Lipids are important components of cellular membranes but also function as signal molecules in many cellular processes including apoptosis, autophagy and inflammation. In the last decade many new inborn errors of metabolism have been identified, many by next generation sequencing, that are caused by a deficiency of genes involved in phospholipid metabolism including several hereditary spastic paraplegias. A complementary technique that is frequently applied to investigate the functional defect in these disorders is lipidomics, which strives to measure and quantitate as many lipids as possible by (tandem) mass spectrometry. This technique is discussed, followed by a recent example that shows that combining next generation sequencing and lipidomics is a synergetic combination that yields novel biomarkers for inborn errors of lipid metabolism. As a distinct subgroup of hereditary spastic paraplegias is caused by mutations in genes related to lipid metabolism, lipidomics is suggested as a tool to investigate functional aspects of these disorders.