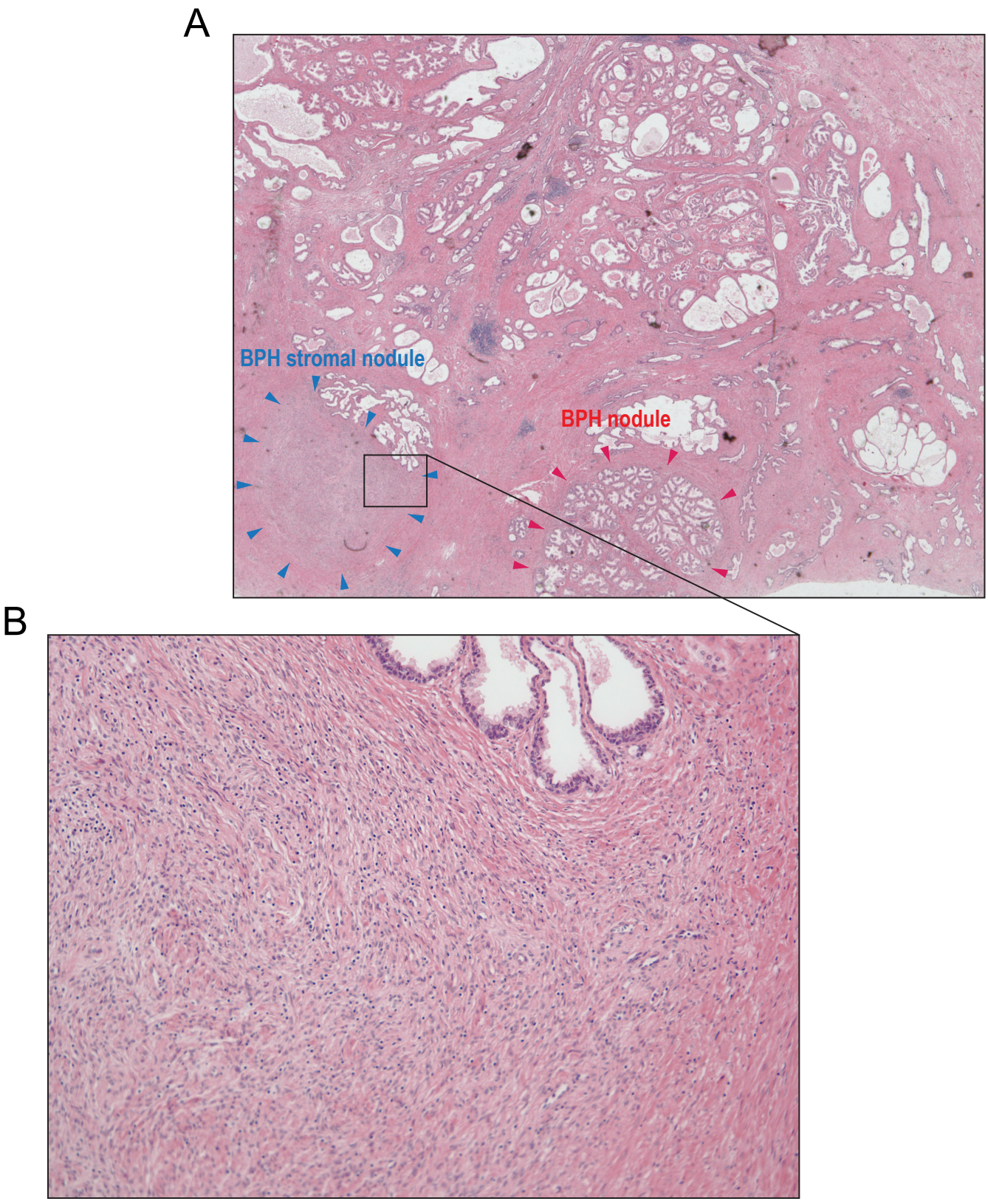
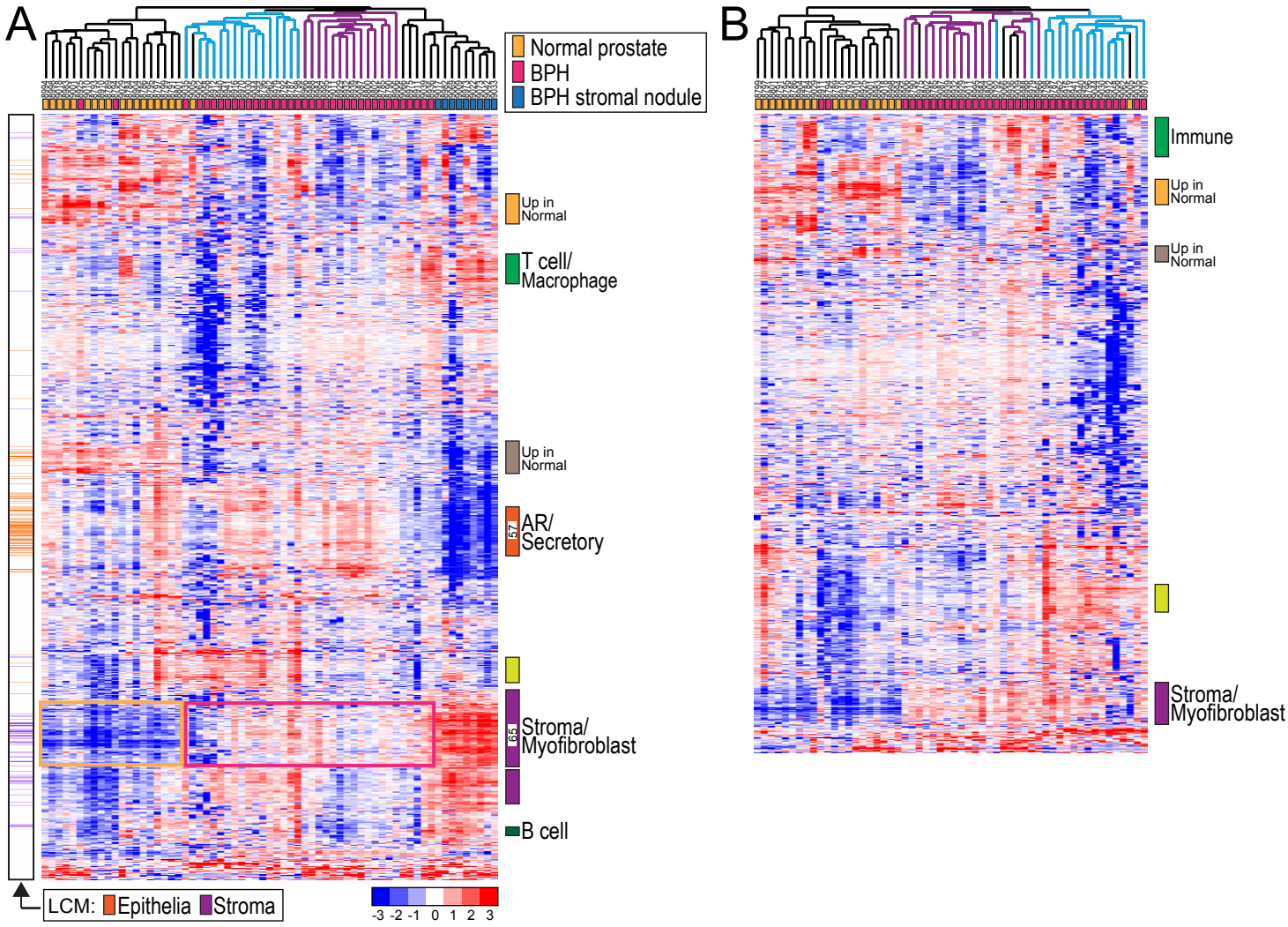
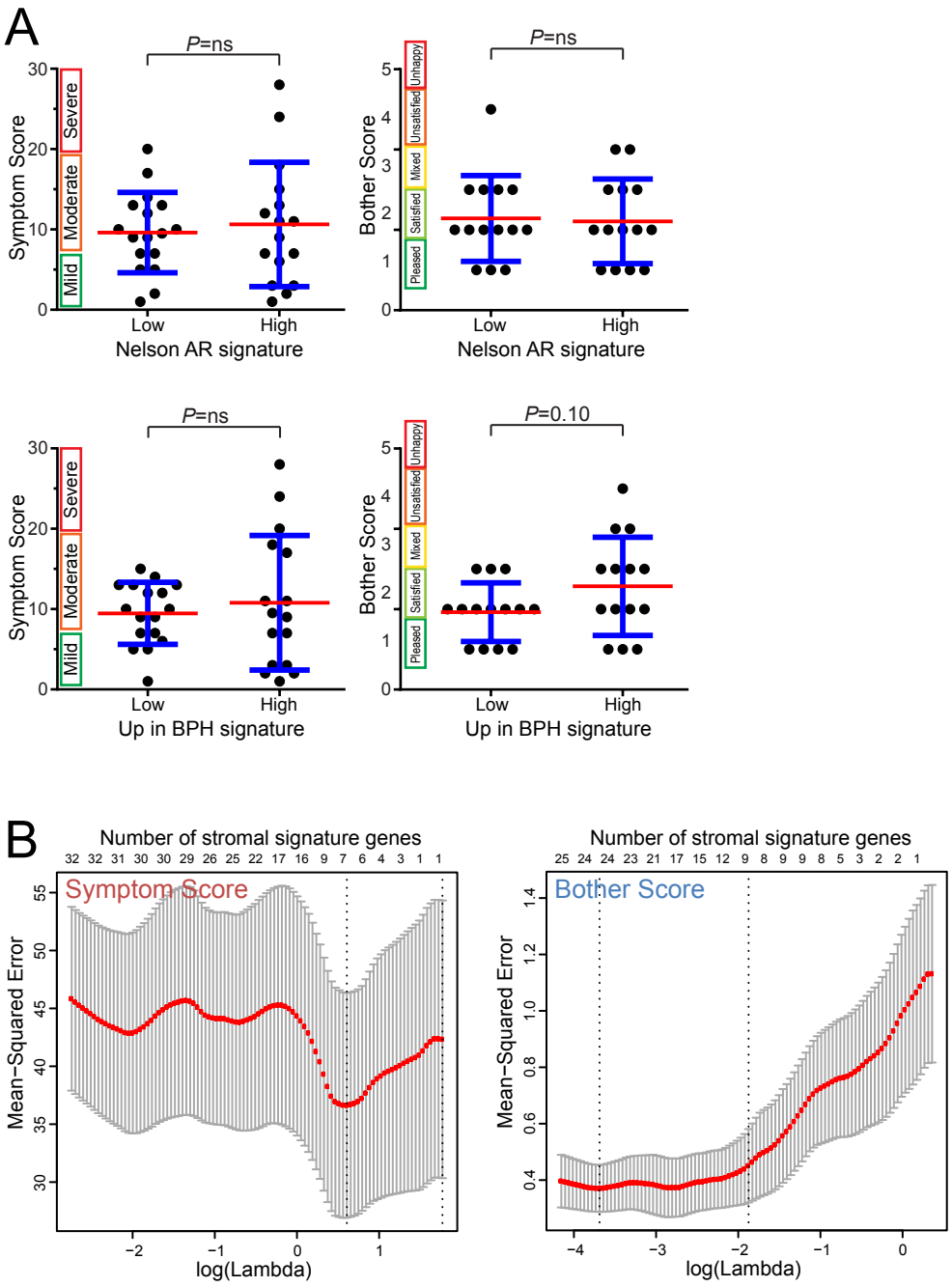


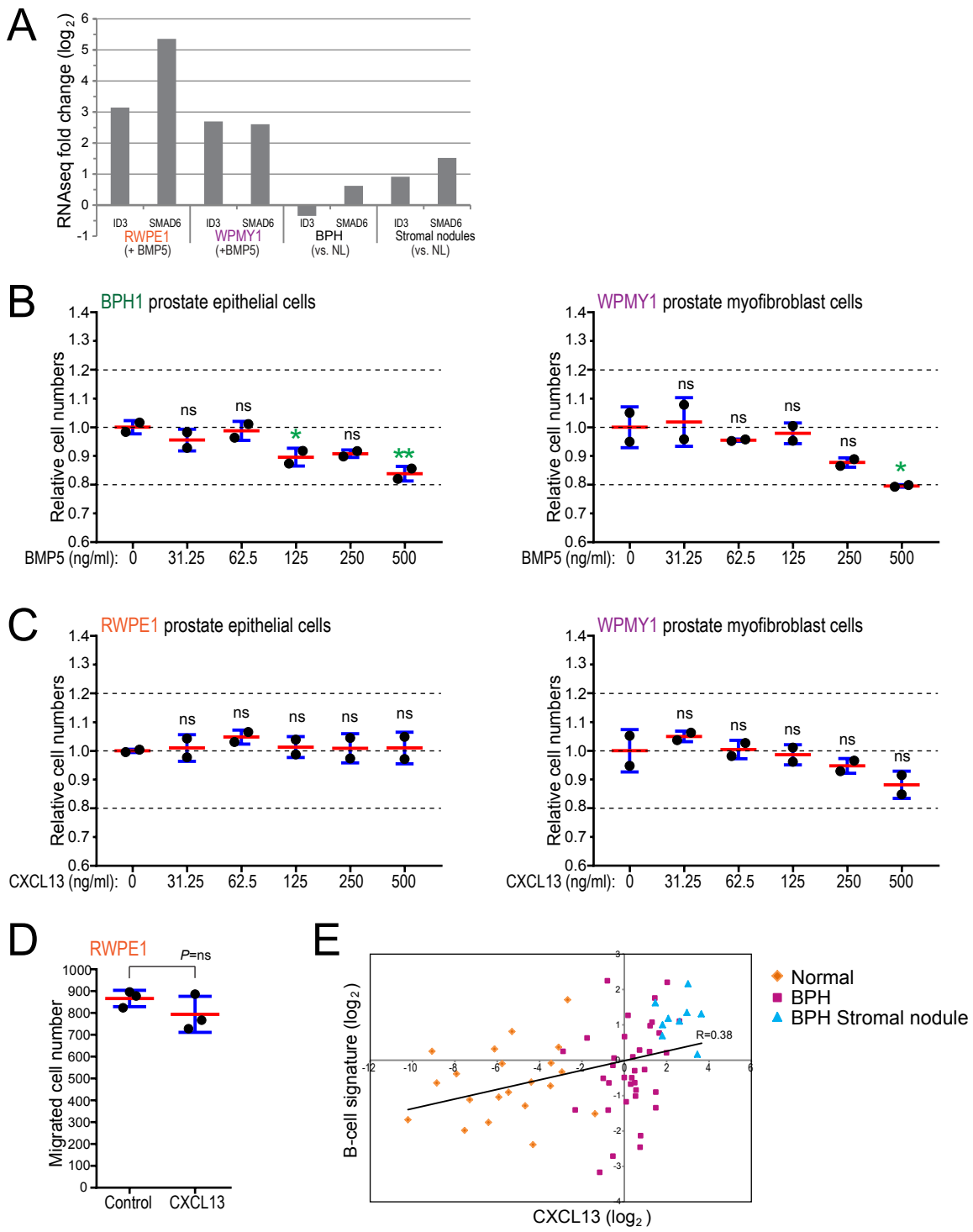
Supplemental Figure 1. BPH stromal nodule. (A) H&E-stained section of prostate showing a typical BPH nodule (right, demarcated by red arrowheads) containing both epithelial and stromal elements, as well as a BPH stromal nodule (left, demarcated by blue arrowheads). Original magnification, 10X. **(B)** Close-up of BPH stroma nodule. Original magnification, 40X. Note, BPH cases with and without stromal nodules show no significant differences with regard to prostate size, BPH Symptom Score, or BPH Bother Score.



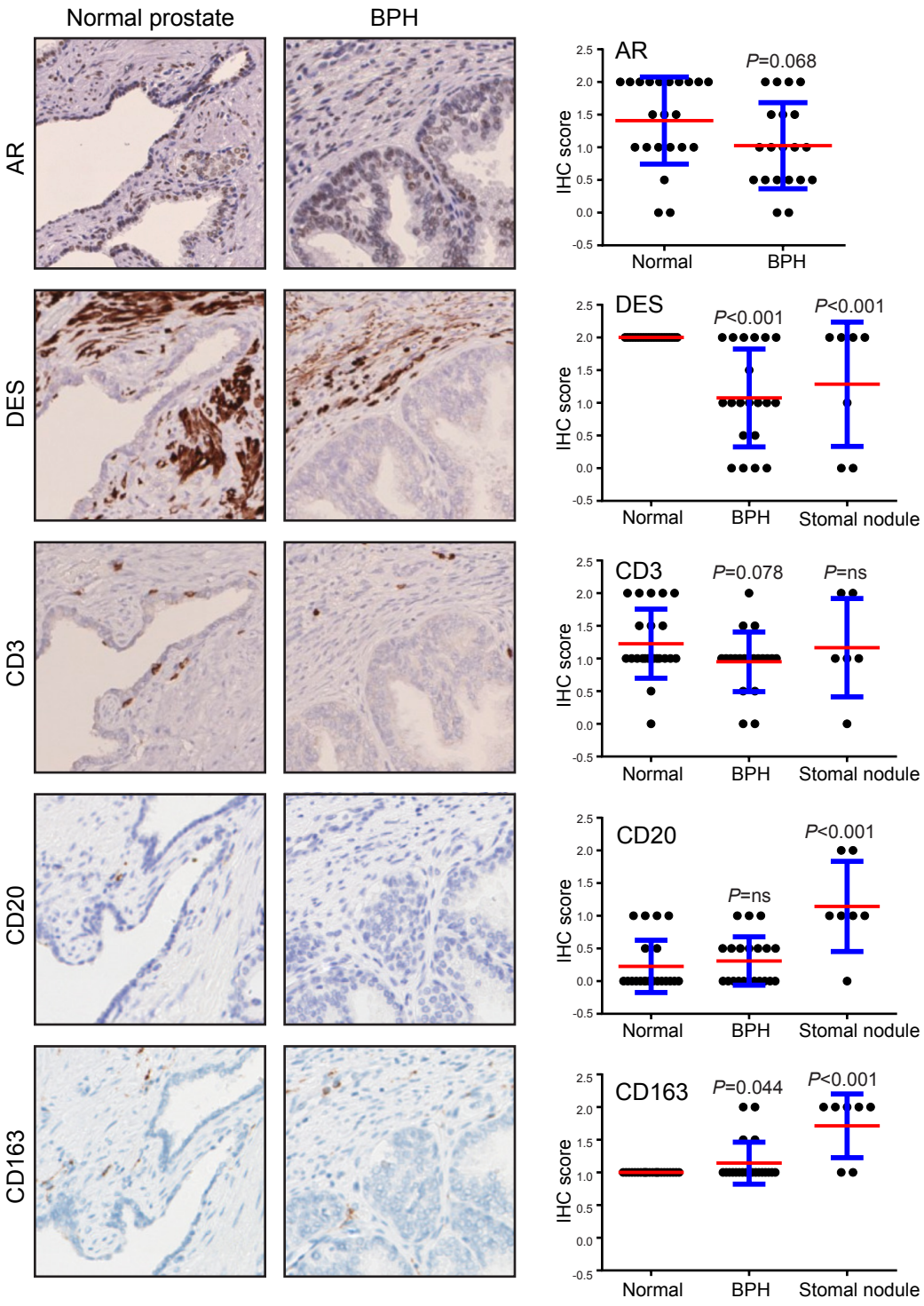
Supplemental Figure 2. BPH transcriptional landscape. Heatmaps of unsupervised clustering of normal prostate and BPH specimens, either **(A)** including, or **(B)** excluding the BPH stromal nodules. The same criteria for variably-expressed genes (StDev ≥1.2) was used, resulting in fewer genes in (B). Note, BPH sample subclusters are preserved (see colored dendrogram branches), as are most but not all gene-expression features.



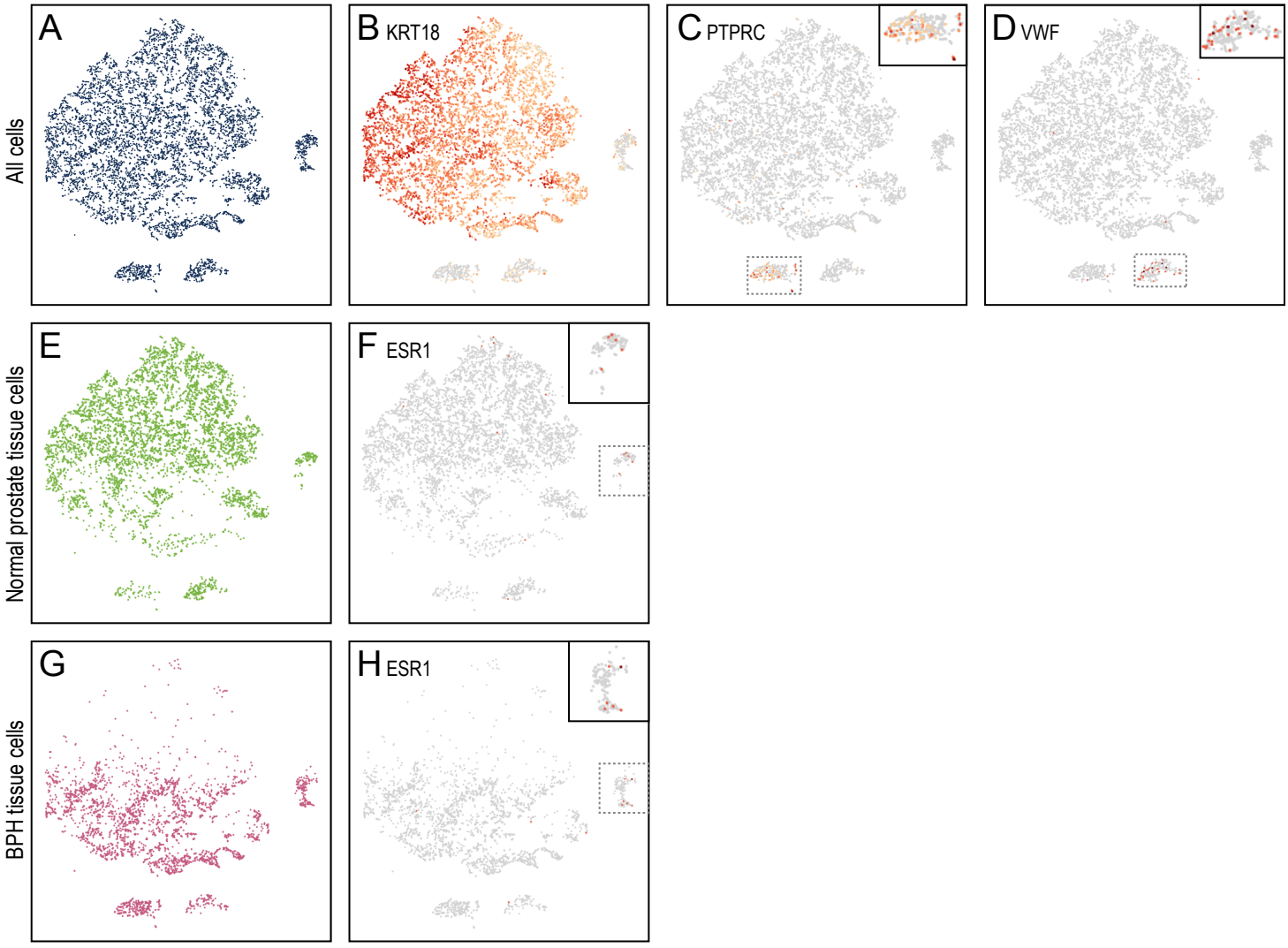
Supplemental Figure 3. Gene signatures and BPH symptoms. (A) High expression (top 50%) of a published "Nelson AR signature" (top) and the SAM-derived "Up in BPH signature" (bottom) are not significantly associated with BPH Symptom score (left) or Bother Score (right). Mean (red) and SD (blue) shown; P-values generated from 2-sided Student's t-test. **(B)** Performance of stromal genes in predicting BPH Symptom score (left) and Bother Score (right). Gene-based predictor built by lasso, and mean-squared error determined by leave-one-out cross validation. Note, inclusion of stromal genes (optimal 9-23) in the Bother Score model reduces the mean-squared error by about 70%.



Supplemental Figure 4. Additional analyses of BMP5 and CXCL13 in BPH. (A) BMP5 induces canonical SMAD transcriptional targets (ID3 and SMAD6) in RWPE-1 and WPMY-1 cells. In BPH tissue, SMAD6 is upregulated in BPH (vs. normal prostate), and both ID3 and SMAD6 are upregulated in BPH stromal nodules (where BMP5 transcript levels are highest). Values plotted represent average fold changes (log2). **(B)** BMP5 addition to BPH-1 prostate epithelial cells (left) and WPMY-1 prostate myofibroblast cell (right) leads to modest reduction in cell numbers. Mean (red) and SD (blue) shown. Multiplicity adjusted P-values generated from one-way ANOVA with post-hoc comparison to no BMP5 control (Dunnett test); *, $P<0.05$; **, $P<0.01$. Data for each cell line are representative of two independent experiments, each done with two samples assayed per concentration. **(C)** CXCL13 addition to RWPE-1 (left) and WPMY-1 (right) does not alter cell numbers. Data for each cell line are representative of two independent experiments, each done with two samples assayed per concentration. **(D)** CXCL13 addition to RWPE-1 cells does not alter cell migration. Mean and SD shown; P-value generated from 2-sided Student's t-test. Data are representative of two independent experiments, each done with three samples assayed per condition. **(E)** Plot of CXCL13 transcript levels vs. B-cell signature (average of 14 genes) demonstrates correlation across bulk prostate tissues. Note, in BPH stromal nodules both CXCL13 and the B-cell signature are elevated, while in BPH tissue only CXCL13 is elevated (relative to normal prostate).



Supplemental Figure 5. IHC analyses of cell lineage markers. (Left) Immunostains of lineage markers are shown of the same representative case illustrated in Figure 4. (Right) IHC scores across all TMA cases. Mean (red) and SD (blue) shown; P-values generated from 2-sided Student's t-test (in comparison to normal prostate).



Supplemental Figure S6. Single-cell RNAseq; visualization of additional markers. (A) Two-dimensional projection (t-SNE plot) of single cell transcriptomes stratifies prostate tissue cells (dots) into distinct clusters, identifiable by characteristic expression of marker genes, including **(B)** KRT18 (all epithelium) (red intensity scales to maximum log2 expression), **(C)** PTPRC (CD45 antigen; leukocytes), and **(D)** VWF (Von Willebrand Factor; endothelium). **(E)** Normal prostate tissue cell subset, illustrating expression of **(F)** ESR1 (within fibroblasts). **(G)** BPH tissue cell subset, illustrating expression of **(H)** ESR1 (within fibroblasts). Insets magnify select cell clusters.