

Title: Clinical Expression of the LRRK2 G2019S Mutation in Ashkenazi Jews

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Objective: To describe the clinical characteristics of the LRRK2 G2019S gene mutation in an Ashkenazi Jewish (AJ) population with Idiopathic Parkinson's Disease (IPD).

Background: The reported frequency of the G2019S mutation in the AJ IPD population ranges from 10.0-29.7%. Phenotypic characterization is mostly through family studies, which may skew reported findings. There is little information on behavioral and psychological symptoms.

Design/Methods: Consecutive AJ IPD patients were recruited in an outpatient setting by movement disorder specialists who performed standardized clinical assessments blinded to genotype. Patients answered questionnaires. DNA samples were obtained and genotyped. Statistical analyses compared clinical, historical, and examination features in mutation carriers and non-carriers.

Results: Of 153 patients, 27 (17.6%) had the G2019S mutation. Gender and disease duration were not significantly different in mutation carriers and non-carriers. Mutation carriers had a lower median age onset (54 vs. 59, $p=.047$). Compared to non-carriers, carriers had lower UPDRS-3 scores ($p=.041$), and a trend to lower H&Y ($p=.087$). Depression prior to PD occurred in 30.4% of carriers vs. 19.3% of non-carriers. Family history of mood disorder was present in 30.0% of carriers vs. 17.0% of non-carriers. In logistic regression models stratified by depression prior to PD, the odds ratio for being mutation positive was 1.9 in those with an affected 1^o relative with PD and no prior depression and increased to 10.8 when depression preceded PD onset.

Conclusions/Relevance: This is the largest reported group of independently ascertained, unrelated AJs with the G2019S mutation in PD. Carriers have significantly earlier onset age and may have a milder disease course as suggested by the UPDRS-3 scores. There is a trend for LRRK2+ patients to have depression prior to PD and have a family history of depression. Further consideration of the relationship of the LRRK2 gene and mood is warranted.