**Genetics of Parkinson’s disease: The South African perspective**

Parkinson’s disease (PD) is a progressive, neurodegenerative disorder which occurs due to a loss of dopamine-producing neurons in a part of the brain known as the substantia nigra pars compacta. This loss of dopamine causes people with PD to suffer from a wide range of problems with movement as well as neuropsychiatric problems such as psychosis and depression. PD is the **fastest growing neurological disorder worldwide** in terms of prevalence, disability, and deaths. Addressing this impending health care challenge requires action aimed at preventing the disease, improving worldwide access to care and existing treatments (eg, levodopa), increasing funding for research (e.g. to understand the underlying causes), and development of new improved therapies.

Our research group focussed on PD, is the only one of its kind in South Africa, and we investigate two of the above-mentioned goals – i.e. studying the underlying causes and development of new therapeutic options. We currently have three main foci: (i) mutation screening, (ii) functional studies and (iii) therapeutic studies on curcumin. For the mutation screening work, we have recruited a unique collection of individuals with PD from diverse ancestries around South Africa for genetic studies. We use various mutation screening techniques starting from candidate gene screening and more recently moving to next-generation sequencing approaches (targeted gene panels, whole-exome sequencing). To date, these studies have revealed very few known mutations leading us to speculate that our populations may harbour novel PD-causing mutations. The talk will elaborate briefly on these approaches and our main findings. Moreover, we are currently embarking on a new collaboration with the Global Parkinson’s Genetics Program (GP2) which will allow us to perform whole-genome sequencing on our study participants.

For the functional studies section, we use *ex vivo* (dermal fibroblasts from individuals with mutations) and *in vitro* (neuroblastoma cell line) approaches to study the effect of pathogenic variants on the cell. Our work to date has implicated mitochondrial dysfunction as a biological process involved in PD. Lastly, our work on curcumin has shown that it is a strong antioxidant and that it may be able to alleviate mitochondrial dysfunction in cellular models of PD.

In summary, this talk will provide a background to our studies on PD, an overview of our main research goals, as well as the approaches used and the main findings. The significance of our work is that understanding the genetic causes and disease mechanisms underlying PD in local populations is necessary for future development of precision medicine strategies for this debilitating disorder.