Parkinson’s disease (PD) is characterized by preferential loss of dopaminergic neurons in the substantia nigra pars compacta. The majority of reported idiopathic PD cases are due to exposure to environmental toxins (PD stressors), such as pesticides (rotenone), recreational drugs (MPTP), and many more. The exact mechanisms by which the dopaminergic neurons die preferentially as a result of exposure to these PD stressors remain elusive. Here, we hypothesize that PD stressors cause dopaminergic neuron death by reducing mitofilin levels through parkin-mediated ubiquitination. We have previously reported that mitofilin loss in hearts of mice subjected to ischemia reperfusion leads to cell death. Additionally, knockdown of mitofilin using siRNA increased cell death via the AIF-PARP cleavage pathway in H9c2 cells. Treatment of N27-A+ dopaminergic neuron cell line with PD stressors increased parkin levels and reduced mitofilin levels. Using confocal microscopy and IP experiments, we found a novel parkin-mitofilin interaction in PD stressor-treated cells, as opposed to vehicle-treated cells. This interaction led to specific mitofilin loss via ubiquitination. Furthermore, the PD stressor-treated cells elicit abnormal mitochondrial structure and altered function following mitofilin loss. This work will be the first of its kind suggesting a distinctive mitofilin loss pathway underlying idiopathic Parkinson’s disease. Conversely, overexpressing the mitochondrial deubiquitinase USP30, attenuated the mitofilin loss induced by PD stressors and enhanced survival of N27-A+ cells. We also found that PD stressors reduced mitochondrial membrane potential, increased ROS production, and increased ER stress in N27-A+ cells. Additionally, C57B6 mice induced to elicit Parkinsonism via rotenone administration, 6-OHDA, unilateral lesion to medial forebrain bundle, and MPTP injection all show remarkable loss of mitofilin as opposed to parkin KO and pink KO counterparts, suggesting that the parkin-mediated ubiquitination of mitofilin underlies the mechanism of mitofilin loss in PD stressor-induced Parkinson’s disease.