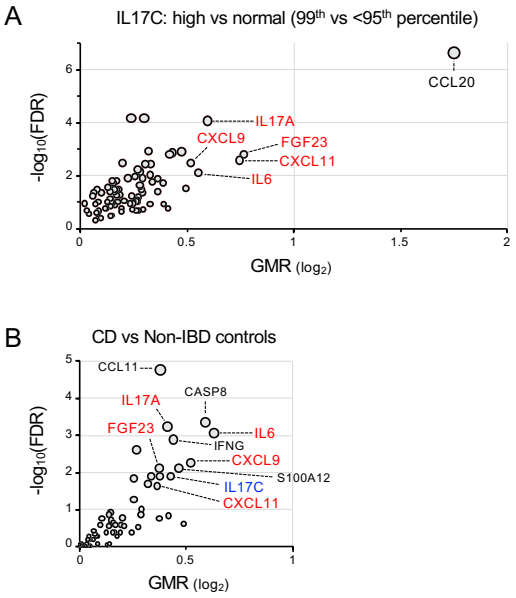
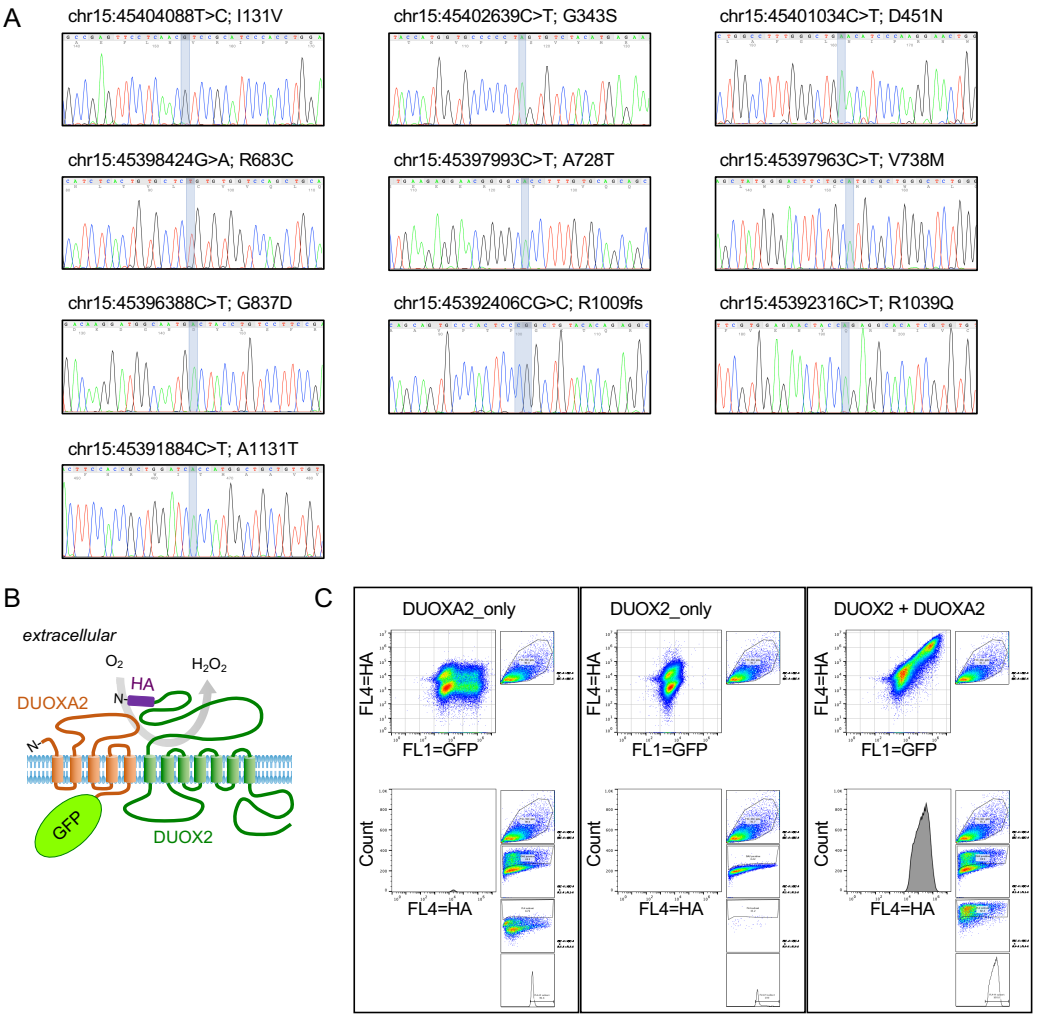
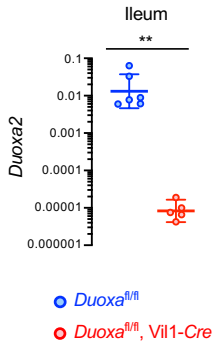
Supplemental Figures



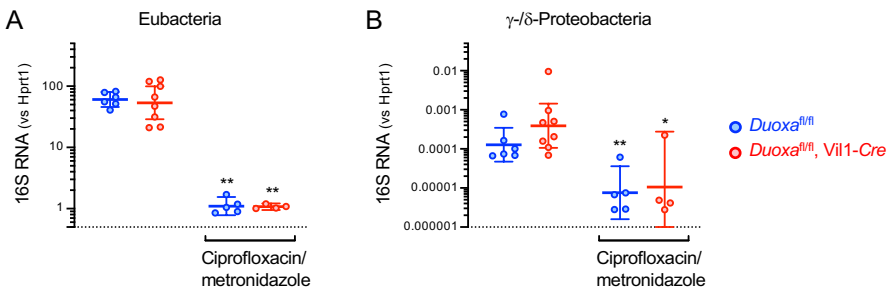
Supplemental Figure 1: Plasma protein profile in IL17C^{high} subjects. (**A**) The plasma level of 91 inflammation-related proteins was compared between subjects with outlier high plasma IL17C level (IL17C^{high}: 99th percentile for IL17C; *n* = 27) and those with normal/low plasma IL17C (< 95th percentile for IL17C; *n* = 2580). The vulcan plot shows the geometric mean ratio (GMR; 99th vs < 95th 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_2) for IL17C was 2.28 (not shown). Note that only one of the IL17C^{high} 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_2) on the x-axis and the corresponding FDR values on the y-axis.



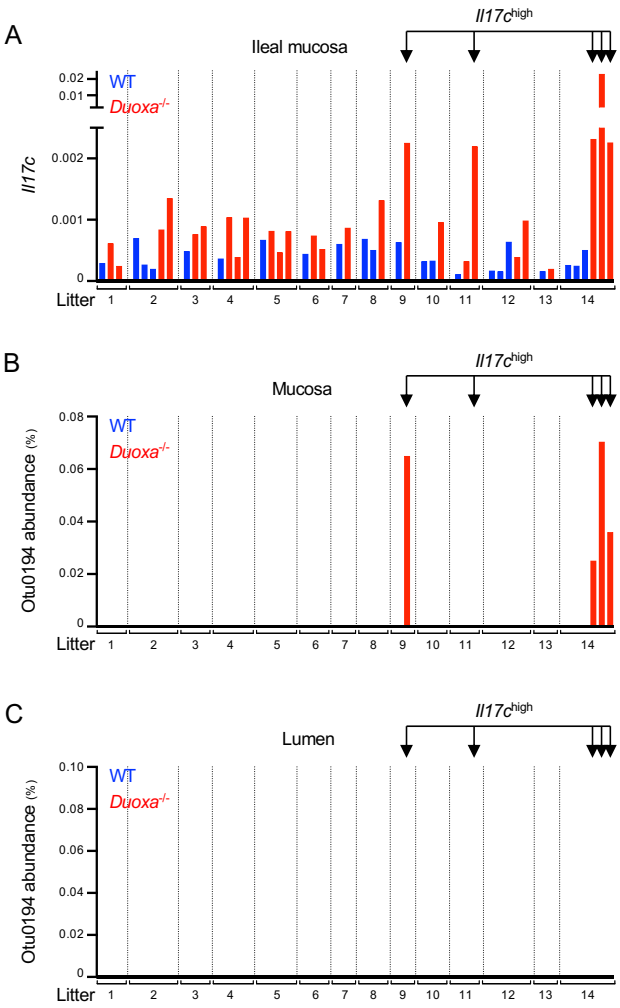
Supplemental Figure 2: In vitro function of selected protein-altering *DUOX2* variants. (**A**) Sequencing electropherograms confirming mutations introduced in a reference sequence DUOX2 expression plasmid. (**B**) Topology model of the DUOX2/DUOXA2 enzyme complex depicting the DUOXA2-EGFP fusion and 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.



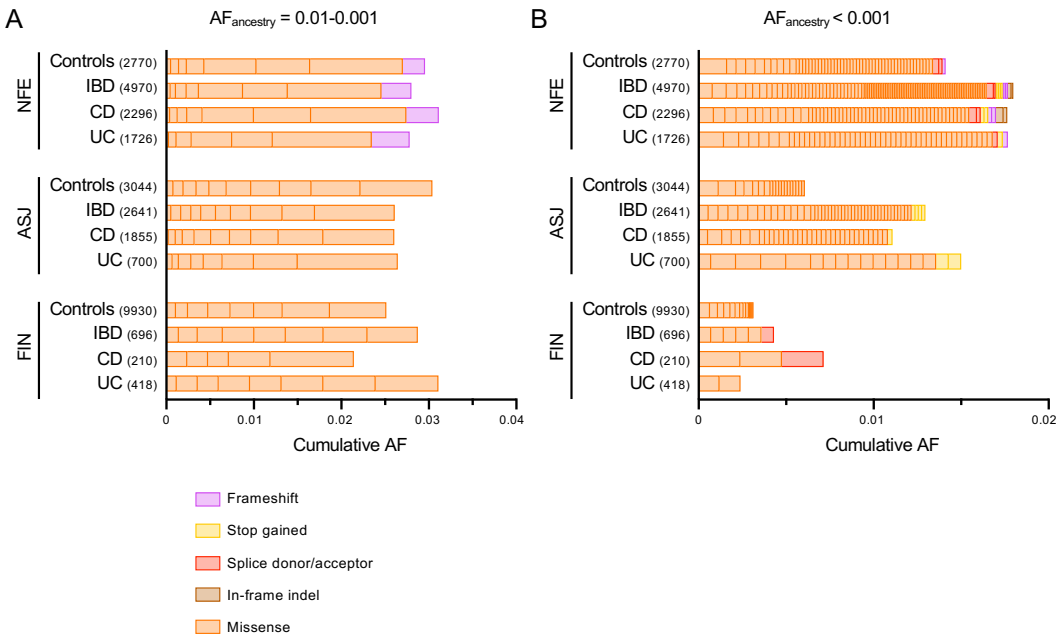
Supplemental Figure 3: Expression of *Duoxa2* in the ileum of intestinal epithelial-specific *Duoxa* KO mice. Data represent geometric means with 95% CI of *Duoxa2* mRNA expression in the terminal ileum of intestinal epithelial-specific *Duoxa* KO (n = 5) and floxed littermate control mice (n = 6). **, $P < 0.01$; 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*^{high} samples. (**A**) Ileal *Il17c* expression in WT (n = 22) and *Duoxa*$^{-/-}$ (n = 26) mice derived from 14 distinct breeding pairs (parental genotypes: *Duoxa*$^{+/-}$). 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 ($AF_{ancestry}$, i.e., gnomAD_NFE_AF, gnomAD_ASJ_AF, or gnomAD_FIN_AF).