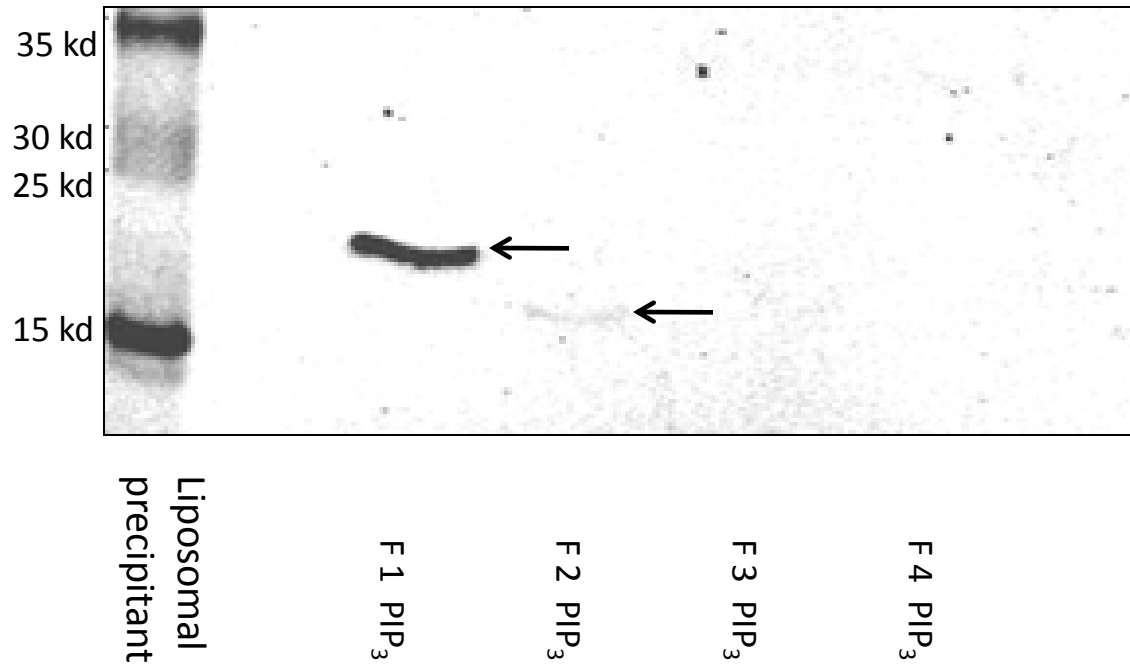


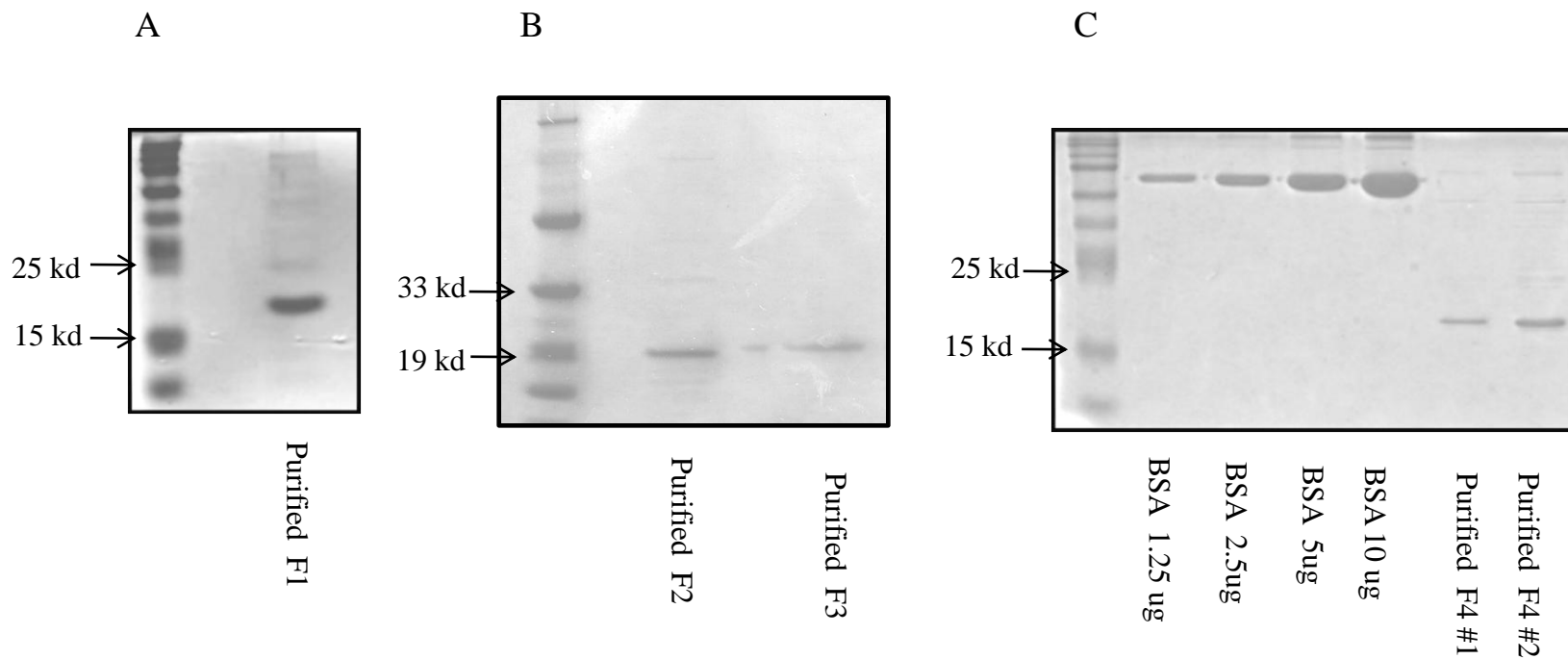
**Supplementary Table 1. Summary of  $K'(H^+)_i$  values** for WT NHE3 and NHE3 point mutations under basal, serum, and wortmannin conditions. \*  $P < 0.05$  comparing each cell type basal vs. serum and wortmannin  $K'(H^+)_i$ . +  $P < 0.05$  comparing basal WT vs. mutant  $K'(H^+)_i$ . Percent changes for serum and wortmannin vs. the basal rate for that cell type are shown only where significant changes occur.

**$K'(H^+)_i$**

Cell Type (PS120 / NHERF2)	Basal $K'(H^+)_i$	Serum $K'(H^+)_i$	Serum % change	Wort $K'(H^+)_i$	Wort % change
1. WT	0.36	0.19*	47%	0.46*	28%
2. Y501A, R503A, K505A	0.70 +	0.68	NS	0.72	NS
3. F509A, R511A, R512A	0.37	0.29*	22%	0.62*	68%
4. R511L, R512L	0.61+	0.40*	34%	0.87*	43%
5. R520F, R527F	0.59+	0.60	NS	0.69*	17%
6. R551L, R552L	0.42	0.47	NS	0.60*	43%
7. Y501A, R503A, K505A + F509A, R511A, R512A	0.49+	0.45	NS	0.41	NS



Supplementary Figure S1. PI(3,4,5)P<sub>3</sub> liposomal pull down using conditions of Fig. 2A with 300ng of proteins F1, F2, F3 and F4. Binding with F1 and F2 proteins is seen (shown in arrows) while F3 and F4 do not bind. Note difference in magnitude of binding of F1 and F2.



Supplementary Figure S2. Purified NHE3 C terminal fragments were separated on SDS-PAGE and stained with Coomassie Blue. Shown in figures are Fragments F1 (Fig. 2A), F2 (Fig.2B), F3 (Fig.2B) and F4 (Fig.2C). Predicted sizes are F1-17 kd, F2-13 kd, F3-13 kd, and F4-14 kd. The fragments run at slightly higher than the predicted size. (BSA : bovine serum albumin).