Supplemental Figures

Supplemental Figure 1: Plasma protein profile in IL17C<sup>high</sup> subjects. (A) The plasma level of 91 inflammation-related proteins was compared between subjects with outlier high plasma IL17C level (IL17C<sup>high</sup>; 99<sup>th</sup> percentile for IL17C; n = 27) and those with normal/low plasma IL17C (<95<sup>th</sup> percentile for IL17C; n = 2580). The vulcan plot shows the geometric mean ratio (GMR; 99<sup>th</sup> vs <95<sup>th</sup> percentile for IL17C) on the x-axis and the significance level (FDR; 2-tailed Mann-Whitney test with Benjamini-Hochberg correction) on the y-axis. The GMR(log<sub>2</sub>) for IL17C was 2.28 (not shown). Note that only one of the IL17C<sup>high</sup> subjects had (self-reported) IBD; exclusion of data for this subject did not meaningfully change the overall protein profile. (B) Analysis of the plasma protein profile in CD patients and non-IBD controls. Protein level data were obtained from a study by Andersson et al. (27). The vulcan plot depicts the geometric mean ratios (CD vs non-IBD controls; log<sub>2</sub>) on the x-axis and the corresponding FDR values on the y-axis.
Supplemental Figure 2: In vitro function of selected protein-altering DUOX2 variants. (A) Sequencing electropherograms confirming mutations introduced in a reference sequence DUOX2 expression plasmid. (B) Topology model of the DUOX2/DUOXA2 enzyme complex depicting the DUOXA2-EGFP fusion and HA-epitope tag of DUOX2 used in the flow cytometry assay. (B) Quantitation of DUOX2 cell-surface expression in non-permeabilized cells. Expression at the cell surface (AUC of the HA signal) is normalized for the number of transfected (i.e., GFP positive) cells.
Supplemental Figure 3: Expression of Duoxa2 in the ileum of intestinal epithelial-specific Duoxa KO mice. Data represent geometric means with 95% CI of Duoxa2 mRNA expression in the terminal ileum of intestinal epithelial-specific Duoxa KO (n = 5) and floxed littermate control mice (n = 6). **, P < 0.01; 2-tailed Mann-Whitney.
Supplemental Figure 4: Effect of antibiotics treatment on mucosal microbiota. Mice were treated for 3 days with a combination of ciprofloxacin and metronidazole (50 mg/kg BW, twice daily by oral gavage). To confirm the effect on the level of live, mucosa-associated microbiota, bacterial 16S rRNA level was determined in mucosal samples from the terminal ileum. Bacterial rRNA levels are normalized to the level of the mouse Hprt1 housekeeping gene. (A) Amplification with universal eubacterial primers. (B) Amplification with primers specific for γ- and δ-Proteobacteria. n = 6 and 5 for control mice without or with antibiotics treatment, respectively, and n = 8 and 4 for intestinal epithelial-specific Duoxa KO mice without or with antibiotics treatment, respectively. Data represent geometric means with 95% CI. *, P < 0.05; **, P < 0.01; 2-tailed Mann-Whitney (vs untreated).
Supplemental Figure 5: *Proteobacteria* otu0194 is detected in the mucosal niche of *Il17c*\textsuperscript{high} samples. (A) Ileal *Il17c* expression in WT (*n* = 22) and *Duoxa*\textsuperscript{−/−} (*n* = 26) mice derived from 14 distinct breeding pairs (parental genotypes: *Duoxa*\textsuperscript{+/−}). For each litter, mice were separated by genotype at weaning (P21). Five KO mice had outlier high *Il17c* expression (arrows). (B) The relative abundance of otu0194 in ileal mucosal samples. (C) The relative abundance of otu0194 in corresponding luminal content of ileal samples.
Supplemental Figure 6: Frequency distribution of rare and very rare DUOX2 protein-altering variants in IBD and control cohorts. (A-B) Frequency distribution of DUOX2 protein-altering variants identified in whole-genome sequencing data of IBD patients and non-IBD controls (IBD Exomes Portal). Variants were stratified by minor allele frequency using data for the corresponding ancestry group in gnomAD (AF\textsubscript{ancestry}, i.e., gnomAD_NFE_AF, gnomAD_ASJ_AF, or gnomAD_FIN_AF).