Supplementary Figure 1: OCT embedded frozen liver sections were stained with Oil Red O. Increased Oil Red O staining is clearly visible in DKO but not in WT, Fxr<sup>-/-</sup> and Shp<sup>-/-</sup> indicating increased lipid accumulation in 8-10 week old DKO liver.
Supplementary Figure 2: Minimal liver injury in individual Fxr−/− and Shp−/− mice.

Hematoxylin-eosin stain, x200 of 5 week old mouse liver. (A) Histology of the WT liver shows hepatocytes between portal tract, PT (left) and terminal hepatic vein, HV (right). (B) Fxr−/− - hepatocyte nuclei are enlarged, cytoplasm is focally vacuolated due to lipid and there is focal hepatitis (C) Shp−/−- depletion of glycogen leaves cytoplasm more eosinophilic. Electron micrographs of the corresponding samples show small lipid
droplets in the cytoplasm of a normal WT hepatocyte in (D). E. Fxr⁻/⁻ displayed moderate hepatocellular microsteatosis; small lipid droplets marked by arrows. (F) Shp⁻/⁻ displayed mild mitochondrial pleomorphism (see inset). The original magnification is x200 for light microscopy; x1500 for EM and x3000 for EM insets. (G-I) Serum ALT (G), AST (H) and bilirubin (I) levels suggest modest liver injury in Fxr⁻/⁻ mice. Data are presented as mean ± SEM, n=8-10. *p<0.05 and **p<0.001 when compared to WT.
Supplementary Figure 3: Individual FXR and SHP null mice display modest biliary dysfunction.

BA levels in serum (A) and liver (B) remain unchanged in \textit{Shp}^{−/−} whereas \textit{Fxr}^{−/−} mice show increased serum levels (A) only at 12 weeks of age. (C) Biliary BA remains unaffected but intestinal BA is slightly induced only in the absence of SHP (D). (E-F) Cholesterol, a precursor for BA production is increased in serum of \textit{Fxr}^{−/−} and liver of \textit{Shp}^{−/−} but not WT mice. (G-I) BA composition reveals increased hydrophobic pool size in serum of \textit{Fxr}^{−/−} and in liver of \textit{Shp}^{−/−} mice. Data are presented as mean ± SEM, n=6. *p<0.05 and **p<0.001 when compared to WT.
Supplementary Figure 4: Dysfunction in BA synthesis and transport pathways in $Fxr^{−/−}$ and $Shp^{−/−}$.

Total RNA (n=4) per time point was prepared from WT, $Fxr^{−/−}$, $Shp^{−/−}$ and DKO mice and gene expression was analyzed in duplicates using nanostring technology.

(A-D) Genes involved in the synthesis of neutral (A) and hydrophobic (D) BA is increased but acidic BA (B&C) is decreased only in $Fxr^{−/−}$ not $Shp^{−/−}$; (E-G) Aberrant expression of genes involved in BA efflux into bile. (H-I) Genes involved in BA efflux into circulation is increased in $Fxr^{−/−}$ but decreased in $Shp^{−/−}$. (J-L) Genes involved in BA
uptake into liver is decreased in $Fxr^{-/-}$ but not changed in $Shp^{-/-}$ at 12 weeks. (M-P) genes involved in BA detoxification is increased only in $Fxr^{-/-}$. CYP7A1 protein is modestly induced in $Fxr^{-/-}$ and $Shp^{-/-}$ (Q). *p<0.05 and **p<0.001 when compared to their respective age matched WT.
Supplementary Table 1: Nanostring probe sets.

100 bp nanostring probes were custom synthesized from NanoString Inc and utilized for quantification of gene expression.