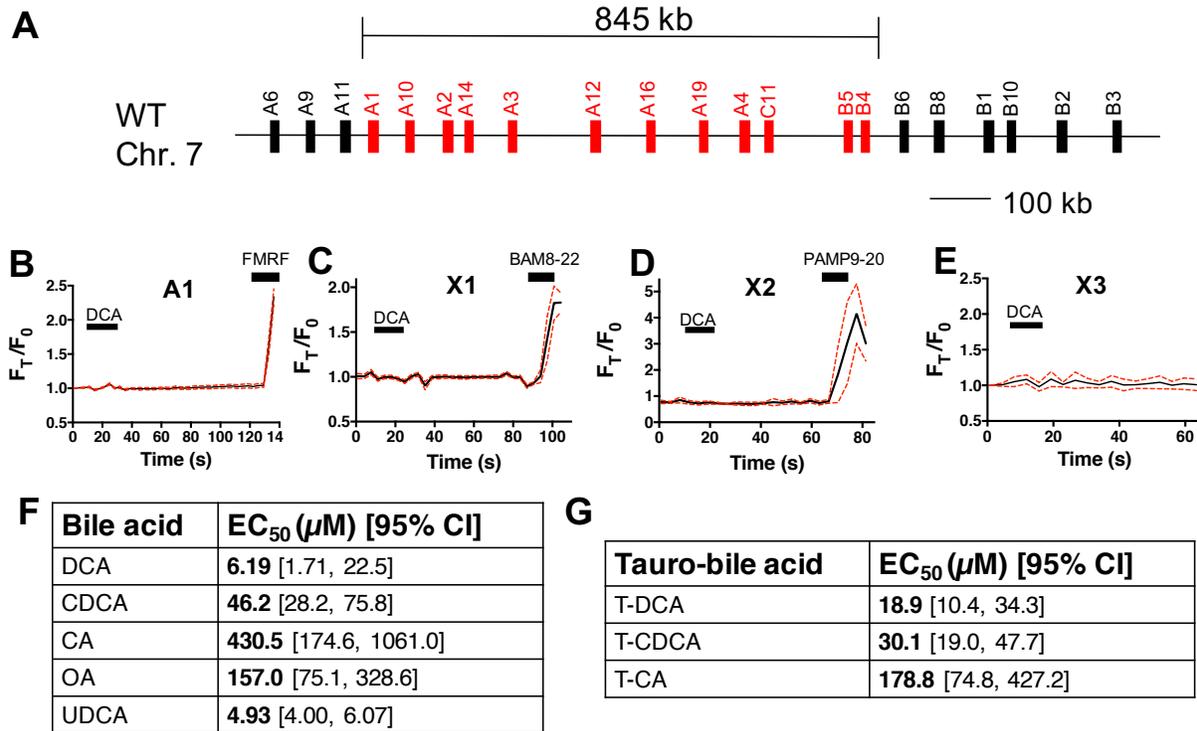
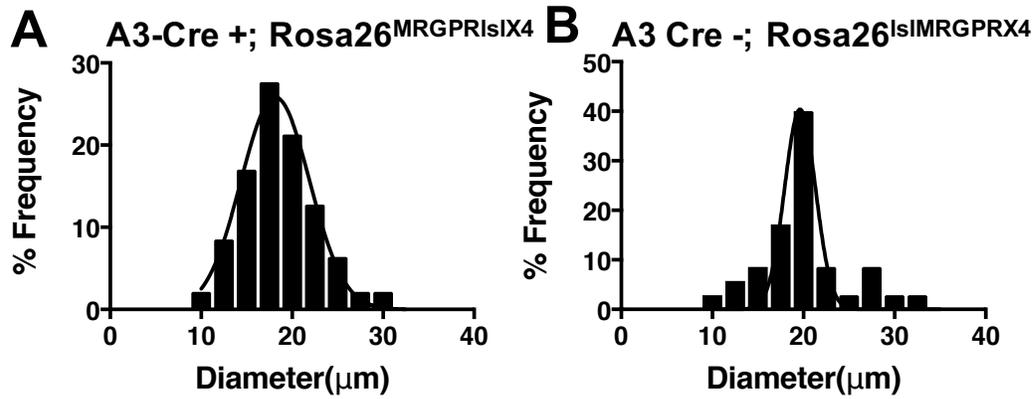


**Supplemental Data: 4 figures**

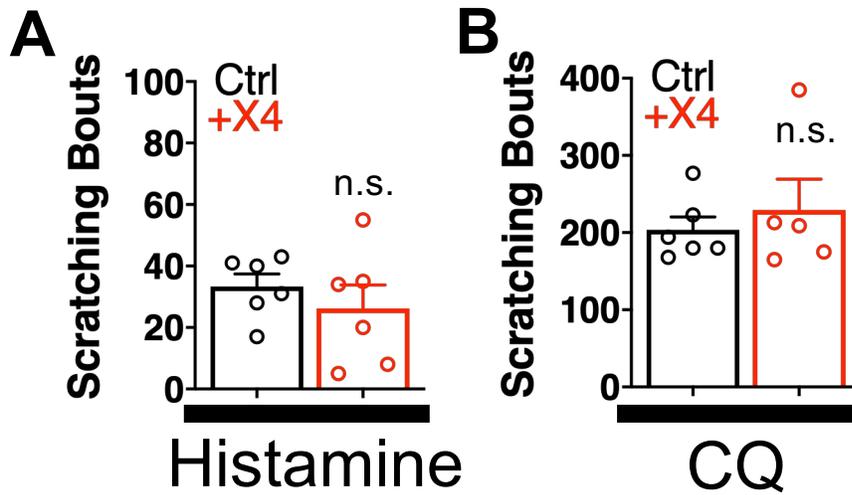


**Figure S1. DCA does not activate the murine ortholog *Mrgpra1* or related human *Mrgprs*.**

(A) Graphical depiction of DCA-screened murine *Mrgprs*. (B-E) Ca<sup>2+</sup> imaging of HEK293 cells stably expressing (B) MRGPRA1, (C) MRGPRX1, (D) MRGPRX2, or (E) MRGPRX3. Mean ± 95% CI depicted. n=10. 10 μM DCA was added where indicated by black bars. When applicable, a positive control was added at the end of imaging trial, (B) 30μM FMRF, (C) 3 μM BAM8-22, or (D) 10μM PAMP9-20. (F) Table of EC<sub>50</sub>s with 95% confidence intervals(CI) of unconjugated bile acids against MRGPRX4. (G) Table of EC<sub>50</sub>s with 95% CI of tauro-conjugated bile acids against MRGPRX4.



**Figure S2. DCA activates small-diameter Ctrl and +X4 sensory neurons.** (A-B) Histograms of bilirubin-activated neuronal soma diameter. (A) +X4 Mean = 18.8 $\mu\text{m}$ . n= 47. (B) Ctrl Mean = 20.1 $\mu\text{m}$ . n= 35.

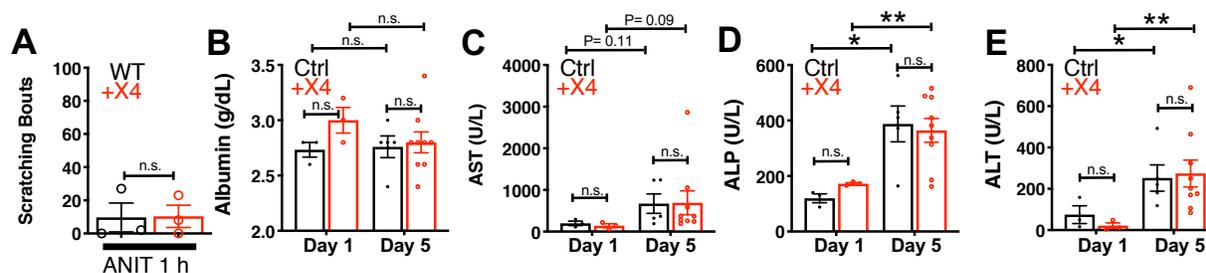


**C**

Total Bilirubin ( $\mu\text{M}$ )	Indirect Bilirubin ( $\mu\text{M}$ )	Albumin (g/dL)	Total protein (g/dL)	Creatinine ( $\mu\text{g/dL}$ )	Bile Acid ( $\mu\text{M}$ )
329	27	2.9	5.3	1.2	221.6

**Figure S3. +X4 humanized mice scratch normally in response to non-bile acid pruritogens.**

(A) Scratching bouts associated with injection of histamine. 50 $\mu$ L of 9mM histamine was injected into the nape of Ctrl and +X4 mice. Ctrl n=6; +X4 n=6. (B) Scratching bouts associated with injection of Chloroquine (CQ). 50 $\mu$ L of 10 mM CQ was injected into the nape of Ctrl and +X4 mice. Ctrl n=6; +X4 n=5. (C) Biochemical characteristics of patient plasma injected.



**Figure S4. +X4 humanized mice exhibit similar degrees of cholestasis compared to Ctrl**

**mice.** (A) Scratching bouts from wild-type and +X4 animals 1 hour after a single 25mg/kg dose of ANIT. For both WT and +X4, n=3. (B) Plasma albumin levels (g/dL) from indicated days of ANIT treatment. (C) Plasma aspartate aminotransferase (AST) levels (U/L) from indicated days of ANIT treatment. (D) Plasma alkaline phosphatase (ALP) levels (U/L) from indicated days of ANIT treatment. (E) Plasma alanine aminotransferase (AST) levels (U/L) from indicated days of ANIT treatment. (A-E) Mean  $\pm$  SEM depicted. Circles represent plasma from individual mice. For Day 1: Ctrl n= 3, +X4 n= 5. For Day 5: Ctrl n= 5, +X4 n= 9. n.s.= not significant; \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; student's t test.