# INTRODUCTION

*N*eurodegenerative diseases like Parkinson's disease (PD) and Alzheimer's disease (AD) affect the central nervous system (CNS) and lead to progressive loss of neuron structure and function (Cannon and Greenamyre, 2011; Kim et al., 2013). These are age-related neurological disorders with no cure till date. It is estimated that these neurological diseases affect approximately one billion people worldwide (Brookmeyer et al., 1998). Parkinson's disease affects 1-2% of the worldwide population above the age of 65 (Fig. 1). The symptoms of this disease are bradykinesia (slowness in movements), rigidity, tremor and immobility of the person. It is caused due to the loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain. It is accompanied by the accumulation of cytoplasmic inclusions, called Lewy bodies in the neurons of the brain (DeMaagd and Philip, 2015; Mhyre et al., 2012). The replacement of brain dopamine (DA) via L-DOPA administration in the initial stages of PD offers symptomatic cure but cannot prevent ongoing dopaminergic neuronal loss. The mutation of some genes including α-synuclein, parkin, DJ-1, PINK1 and LRRK2 has been implicated in the familial forms of PD (Lim and Zhang, 2013). Despite the ongoing efforts over the past two decades, the etiology of PD especially the sporadic form remains largely unknown.

Mitochondrial dysfunction and axonal loss is an early pathology of aging as well as neurodegenerative diseases like PD where axons from the synaptic region gradually degenerate to the cell body often termed as a 'dying back' phenomenon (Milton Yu and Luo, 2012; J. M. Osterloh et al., 2012).While neurodegeneration has been studied in the context of various pathological conditions including PD, not much is known about the molecular mechanisms that causes/regulates the axonal retraction during aging. Identification of key targets that delay this process of axonal retraction before they reach the 'point of no return' may prevent axonal degeneration and promote neuronal surival. Recently, in Drosophila melanogaster a protein named dSarm/SARM1 was found to play an essential role in programmed axonal degeneration (Jeannette M. Osterloh et al., 2012). The TIR domain of SARM1 was shown to possess NADase activity causing energy depletion within the cells that played a pivotal role in this process (Essuman et al., 2017; Summers et al., 2016). It has been previously shown that SARM1 is required for mitochondrial reactive oxygen species (ROS) generation and mitochondrial damage in virus-induced neuronal death

(Mukherjee et al., 2013). However, the role of SARM1 in age-associated neurodegeneration remains undetermined so far.
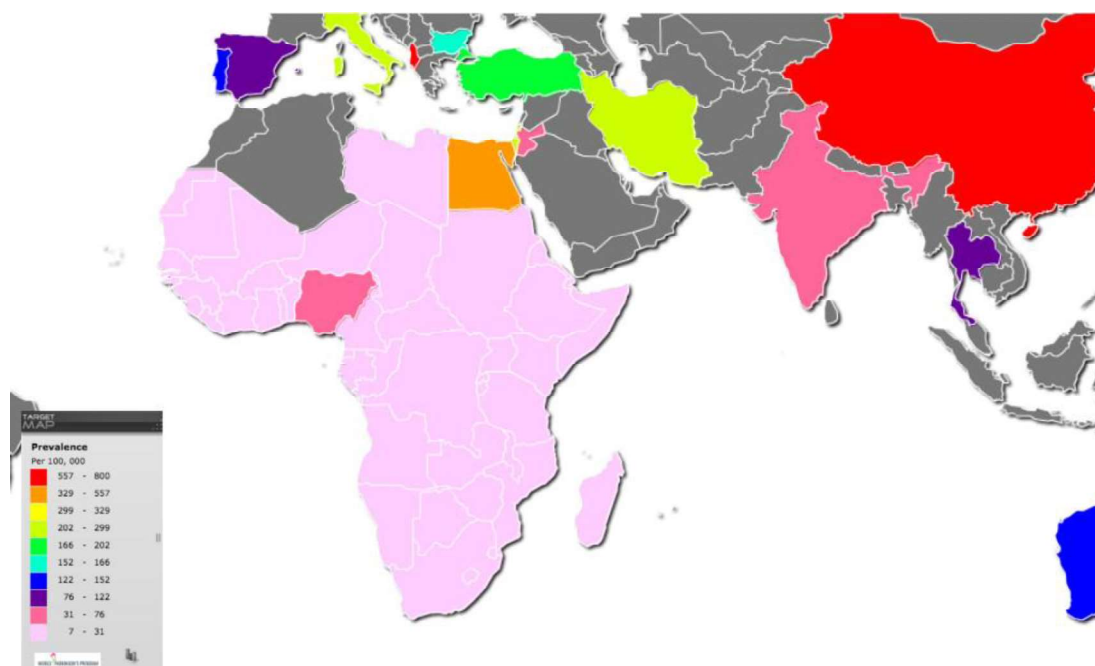
Fig. 1. World map of prevalence of Parkinson's disease

Axonal transport of mitochondria is an important phenomenon that meets the high energy demands of the neuron (Karbowski and Neutzner, 2012; Millecamps and Julien, 2013). Interestingly, mitochondrial defects are quite common in several models of axonal degeneration and aging and provide a significant point of convergence of metabolic regulators that maintain cellular homeostasis (Brookes, 2004; Court and Coleman, 2012). Bioenergetic changes in the neurons associated with defective respiration in the axonal mitochondria are emerging as an important phenomenon in the etiology of neurodegenerative diseases (Schon and Przedborski, 2011; Yin et al., 2012). A constant supply of ATP to meet the cell's bioenergetic demand, scavenging of excess ROS to prevent mitochondrial damage and a rapid turnover of damaged mitochondria are a few challenges which needs to be addressed for the management of age-associated neurodegenerative disorders. This study focuses on whether SARM1 is a master regulator of this well-orchestrated metabolic network at the axonal mitochondria which would be a major breakthrough in our understanding of the pathways to neurodegeneration and development of key therapeutic strategies.

The interaction between gene and environment has been implicated in the increased occurrence of these neurological disorders. Environmental toxins like pesticide exposure may increase age-related neurodegeneration and has been found to play a role in sporadic form of PD. However, there is lack of a proper model system for studying the nature and molecular mechanism of environmental toxin induced neurodegeneration. Though, several mouse models have been developed to study PD, but the dissimilarities between inbred strains of mouse and a difference in their response to toxic substances brings serious limitations in their use for aging studies. We developed a Drosophila aging model system in our laboratory, where we could establish PD like symptoms to study age-associated neurodegeneration. Further, rotenone, inhibits mitochondrial complex I, induces oxidative stress, α-synuclein accumulation, and dopaminergic neuron death which are the principal pathological features of Parkinson's disease (Post et al., 2008; Radad et al., 2006; Spivey, 2011). Hence treatment of cells with rotenone not only enabled us to study the mechanistic details underlying sporadic PD but also correlate mitochondrial dysfunction with neuronal death in correlation to endogenous SARM1 level following exposure to rotenone both in the Drosophila brain as well as cellular model.

We hereby aim to provide a mechanistic insight into the novel regulation of mitochondrial homeostasis by the pro-neurodegenerative molecule SARM1 and its global effect on the neurodegenerative pathway that may provide a common route of therapeutics in the treatment of these diseases. Previous studies have implicated the important role of the TLR adaptor protein SARM1 in axonal degeneration and mitochondrial dysfunction ultimately leading to neuronal death and hence SARM1 seem to be an attractive candidate in neurodegeneration (Josiah Gerdts et al., 2013; Daniel W Summers et al., 2014). We hypothesize that alteration in the mitochondrial energy metabolism is an important phenomenon in axonal degeneration and SARM1 may provide the missing link between mitochondrial dysregulation and axonal loss.