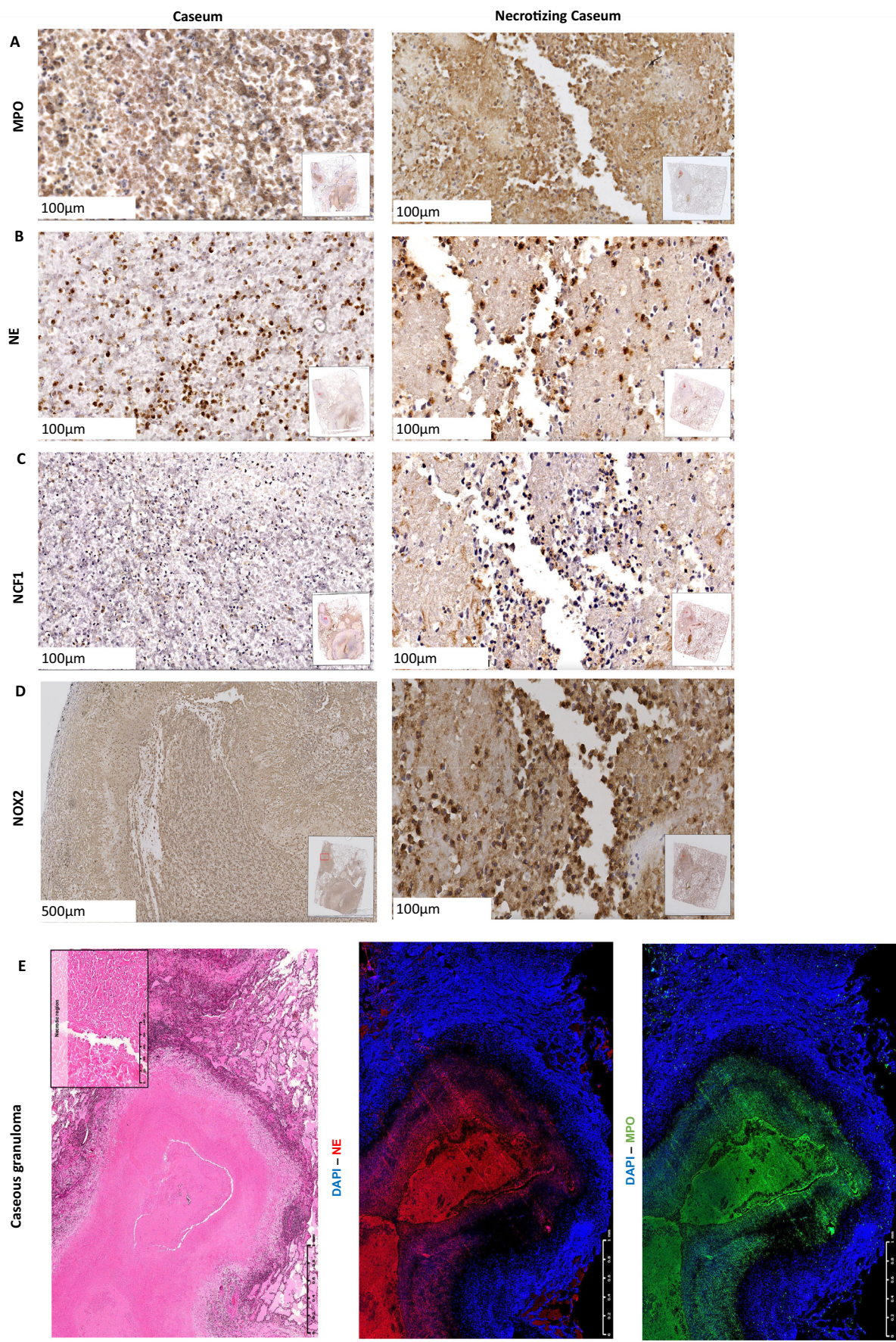


Expanded View Figures

Figure EV1. Neutrophil-specific proteins are enriched and colocalize in necrotic caseum.

(A) MPO and (B) NE were abundant in early caseum (containing cellular debris) and necrotizing caseum. (C) NCF had a positive stain in caseum, which was more pronounced in necrotic regions. (D) NOX2 was more enriched in the borders of necrotizing caseum. IF staining of MPO (green) and NE (red) in the caseum (E). Scale bar represents 100, 500, and 1 mm.



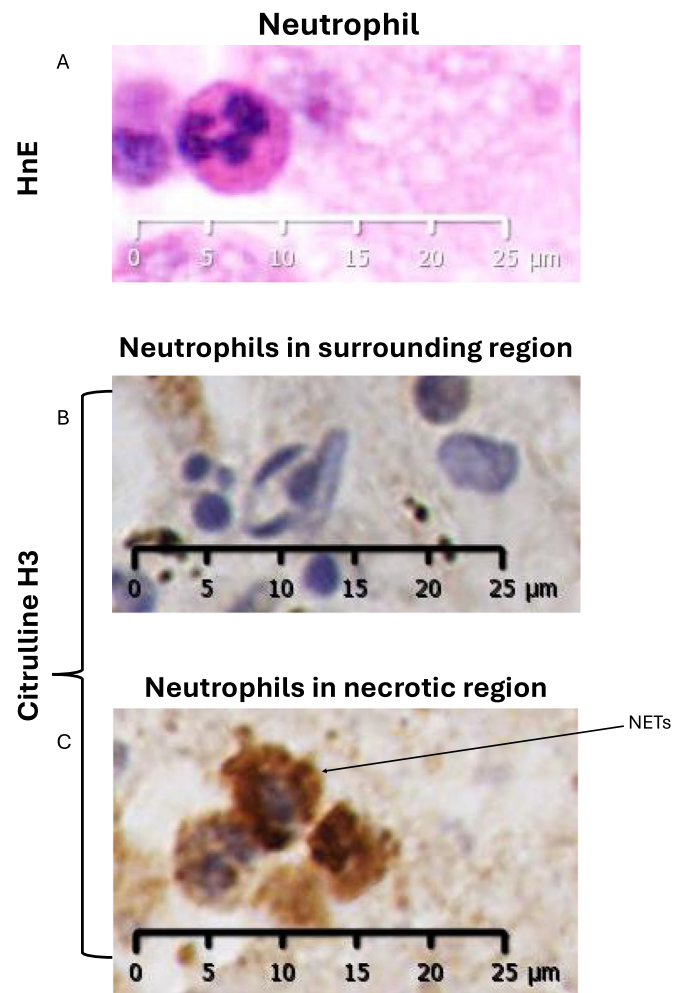


Figure EV2. NETs are more abundant in the caseum than in cellular regions.

Lung tissue samples were stained with hemolysin and eosin (A). IHC-stained tissue showing Citrulline H3-negative neutrophils in the cellular region of TB granuloma (B). IHC-stained tissue showing neutrophils extruding NETs in the caseum of TB granulomas (C). Scale bar = 25 μm.

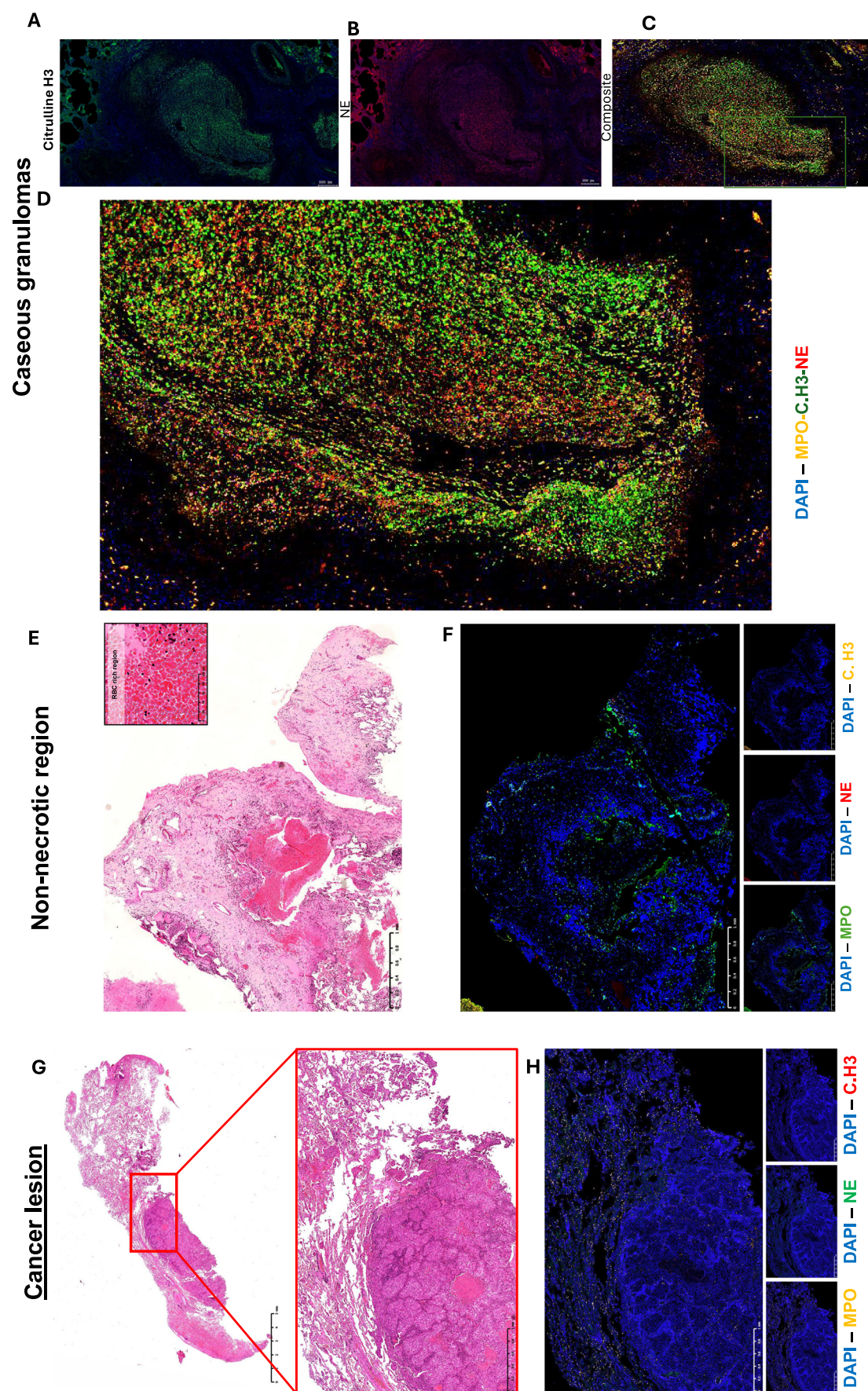


Figure EV3. Neutrophil elastase colocalizes with NETs in the granuloma caseum.

Immunofluorescence (IF) staining showing citrulline H3 (green) (A), NE (Red) (B), and composite citrulline H3, NE, and MPO (yellow) co-staining on the same caseous granuloma (C), which is zoomed in to show colocalization of NE and citrulline H3 (D). H&E staining of human TB lung illustrating a non-necrotic granuloma (E). IF staining of MPO (Green), NE (Red) and citrulline H3 (Yellow) on non-necrotic granuloma (F). H&E staining of control human adenocarcinoma associated lung pathology (G). IF staining of the adenocarcinoma lesion showing MPO (Yellow), NE (Green), and citrulline H3 (Red). Scale bars represent 5 mm, 1 mm, 500 μ m, and 50 μ m as indicated on each image.

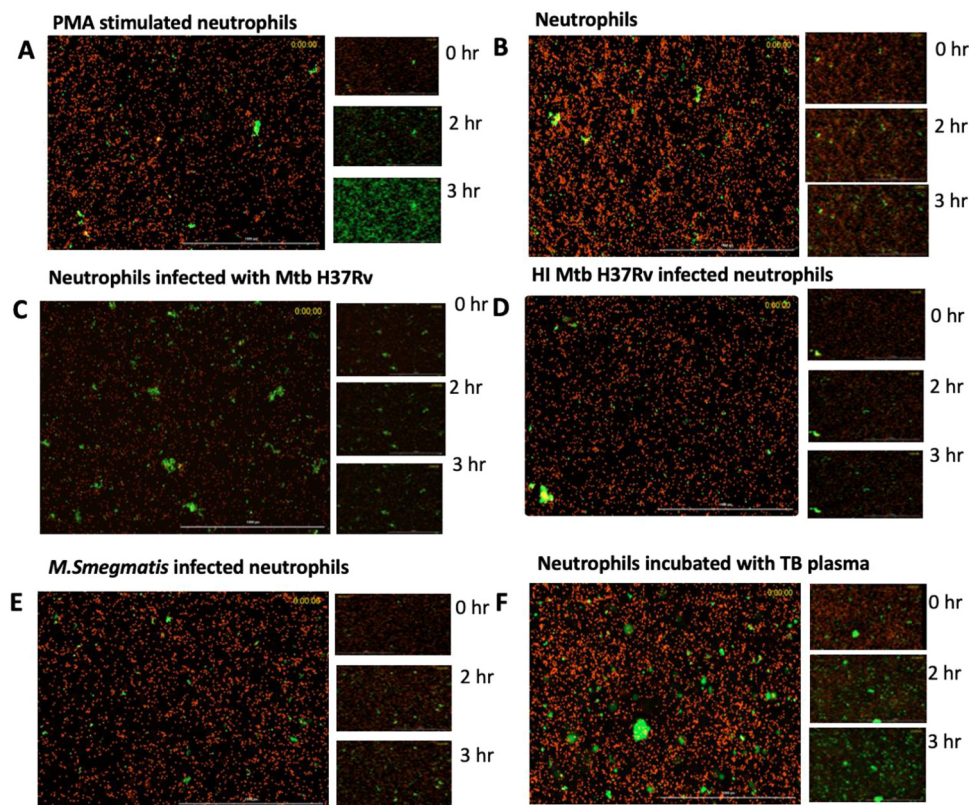


Figure EV4. Pathogenicity and viability of Mtb H37RV impact NETosis.

Neutrophils were stimulated/infected with (A) PMA stimulated neutrophils ($n = 3$), (B) neutrophils ($n = 3$), (C) neutrophils infected with Mtb H37RV ($n = 3$), (D) neutrophils infected with Heat-Inactivated Mtb H37RV ($n = 3$), (E) neutrophils infected with *M. smegmatis* ($n = 3$), and (F) Neutrophils incubated with TB plasma ($n = 3$). The indicated scale represents magnification with the Biotek® cytation 5 Gen 5 software at 1000 μm . Green fluorescence at an excitation/emission of 503/526 nm was detected with GFP filter, and Permeable nuclear red at 622/645 nm was detected with Cy5 filter using the Biotek® Cytation 5 cell imaging multi-mode reader. Images were captured every 30 min for 6 h and represent a single section within each well.

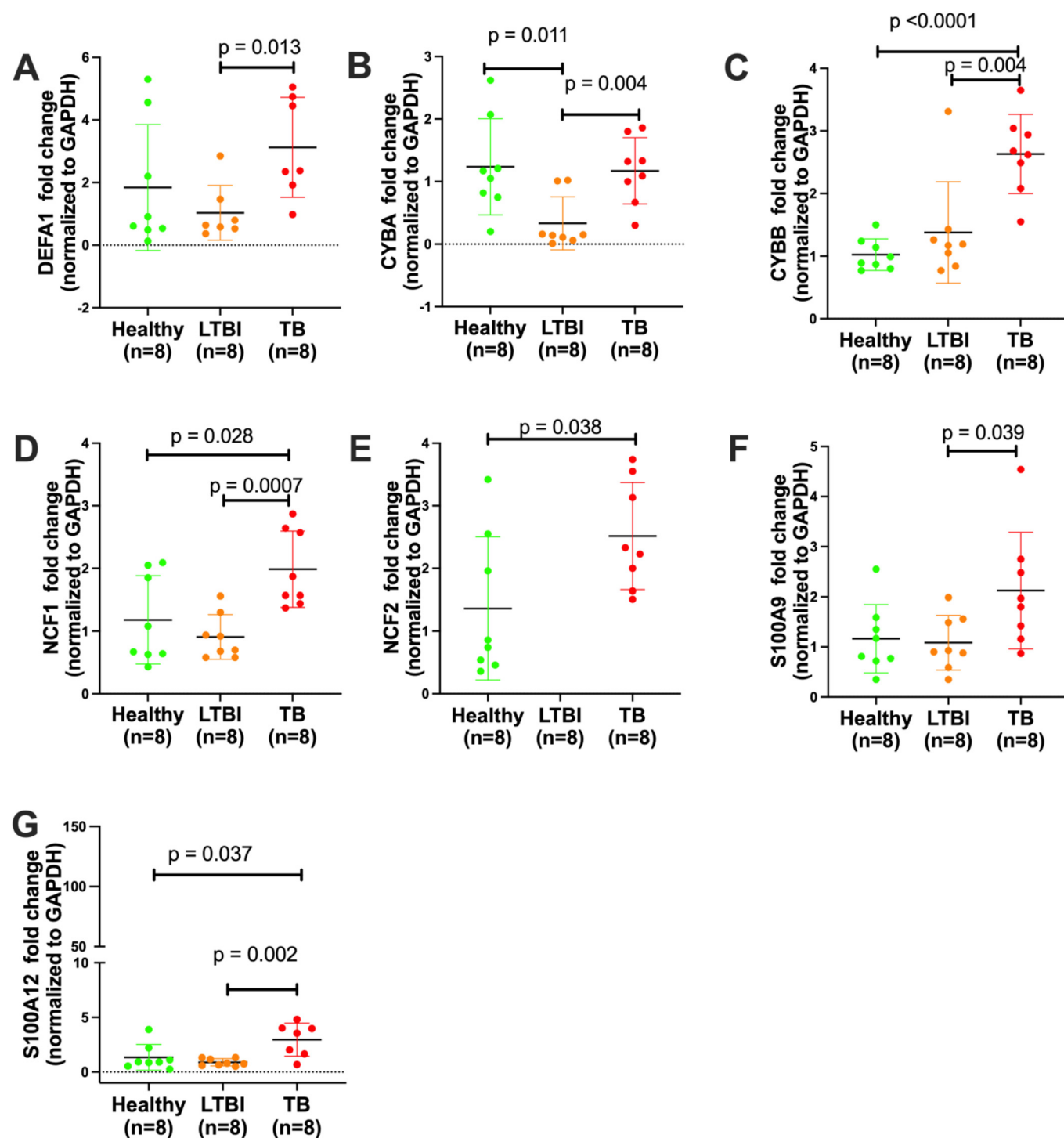


Figure EV5. Gene expression analysis of candidate genes in healthy ($n = 8$), LTBI ($n = 8$), and TB ($n = 8$) participants.

(A) DEFA1 was significantly upregulated in the TB arm compared to the LTBI arm ($p = 0.013$), (B) CYBA was more upregulated in the healthy arm compared to the LTBI arm ($p = 0.011$) and in the TB arm compared to the LTBI arm ($p = 0.004$), (C) CYBB was upregulated in the TB arm compared to the healthy arm ($p < 0.0001$) and LTBI arm ($p = 0.004$), (D) NCF1 was upregulated in the TB arm compared to the healthy arm ($p = 0.028$) and the LTBI arm ($p = 0.0007$), (E) NCF2 was more upregulated in the TB arm compared to the healthy arm ($p = 0.038$), (F) S100A9 was more upregulated in the TB arm compared to the LTBI arm ($p = 0.039$) and (G) S100A12 was upregulated in the TB arm compared to the healthy arm ($p = 0.037$) arm and LTBI arm ($p = 0.002$). All gene expression values were normalized to GAPDH using the $2\Delta\Delta^{ct}$ method. Unpaired t-tests were used to determine significant ($p < 0.05$) differences between groups.