VMA8 encodes the D subunit of the yeast V-ATPase V1 domain. Vacuolar-ATPasesare ATP-dependent proton pumps that acidify intracellular vacuolar compartments. Vacuolar acidification is important for many cellular processes, including endocytosis, targeting of newly synthesized lysosomal enzymes, and other molecular targeting processes. The V-ATPase consists of two separable domains. The V1 domain has eight known subunits, is peripherally associated with the vacuolar membrane, and catalyzes ATP hydrolysis. The V0 domain is an integral membrane structure of five subunits, and transports protons across the membrane. The structure, function, and assembly of V-ATPases are reviewed in references 3, 6, 7 and 8. The vma8 null mutant is viable but lacks vacuolar-ATPase activity, cannot grow at neutral pH or on nonfermentable carbon sources, and fails to accumulate quinacrine in the vacuole. In the absence of Vma8p, the remaining V1 subunits do not associate with the vacuolar membrane. A specific interaction between Vma8p and the V-ATPase F subunithas been detected. Several mutations in VMA8 cause uncoupling of proton transport from ATPase activity, suggesting that the D subunit normally plays an important role in coupling these activities. V-ATPases have been identified in numerous eukaryotes; a bovine cDNA encoding a homolog of the V-ATPase D subunit has been cloned.