The seipin/ Berardinelli-Seip congenital lipodystrophy type 2 (BSCL2) gene encodes for an ER integral membrane protein consisting of 398 or 462 amino acids, the latter as the predominant form in human. Heterozygosity for missense mutations, namely N88S and S90L, destroys the N-glycosylation motif and is associated with a broad spectrum of motor neuron diseases referred to as seipinopathies. So far no in vivo studies of seipin have been done and functions of seipin in neuronal systems are still unknown. Herein we report our results from a study of N88S/S90L double mutant human seipin transgenic mice. We checked the overexpression of transgenic seipin in tgWT (WT seipin transgenic) or tgMT (double mutant seipin transgenic) mice, which showed abnormal movements at late stage based on metabolic chamber analysis and behavior tests. We found that mutant seipin forms protein aggregates in cortical neurons and spinal cord motor neurons, which also exhibits enlarged axons with accumulated neurofilaments despite no obvious motor neuron loss, and also increased GFAP expression. FM-dye destaining analysis of primary neurons showed reduced vesicle exocytosis in neurons expressing mutant seipin, and in vitro studies revealed the effects of seipin on neurite outgrowth of PC12 cells. Live cell imaging indicated the obstructed vesicle trafficking by seipin aggregates in the axons. Taken together, mutant seipin forms protein aggregates in neurons, which leads to the accumulation of neurofilaments and defects in synaptic vesicle trafficking / exocytosis as well as neurite growth, and eventually results in seipinopathies.