RSP5 encodes an essential protein that is the only S. cerevisiae member of the NEDD4 family of E3 ubiquitin ligases. NEDD4 ubiquitin ligases are structurally similar and are comprised of an N-terminal C2 domain, a series of WW domains, and a C-terminal catalytic HECT domain. For Rsp5p, the C2 domain binds phosphoinositides, the C2 and WW domains mediate substrate recognition, the C2 and HECT domains are important for proper cellular localization, and the HECT domain contains two ubiquitin binding sites. One of these ubiquitin binding sites is the active site and forms a covalent thioester intermediate with ubiquitin and the other is a non-covalent ubiquitin binding site that may regulate the length of polyubiquitin chains formed on subtrates. Rsp5p is a multifunctional enzyme that is able to both mono- and polyubquitinate target proteins thereby regulating many cellular processes including endocytosis, multivesicular bodysorting, RNA export, transcription, lipid biosynthesis, mitochondrial inheritance, and protein catabolism. While Rsp5p is able directly interact with some of its targets, in other cases substrate interaction is mediated by adapter proteins. Human NEDD4 is associated with a hereditary form of hypertension known as Liddle syndrome.