IS PARKINSON’S DISEASE GENETIC?

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The role of genetics versus environment in the etiology of Parkinson’s disease (PD) has been a matter of debate for long time. The current evidence supports the view that the common PD form is determined by a complex interplay of several genetic as well as non-genetic factors.

Strong support for the environmental theories came from the occurrence of post-encephalitic parkinsonism, from some geographical clusters of PD-like neurodegenerative diseases (the “Guam complex” and the “Guadeloupean parkinsonism”), and from animal models of parkinsonism induced by toxins such as MPTP, rotenone and proteasome inhibitors. However, despite the epidemiological association of PD with environmental factors such as the occupational exposure to pesticides, a specific toxin causing the disease has not been identified yet.

On the other hand, cigarette smoking has emerged consistently in epidemiologic studies as a protective factor for PD. The mechanisms underlying this inverse association remain unknown. Recent epidemiological studies have suggested that high plasma urate, history of gout, and some statins might also represent protective factors for the development of PD, but further studies are needed in order to confirm/substantiate these more recent findings.

In the past few years, family-based linkage and positional cloning approaches led to the identification of several monogenic forms of PD, and yet, other PD-causing genes probably remain to be found. Mutations in the SNCA and LRRK2 gene cause autosomal dominant forms, whereas mutations in the PARK2 (parkin), PARK7 (DJ-1), and PARK6 (PINK1) gene cause autosomal recessive forms of PD (usually with early-onset). Furthermore, mutations in the PARK9 (ATP13A2), PARK14 (PLA2G6), and PARK15 (FBXO7) gene cause autosomal recessive, juvenile-onset parkinsonism with atypical features, whose relationships with Parkinson’s disease remain more controversial.

Perhaps, the most important genetic discovery is that a single, low-penetrance mutation in the LRRK2 gene (Gly2019Ser) is a very common determinant of both familial and sporadic PD in large North-African and Middle-Eastern populations, providing the proof-of-principle for the existence of a specific genetic factor in the etiology of the common, typical late-onset form of this disease. Furthermore, two different LRRK2 variants (Gly2385Arg, Arg1628Pro) are risk factors for PD in large Asian populations.
Although some of the Mendelian forms of PD are rare, they might facilitate the dissection of molecular pathways leading to death of dopaminergic neurons; these pathways might also be implicated in the pathogenesis of the common forms of PD. The several Mendelian forms are also challenging the concept of PD as one disease, as well as the validity of the current clinico-pathological disease definition. Last, mutations in some of these genes (parkin, LRRK2) are frequent enough to have relevance in clinical practice, especially in some populations.

SELECTED REFERENCES