The evolution of Parkinson's disease

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Parkinson's disease (PD) is the fastest growing neurodegenerative disease. Best known as a movement disorder, the age of motor onset spans a wide range (median ~60 years) and has a broad range of clinical expression. Non-motor features include autonomic, cognitive, mood, psychiatric, sensory and sleep disorders. There are currently only symptomatic therapies and none that slows disease progression. In the past 20 years our team has 'genetically linked' autosomal-dominantly inherited mutations to typical late-onset PD in families, indistinguishable from the idiopathic disease. These discoveries include leucine-rich repeat kinase 2 p.G2019S (LRRK2), vaculoar protein sorting 35 p.D620S (VPS35) and most recently, Rab GTPase 32 p.S71R (RAB32). Despite being inherited, and often identified in families, the age-associated penetrance of mutations in these genes is incomplete. Worldwide, this is estimated to be ~26% for Lrrk2 p.G2019S, which is most common. However, substitutions in all three proteins coalesce about the same evolutionary mechanism. Their frequency and distribution have been driven by positive selection against environmental pathogens, to activate Lrrk2 kinase and enable survival of the human host. Data that illustrates the circuity of PD, and the multifactorial, multicellular and immunoresponsive mechanisms that underlie its temporal evolution are to be presented.