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Phosphoinositides are important lipid signals in plant developments and stress responses. However, multiple isoforms of the phosphoinositide biosynthetic genes hamper our understanding of the pivotal enzymes in each step of the pathway. In this study, we report that Arabidopsis phosphoinositide-specific phospholipase C2 (AtPLC2) is the primary phospholipase in phosphoinositide metabolism and is involved in the endoplasmic reticulum (ER) stress responses. Lipidomic profiling of multiple *plc* mutants showed that the *plc2-1* increased levels of its substrates phosphatidylinositol 4-phosphate and phosphatidylinositol 4,5-bisphosphate, suggesting that the major phosphoinositide metabolic pathway is impaired. AtPLC2 displayed a distinct tissue expression pattern and localized at the plasma membrane in different cell types. Moreover, the *plc2-1* showed hypersensitive response to ER stress as evidenced by changes in relevant phenotypes and gene expression profiles. Our results revealed the primary enzyme in phosphoinositide metabolism and an emerging link between phosphoinositides and the ER stress response in plants.