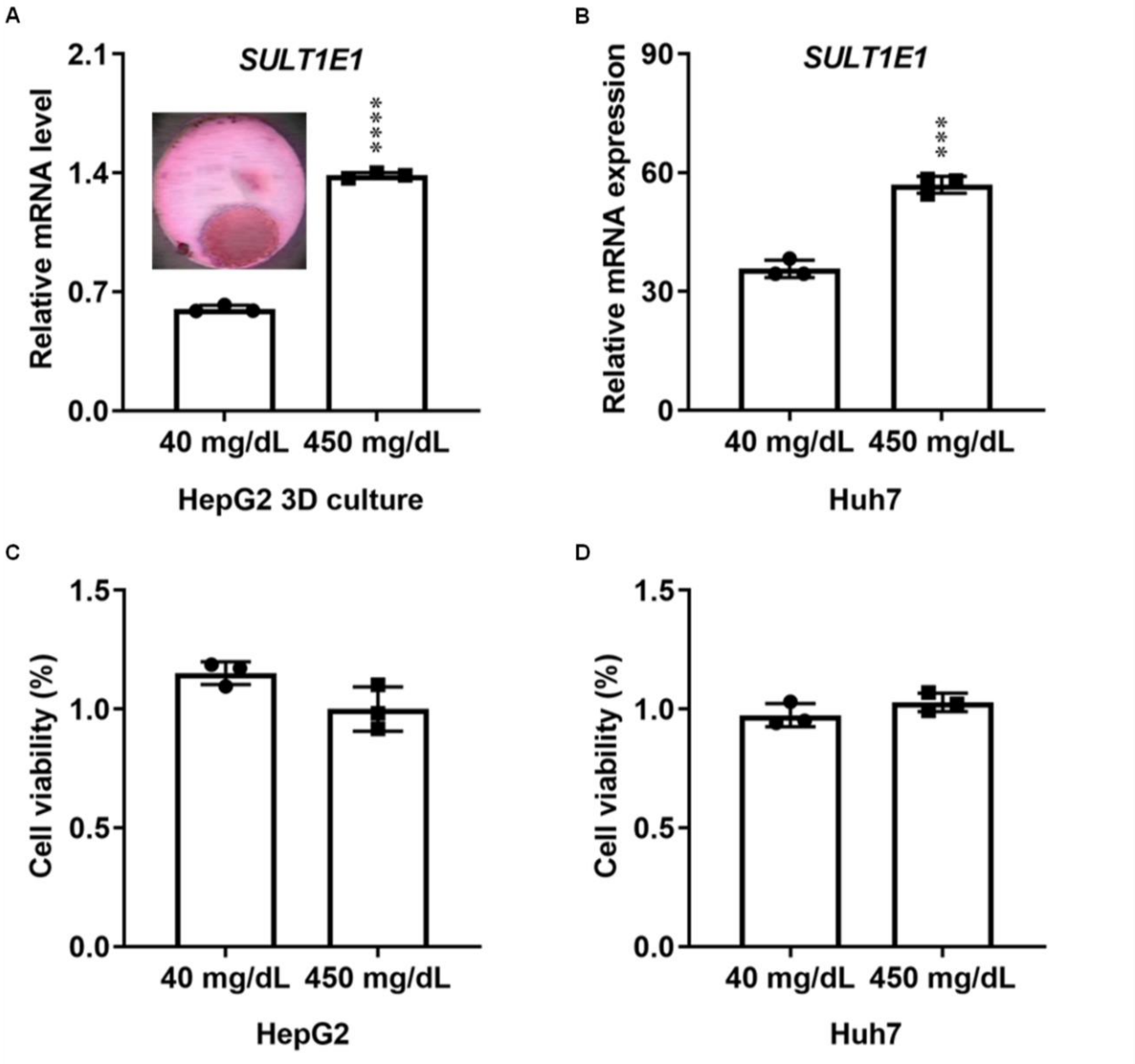
Supplementary Table 1. Glucose exposures alter xenobiotic metabolism in HepG2 cells.

Microarray analysis of the glucose treated HepG2 cells. Gene expression analysis was conducted using Agilent Whole Human Genome 4 × 44 Version 2 multiplex format oligo arrays (026652) (Agilent Technologies) following the Agilent 1-color microarray-based gene expression analysis protocol. The values (N = 4) represent means ± S.D. Mean difference between low glucose treated group and high glucose treated group was compared by an ANOVA and Benjamini-Hochberg multiple test correction with a p-value of $p<0.05$. Xenobiotic related genes that have a fold change (high glucose group/low glucose group) more than ±2 were listed in the table. The data sets (accession: GSE140867) are accessible at GEO.

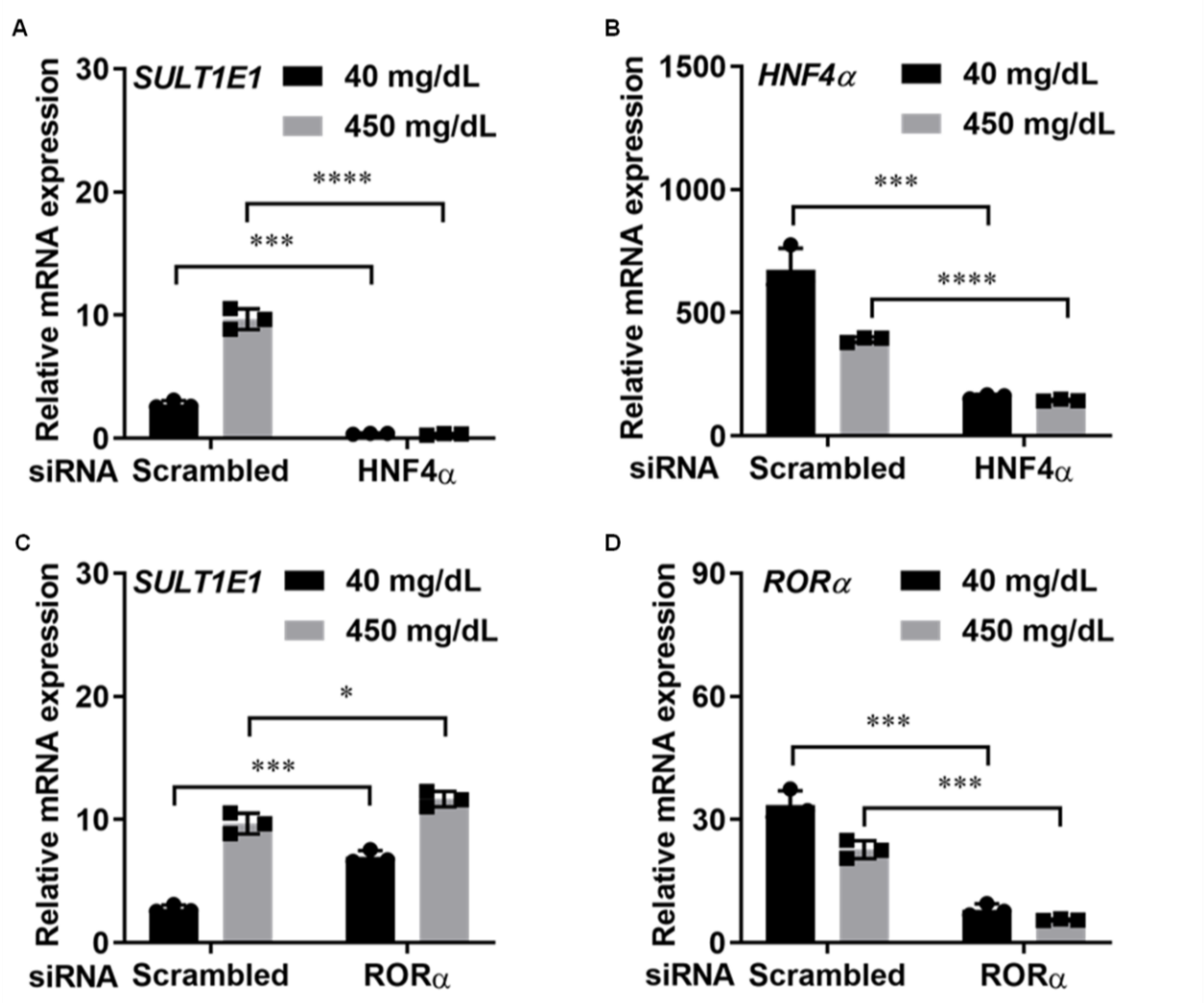
Supplementary Table 2. Primers, oligonucleotides and probes used in the study.

The primers, oligonucleotides and probes used for plasmid constructions, DNA affinity chromatography-mass spectrometry, qRT-PCR, EMSA, ChIP and 3C assays in the study are listed in the table. The mutated sequences are underlined.

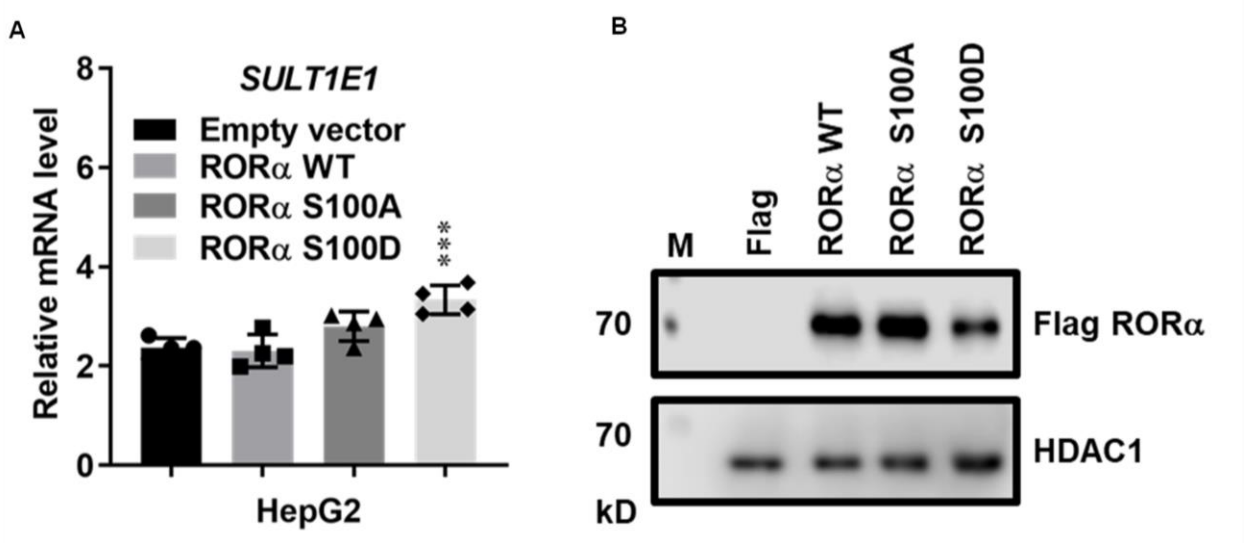
Supplementary Figure 1



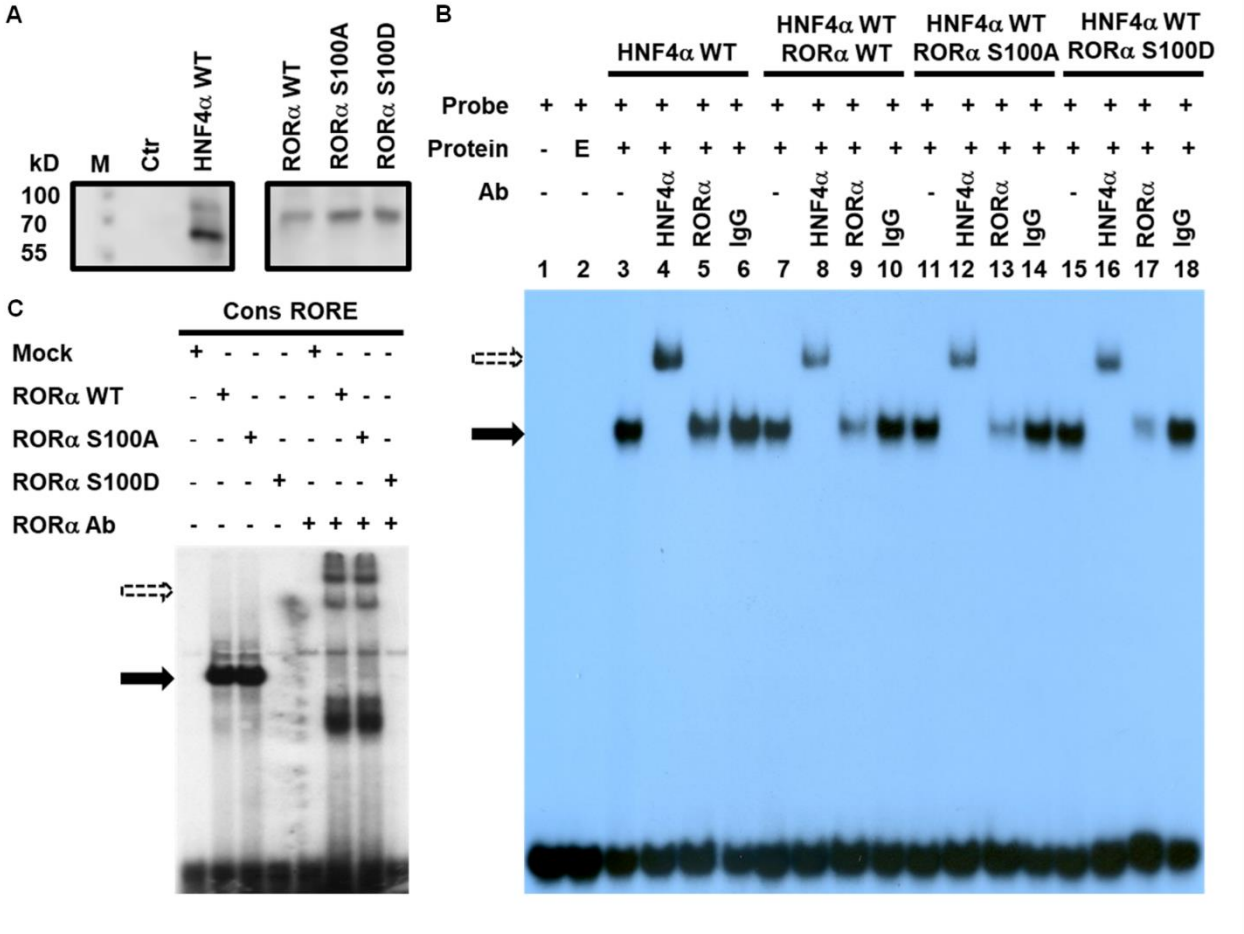
Supplementary Figure 2



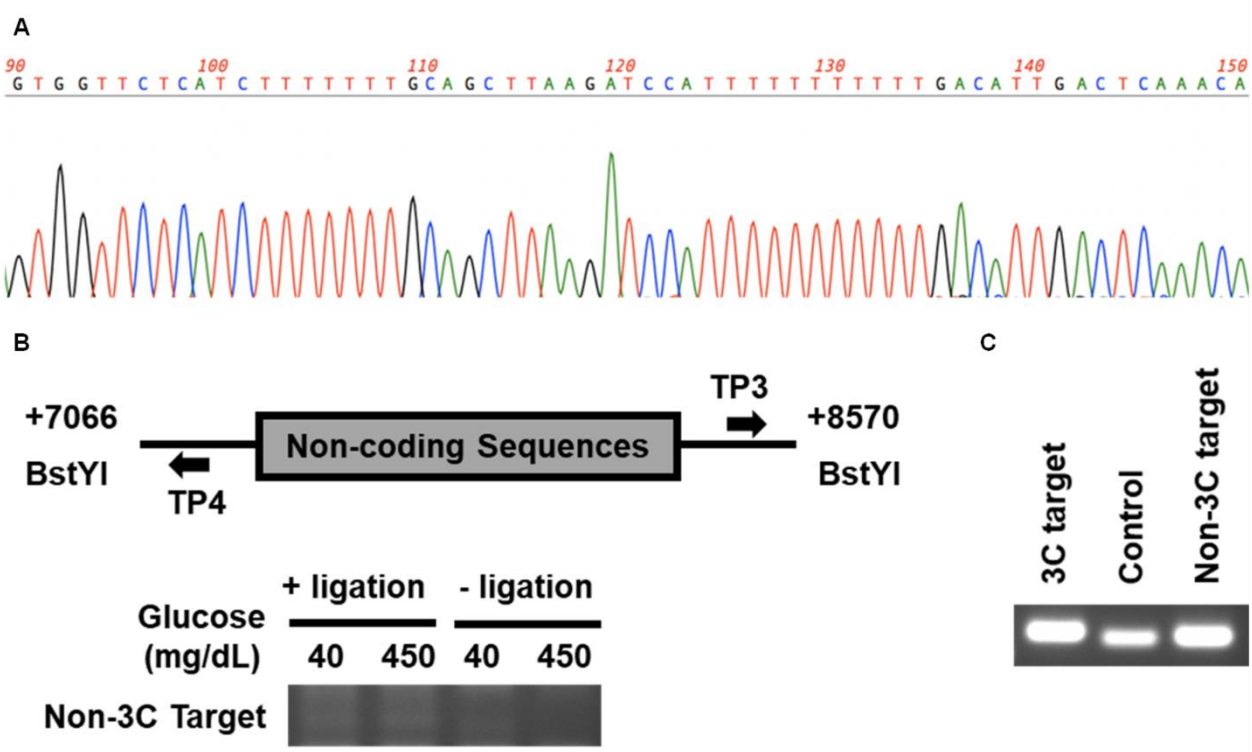
Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5



Supplementary Table 1

Name	Fold Change*	p-value
	SULTs	
SULT2A1	9.569	1.19E-12
SULT1E1	7.484	1.26E-05
SULT1B1	2.87	0.032
SULT1C2	2.597	7.53E-07
SULT1C4	-2.1	0.0295
	CYPs	
CYP3A7	3.721	4.87E-09
CYP3A5	2.798	1.69E-05
CYP2D6	2.3407	1.49E-05
CYP2U1	2.3151	5.5645E-06
CYP4F3	2.2599	2.6359E-07
CYP2R1	-2	1.3834E-09
CYP2S1	-3.1089	0.0025
CYP1A1	-4.311	1.84E-09
CYP4F11	-6.4977	1.9544E-11
	UGTs	
UGT2B11	2.843	1.89E-12
UGT2B15	2.595	5.53E-06
UGT2B10	2.419	1.03E-09
UGT2B7	2.29	2.74E-07
	GSTs	
GSTM2	16.404	2.64E-05
GSTM4	5.076	7.74E-09
GSTO2	3.356	1.43E-10
MGST2	2.748	1.22E-12
GSTA4	2.426	2.24E-10
GSTT1	2.343	2.41E-11
GSTK1	2.341	2.24E-09
MGST1	-2.836	2.4E-12
GSTA2	-3.947	5.5E-11
GSTA5	-5.966	2.33E-08

* Fold change represents high glucose group/low glucose group.

Supplementary Table 2

Construction of mutant *SULT1E1* promoters	
Δ-1081 DR1 mutant	5’-TGATTTACAACACAGTAAAATAAATACTAGTTAGGAGAAAGTTTGGGATTTAAAAGTCACTAAGAGAAACATAACATCTACATTAACTATT-3’ 5’-AATAGTTAATGTAGATGTTATGTTTCTCTTAGTGACTTTTAAATCCCAAACTTTCTCCTAACTAGTATTTATTTTACTGTGTTGTAAATCA-3’
Δ-1081 RORE mutant	5’-TGATTTACAACACAGTAAAATAAATACTAGTTAGGAGAAAGTTCAAAGTTTAAGGACTACTAAGAGAAACATAACATCTACATTAACTAT-3’ 5'-ATAGTTAATGTAGATGTTATGTTTCTCTTAGTAGTCCTTAAACTTTGAACTTTCTCCTAACTAGTATTTATTTTACTGTGTTGTAAATCA-3’
Δ-1081 DR1_RORE mutant	5’-ACAGTAAAATAAATACTAGTTAGGAGAAAGTTTGGGATTTAAGGACTACTAAGAGAAACATAACATCTACATTAACTATTGCATC-3’ 5’-GATGCAATAGTTAATGTAGATGTTATGTTTCTCTTAGTAGTCCTTAAATCCCAAACTTTCTCCTAACTAGTATTTATTTTACTGT-3’
Construction of HNF4α expression plasmid	
HNF4α_F	5’-ATCATTAAGCTTATGCGACTCCAAAACCC-3’
HNF4α_R	5’-ATCATTGGATCCCTAGATAACTTCCTGCTTGGTG-3’
Oligonucleotides for DNA affinity chromatography-mass spectrometry	
4×DR1_RORE_F	5’-CTAGGAGAAAGTTCAAAGTTTAAAAGTCACTAAGATAGGAGAAAGTTCAAAGTTTAAAAGTCACTAAGATAGGAGAAAGTTCAAAGTTTAAAAGTCACTAAGAG-3’
4×DR1_RORE_R	5’-GATCCTCTTAGTGACTTTTAAACTTTGAACTTTCTCCTATCTTAGTGACTTTTAAACTTTGAACTTTCTCCTATCTTAGTGACTTTTAAACTTTGAACTTTCTCCTATCTTAGTGACTTTTAAACTTTGAACTTTCTCCTAGGTAC-3’
4×1E1_F	5’-AAGTTGGCCGCAGTGTTATC-3’
4×1E1_R	5’-TGGGCGGGGCCAGATCC-3’
Assay on demand primers	
Human SULT1E1	Hs00193690_m1
Human STS	Hs00996676_m1
Human TFF1	Hs00907239_m1
Human HNF4α	Hs00230853_m1
Human RORα	Hs00536545_m1
Human ACTB	Hs99999903_m1

EMSA probes	
DR1_RORE	5’-GATCTAGGAGAAAGTTCAAAGTTTAAAAGTCACTAAGA-3’ 5’-GATCTCTTAGTGACTTTTAAACTTTGAACTTTCTCCTA-3’
DR1	5’-GATCAGGAGAAAGTTCAAAGTTTAAAA-3’ 5’-GATCTTTTAAACTTTGAACTTTCTCCT-3’
RORE	5’-GATCTCAAAGTTTAAAAGTCACTAAGA-3’ 5’-GATCTCTTAGTGACTTTTAAACTTTGA-3’
Consensus RORE	5’-GATCTCGACTCGTATATCAAGGTCATGCTG-3’ 5’-GATCCAGCATGACCTTGATATACGAGTCGA-3’
ChIP assay primers	
SULT1E1 enhancer_F	5’-AAAGTACTCTGGACAAGCAAAC-3’
SULT1E1 enhancer_R	5’-GAGGCTCACTCTTACAAGACTC-3’
3C assay primers	
Control (CP1)_F	5’-CTCTGGACAAGCAAACATTGA-3’
Control (CP2)_R	5’-CATTTCCTTTGAGAGGCTCACTC-3’
Ligated (TP1)_F	5’-TCACCAGAAACATTCCAAATGCAG-3’
Ligated (TP2)_R	5’-CTGAAACCTCATTCTTCTCCATGA-3’
Ligated (TP3)_F	5’-TGGCTGGGTCAAATGGTATT-3’
Ligated (TP4)_R	5’-GCATGGAATGACTTCAGCAG-3’
Non-3C target template	5’-TGGCTGGGTCAAATGGTATTTCTAGTTCTAGATCTACAGACAA AAATCAAAGATTGCCAGGTTAGTTTGTTTTTATCATTAGCAATCC TAGATAGACGATATACGTCCTGCTGAAGTCATTCCATGC-3’

Mutated sequences are underlined