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Gene Mutations Associated with Dystonia-Parkinsonism Do Not Impair PLA2G6 Phospholipase Activity Sthitadhi Chakraborty

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Mutations in the PLA2G6 gene have been identified in autosomal neurodegenerative diseases, such as dystonia-parkinsonism and infantile neuronal dystrophy (INAD). Those with dystonia-parkinsonism develop a parkinsonian movement disorder between the ages of 15 and 30. The PLA2G6 gene encodes an enzyme known as calcium-independent phospholipase A2 beta (iPLA₂ β), which hydrolyzes the sn-2 acyl groups of phospholipids and lysophospholipids, producing free fatty acids. In previous studies we found that PLA2G6 mutations associated with INAD cause loss of function for the enzyme, but PLA2G6 mutations associated with a dystonia-parkinsonism phenotype do not impair the catalytic function in A2 phospholipase and lysophospholipase assays. Due to the recessive nature of dystonia-parkinsonism, we hypothesize that mutations in PLA2G6 cause loss of PLA2G6 function. In this study, we investigated the A1 phospholipase activity of PLA2G6 and whether dystonia-parkinsonism mutations impair this aspect of PLA2G6 function.

We produced wild-type (WT) PLA2G6 and mutant PLA2G6 proteins in HEK293 cells by transient transfection of expression plasmids. The A1 phospholipase activity (hydrolysis of the sn-1 acyl group) was measured in sonicated cell extracts using the fluorogenic phospholipase substrate, *PEDA1*, at 37°C. We find that after controlling for enzyme concentration, catalytic activity of mutant PLA2G6 proteins is not significantly different from WT. Some mutations even have slightly greater catalytic activity for *PEDA1* when compared to WT.

These results were compared to previous studies involving mutations in *PLA2G6* and their association with diseases such as INAD and dystonia-parkinsonism. The findings solidified the notion that dystonia-parkinsonism mutations do not directly impair *PLA2G6* catalytic activity in a significant manner, and therefore may impair PLA2G6 function by other mechanisms.