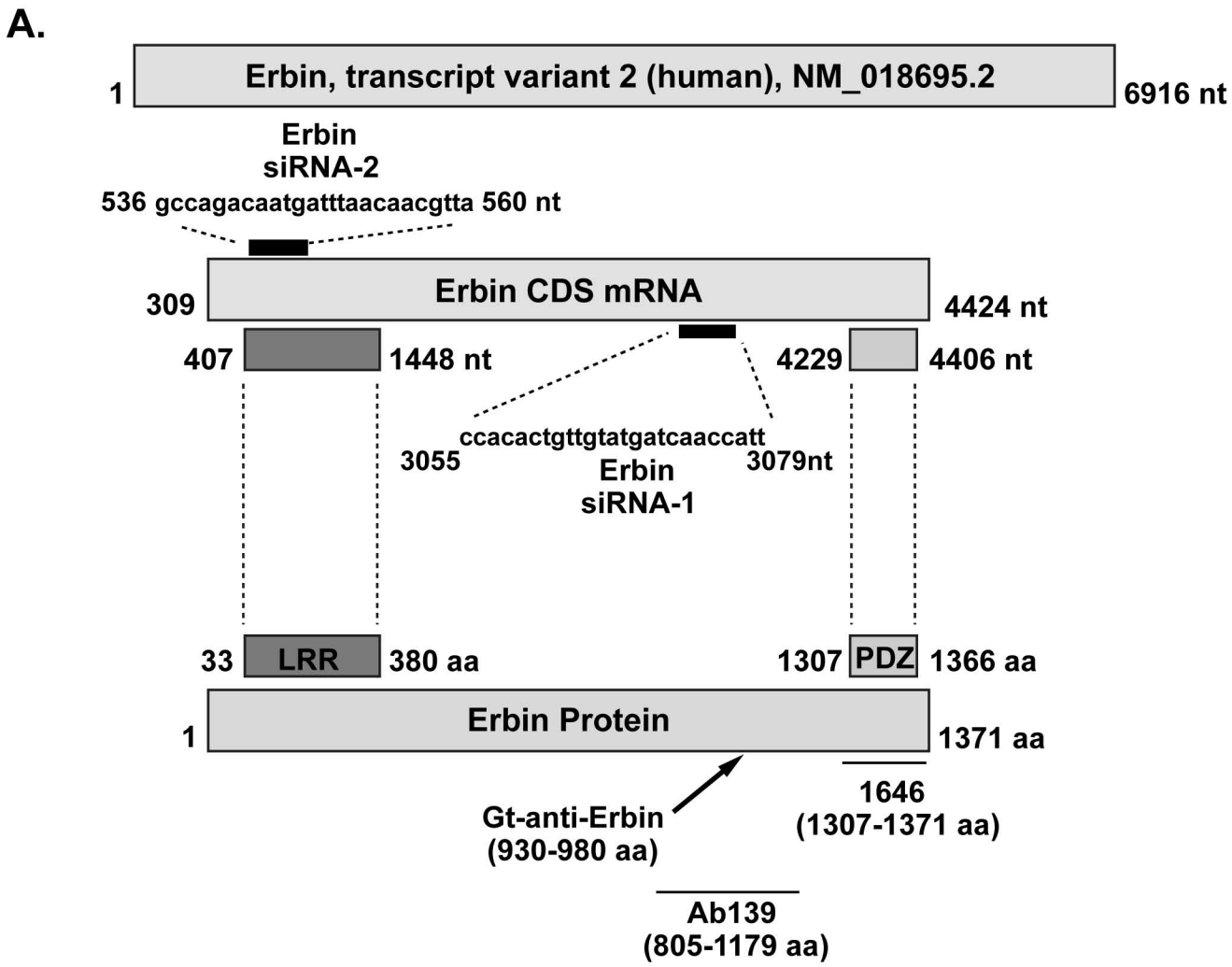
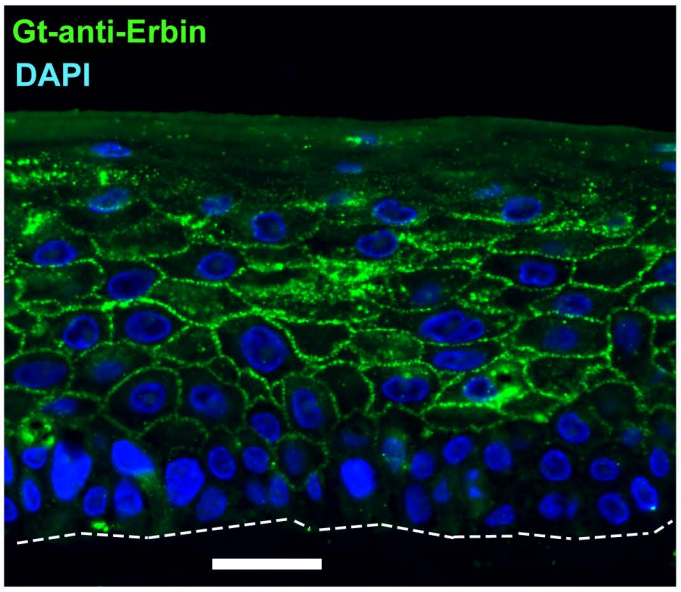
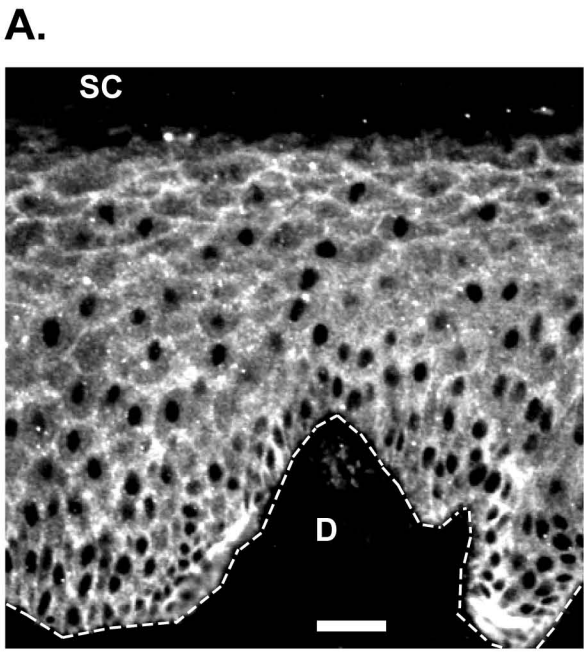


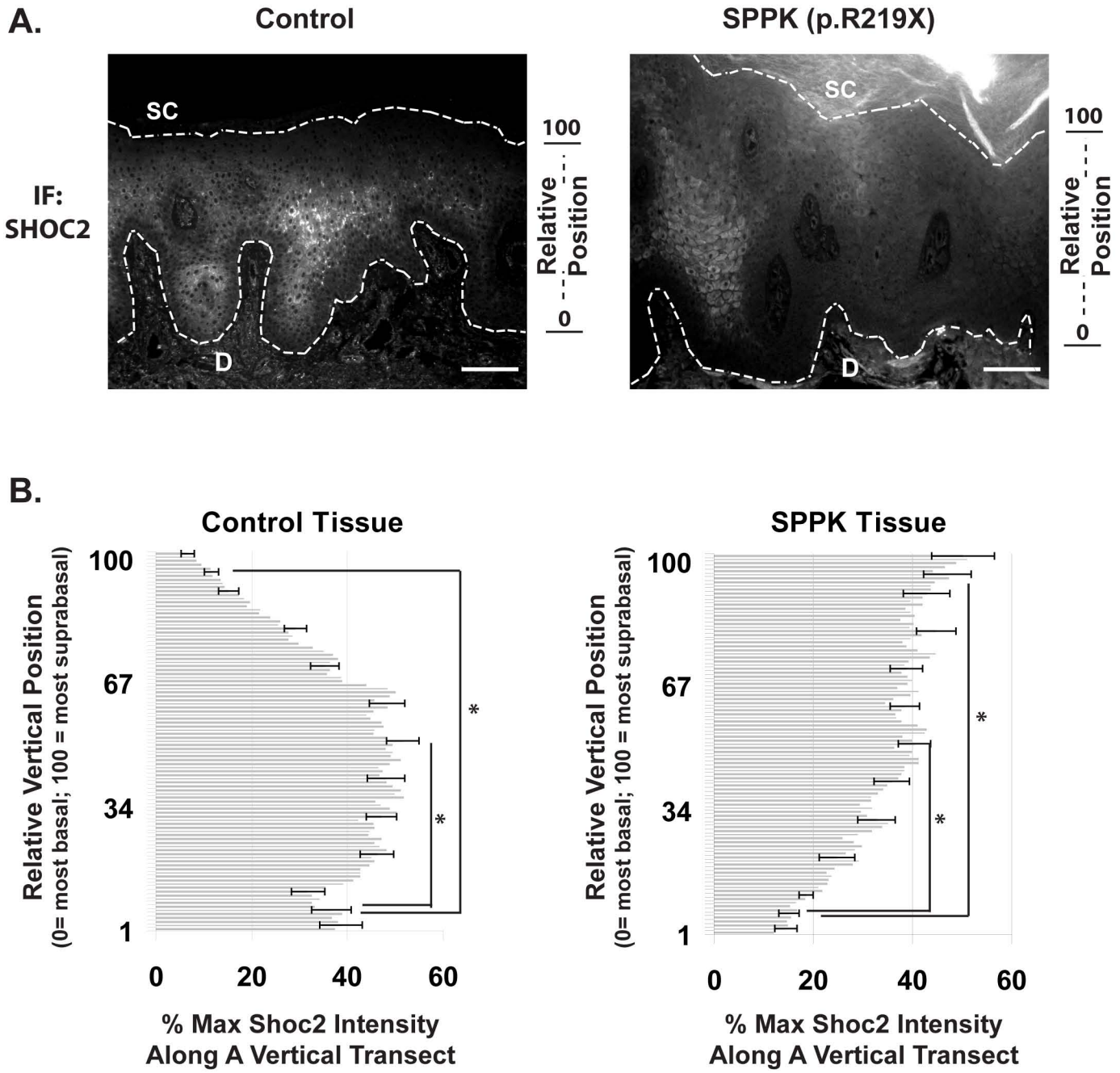
Supplemental Figure 1. (**A**) Map of Erbin demonstrating siRNA target sites and antibody epitopes. (**B**) NHEKs were treated with a control siRNA, Erbin siRNA-1 or Erbin siRNA-2. Cells were switched to 1.2mM $CaCl_2$ for 48hrs to induce differentiation in the presence of DMSO, the Mek/Erk signaling inhibitor U0126 or the Alk5/TGFβ signaling inhibitor SB431542. Urea/SDS lysates were collected, subjected to SDS-PAGE and analyzed by western blot for the indicated proteins.



Supplemental Figure 2. (**A**) Immunofluorescent gt-anti-Erbin staining of a three dimensional NHEK culture, stratified for 6 days. Scale bar: 25μm. (**B**) Western blot analysis of organotypic NHEK cultures, +/- Erbin siRNA, cultured in parallel with those shown in Figure 3e. Lysates were collected 3 days after initiating stratification whereas cultures shown in Figure 3e were allowed to stratify for 6 days. (**C**) The RIPA insoluble pellets from Figure 6 were solublized in a volume of Urea/SDS buffer equivalent to that of the RIPA buffer from which the pellet was isolated. Equal volumes of the solubilized pellets from cells infected with the indicated constructs were analyzed by western blot with antibodies against the FLAG-tag or Dsg1 (capable of detecting endogenous and ectopic protein).



Supplemental Figure 3. (**A**) Immunofluorescence staining of human plantar epidermis with mouse anti-pan-Ras. Scale bars: 50 μm. (**B-C**) Staining of plantar epidermis with goat anti-Erbin, high and low magnification, scale bars: 50μm. Dashed line represents approximate locations of the basement membrane. D = dermis; SC = stratum corneum.



Supplemental Figure 4. Dsg1-deficiency alters the localization pattern of the Erbin-binding partner, Shoc2. (**A**) Localization of Shoc2 by immunofluorescence in plantar epidermal samples from a control patient or a striate palmoplantar keratoderma (SPPK) patient harboring a mutant Dsg1 allele (p.R219X). Dotted lines represent the border between epidermal cells and the underlying dermis (D) as well as the border between granulosum keratinocytes and the overlying stratum corneum (SC) as assessed by morphology. These boundaries were assigned the arbitrary values of 0 (basal boundary) and 100 (boundary with SC) for the quantitation presented in panel B. Scale bars: 100 μm. (**B**) Graphical representation of Shoc2 localization patterns with respect to vertical position in the epidermis (0-most basal; 100-most suprabasal). Staining intensity is expressed as a percentage of most intense pixel observed along a vertical transect. One hundred evenly spaced sample measurements were taken along each transect. Ten transects spaced roughly 70 microns apart were analyzed on sections obtained from three control patients and three SPPK patients carrying the following Dsg1 mutations: p.R26X, p.R219X and p.D644fs. The mean values at each position (1-100) were calculated for control and diseased tissue. Error bars represent standard error of the mean, brackets represent significantly different measurements (student t-test p-values<0.05*).