Expression of Parkinson's disease and associated neurophenotypes in 22q11.2 deletion syndrome

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Abstract

The etiology of Parkinson's disease (PD) remains largely unknown with the exception of a few genetic mutations that affect a small proportion of patients. Case reports suggest that individuals with 22q11.2 deletion syndrome (22q11.2DS), a multisystem genomic disorder associated with hemizygous 22q11.2 deletions, may be at increased risk of early-onset PD. The aim of this thesis was to investigate 22q11.2 deletions as a risk factor for early-onset PD.

The prevalence of PD was assessed in a well-characterized cohort of adults with 22q11.2DS. Neuropathological studies were performed in cases with available post-mortem tissue. Whole-genome sequencing was used to investigate the possible contribution of genome-wide rare coding mutations to disease penetrance in neuropathologically confirmed PD cases. Assessment of putative pre-diagnostic clinical and neuroimaging markers of PD in a subset of the older adults (30 to 54 years) provided evidence of an elevated prevalence of pre-morbid motor and olfactory deficits, and of nigrostriatal dopaminergic dysfunction assessed using ^{11}C-dihydrotetrabenazine and positron emission tomography.

The clinical context of early-onset PD in this adult cohort of individuals with 22q11.2DS was also investigated. Treatment response was excellent to the atypical antipsychotic, clozapine, a candidate for use in psychotic patients at risk of, or with, PD. Cognitive level and severe psychiatric disorders were mediators of baseline functional capacity in 22q11.2DS adults. Practical guidelines were developed from a review of the 22q11.2DS literature to help inform the management of 22q11.2DS-associated conditions, including PD.

The results of these studies provided evidence that early-onset PD is associated with the 22q11.2 deletion with important implications for PD pathogenesis and for the clinical management of 22q11.2DS.