# Phenotype associated with *LRRK2* mutations – Motor and Non-Motor Features

C. Marras[1], B. Schuele[2], R.P. Munhoz[3], E. Rogaeva[4], J.W. Langston[2], P. Wadia[1,5], S-Y. Lim[1,6], R. Chuang[1], C. Zadikoff[7], T. Steeves[1], K.M. Prakash[1,8], R.M.A. de Bie[1,9], G. Adeli[1,10], T. Thomsen[1,11], K. Johansen[1,12], H.A. Teive and A.E. Lang[1].

1. Toronto Western Hospital, University of Toronto, Toronto, ON, Canada. 2. The Parkinson's Institute, CA. 3. State of Paraña Parkinson Association, Curitiba, PR, Brazil. 4. Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, ON, Canada. 5. Jaslok Hospital and Research Center, Mumbai 6. University of Malaya, Kuala Lumpur 7. Northwestern University, Chicago, IL., 8. National Neuroscience institute, Singapore 9. Academic Medical Center, Amsterdam, 10. Hamad Medical Corporation, Doha, Qatar 11. University of Iowa, 12. Norwegian University of Science and Technology, Trondheim

## Background:

The phenotype of *LRRK2*-associated Parkinson's disease (PD) has been described as indistinguishable from idiopathic PD. Descriptions have been based on either small samples or combining data across multiple centres using different methods. Little is known about non-motor features in mutation carriers without parkinsonism. Such features may be clues to the earliest manifestations of PD and may guide attempts at early detection.

## Aims:

1. To provide detailed clinical descriptions of PD associated with *LRRK2* G2019S mutations, obtained using standardized evaluation methods.
2. To identify non-motor manifestations of LRRK2 mutations in non-parkinsonian mutation carriers.

## Methods:

- Probands were identified through genetic testing of PD patients with a family history of PD or young age at onset presenting to the participating centres.
- Probands sent invitations to their first and second degree relatives Relatives responded directly to the participating centre.
- In-person evaluations included a neurologic examination and videotape, the Cognitive Abilities Screening Instrument (CASI), the State-trait Anxiety Inventory (STAI), the Penn State Worry questionnaire (PSWQ), the Beck Depression Inventory (BDI), the Brief Smell Identification Test (B-SIT), the Farnsworth-Munsell 100-Hue test for colour discrimination (100-Hue test).
- Blood samples of relatives were tested for the mutation found in the proband.
- Immortalized lymphoblastoid cell lines were established on all subjects who consented to this procedure.
- Diagnoses of parkinsonism and PD (UK Brain Bank Criteria and the subjective 'most likely diagnosis') were assigned by majority opinion of three neurologists (CM, AEL and the in-person examiner). CM and AEL independently reviewed the videotapes blind to mutation status. Individuals with parkinsonism were designated as manifesting regardless of whether or not they met criteria for PD.

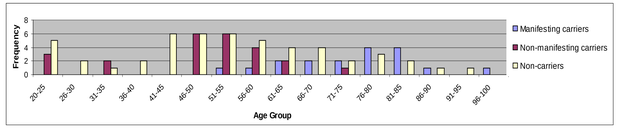
## Results:

- 9 probands with G2019S mutations and one with an I1371V mutation were identified and recruited. Only G2019S families are described.

| | Toronto Western Hospital | The Parkinson's Institute | Curitiba, Brazil | Total |
|---|---|---|---|---|
| Number of families | 4 | 3 | 2 | 9 |
| Subjects of interest | 192 | 14 | 22 | 228 |
| Subjects evaluated | 76 | 9 | 6 | 91 |

*First degree relatives of family members with parkinsonism or first degree relatives of non-manifesting carriers.

Figure 1: Age distribution of subjects by disease and mutation status




### Disease Characteristics in Manifesting Carriers

Table 1: Presenting characteristics

| | | |
|---|---|---|
| N | | 16 |
| Gender (M:F) | | 7:9 |
| Age at onset (mean +/- SD) | | 62 +/- 9 |
| Initial symptom (n) reported on history | -tremor | 11 |
| | -change in writing | 1 |
| | -loss of energy | 1 |
| | -frozen shoulder | 1 |
| | -arm swing | 1 |
| | -gait disorder | 1 |
| Good response to levodopa (n) | | 16 |
| Prior to PD, diagnosed or treated for | - depression | 3 |
| | - anxiety | 6 |

Table 2: Characteristics by disease duration at examination

| | 0-5 years | 6-10 years | 11-15 years | 16+ years |
|---|---|---|---|---|
| **N** | **5** | **4** | **2** | **5** |
| UPDRS Non-motor EDL* score, mean (SD) | 9 (11) | 5 (8) | 10 (10) | 6 (14) |
| UPDRS Motor EDL score, mean (SD) | 13 (15) | 7 (11) | 25(17) | 19 (28) |
| UPDRS Motor score, mean (SD) | 34 (31) | 32(18) | 53 (28) | 39 (36) |
| **Motor features** | | | | |
| Rest tremor Present (n) | 4 | 2 | 0 | 4 |
| UPDRS item score, median (range) | 2 (1) | 1.5 (1) | | 2 (1) |
| Action tremor Present (n) | 4 | 3 | 0 | 2 |
| UPDRS item score, median (range) | 2 (1) | 2 (1) | | 3 (2) |
| Modified Hoehn and Yahr stage median (range) | 3 (2) | 3(2) | 5(1) | 4 (3) |
| Gait disorder (n) | 4 | 4 | 2 | 3 |
| Freezing (n) | 0 | 0 | 2 | 3 |
| Postural instability by pull test (n) | 4 | 3 | 2 | 5 |
| Motor fluctuation Present (n) | 0 | 1 | 2 | 5 |
| UPDRS functional impact score, median | - | 1 | 1 | 3 |
| Dyskinesias Present (n) | 1 | 1 | 2 | 5 |
| UPDRS functional impact score, median | 1 | 1 | 1 | 3 |

*EDL=Experiences of Daily Living

**Table 2 continued:**

| | 0-5 years | 6-10 years | 11-15 years | 16+ years |
|---|---|---|---|---|
| **Non-motor features** | | | | |
| Cognitive impairment By history (n) | 0 | 0 | 1 | 5 |
| CASI raw score | 96 (5) | 92 (10) | 95 (8) | 90 (12) |
| Urinary problems (n) | 3 | 1 | 2 | 3 |
| Constipation (n) | 3 | 3 | 1 | 1 |
| Depression since PD onset (n) | 2 | 1 | 2 | 2 |
| Beck Depression Inventory score, mean (SD) | 12(n=1) | 7 (3) | 12 (11) | 12 (9) |
| Anxiety since PD onset (n) | 1 | 0 | 0 | 1 |
| Anxiety inventory (STAI –S) Mean score | 66 | 66 | 63 (27) | 84 (11) |
| >44, abnormal (n) | 1 | 3 | 0 | 3 |
| Anxiety inventory (STAI-T) Mean score | 69 | 69 | 44 (14) | 76 (37) |
| >44, abnormal (n) | 1 | 0 | 1 | 2 |
| B-SIT percentile score, median (range) | 61 (53) | 18 (45) | 54 (34) | 34 (56) |
| normal:abnormal for age | 5:0 | 4:0 | 2:0 | 4:1 |
| Epworth sleepiness score, median (range) | 5 (7) | 3 (4) | 6 (3) | 7 (13) |
| Farnsworth-Munsell 100-Hue test error score (mean, SD) | 175 (76) | 193 (107) | 348 (n=1) | 231 (54) |

### Clinical features in non-manifesting mutation carriers

We identified 24 non-manifesting carriers of G2019S mutations (m:f 14:10, mean age 49+/- 14). These individuals were matched by age (+/- 5 years) and gender to family members without *LRRK2* mutations.

Table 3: Neurological and psychiatric features in non-parkinsonian mutation carriers vs non-carriers.

| | Mutation carrier (N = 24) | Non-carriers (N = 24) | p-value |
|---|---|---|---|
| **Motor features** | | | |
| UPDRS Non-motor EDL score* | 1.9 (1.9) | 3.5 (4.1) | 0.20 |
| UPDRS Motor EDL score* | 0.3 (0.6) | 0.6 (2.1) | 0.91 |
| UPDRS Motor score* | 2.9 (4.3) | 3.0 (3.8) | 0.99 |
| Postural tremor (n) | 3 | 2 | 1.00 |
| Action tremor (n) | 5 | 5 | 1.00 |

*mean (SD)

**Table 3 continued:**

| | Mutation carrier (N = 24) | Non-carriers (N = 24) | p-value |
|---|---|---|---|
| **Non-motor features** | ` | | |
| B-SIT percentile | 38 (33) | 33(28) | 0.75 |
| Abnormal for age (n) | 4 | 1 | 0.35 |
| 100-Hue test error score mean (SD) | 146 (99) | 118 (89) | 0.18 |
| Prior or current depression (n) | 6 | 11 | 0.13 |
| Prior or current anxiety (n) | 7 | 6 | 0.75 |
| BDI score, mean (SD) | 5 (4) | 7(7) | 0.49 |
| Anxiety inventory (STAI –S) Mean score | 36 (23) | 47 (29) | 0.20 |
| >44, abnormal (n) | 8 | 11 | 0.38 |
| Anxiety inventory (STAI-T) Mean score | 43 (28) | 52 (35) | 0.39 |
| >44, abnormal (n) | 9 | 11 | 0.56 |
| Epworth Sleepiness score, median (range) | 2 (5) | 3 (10) | 0.47 |
| Initial insomnia (n) | 4 | 8 | 0.18 |
| Difficulty staying asleep (n) | 3 | 4 | 1.00 |

## Conclusions:

- Parkinsonism in individuals with *LRRK2* mutations was similar to idiopathic PD. Clinically recognized anxiety and depression were common prior to the onset of motor symptoms.
- Non-motor features encompass a spectrum similar to idiopathic PD, but olfactory disturbance was usually within the normal range.
- Across a wide age range (20-74), *LRRK2* mutation carriers without parkinsonism as a group do not display non-motor features suggesting early PD. Whether or not a subgroup of older mutation carriers would show non-motor features suggestive of PD would be of interest to investigate.

## Caveats:

- The subjects in this sample are from a limited number of families. Features may be particular to certain families.
- This is a cross-sectional study. A longitudinal evaluation would be better able to characterize the evolution of disease.
- The number of subjects is small, and power to detect differences between groups was limited. Similarly, the precision of estimates was low for characterizing the features of *LRRK2*-associated PD at different disease durations.

## Acknowledgements:

- The authors would like to acknowledge the assistance of the following individuals with project and data management:
  - Abena Asante, Francis Baraquio, Patricia Williams, Hannah Reay, Tea Mutabdzic, Manoj Enjati.

**Funded by The National Parkinson Foundation**