S. cerevisiae has five genes encoding type 4 P-type ATPases: NEO1, DRS2, DNF1, DNF2, and DNF3. The \"P-type\" designation indicates that these integral membrane proteins form a covalent aspartyl-phosphate catalytic intermediate during ATP hydrolysis. Most P-type ATPases mediate the transport of small cations across biological membranes. However, members of the \"type 4\" subfamily are aminophospholipid translocases, rather than cation transporters, and move phospholipids from one side of a membrane bilayer to the other. Of the five S. cerevisiae type 4 P-type ATPases, only NEO1 is essential. Although the four other genes appear to have substantial functional overlap, they are distinct in their localization, specificity, and cofactor association.Dnf1p and Dnf2p localize primarily to the plasma membrane where they maintain aminophospholipid asymmetryand play roles in endocytosisand cell polarity. Both proteins are relatively non-specific and are capable of translocating phosphatidylcholine, phosphatidylserine, and phosphatidylethanolamine. The non-catalytic subunit Lem3p associates with both Dnf1p and Dnf2p, but this interaction has been best characterized with Dnf1p.The P-type ATPase superfamily is evolutionarily conserved, but the type 4 subfamily is found only in eukaryotes. Fourteen type 4 P-type ATPases have been characterized in humans, including the DRS2 homolog, ATP8A1and the DNF1/DNF2 homolog ATP8B1. Mutations in ATP8B1 result in progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis, and intrahepatic cholestasis of pregnancy.