

Spectrum of *LRRK2* Variants in a Dementia-Focused Clinical Cohort: A Case Series of Dementia and Parkinsonism Presentations

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Background

LRRK2 (leucine-rich repeat kinase 2) is the most common genetic contributor to both familial and sporadic Parkinson's disease (PD), with the recurrent kinase-domain variant p.Gly2019Ser (G2019S) accounting for most pathogenic cases. Although *LRRK2*-related disease is classically viewed as a motor-predominant Parkinsonism, a broader phenotypic spectrum is increasingly recognised, including cognitive impairment, dementia, and mixed dementia–parkinsonism presentations. In parallel, the expanding use of clinical genetic panels has produced a growing number of *LRRK2* variants of uncertain significance (VUS), whose pathogenicity and phenotypic correlates remain poorly defined. Because dementia-focused cohorts are under-represented in existing *LRRK2* series, systematically profiling the variant spectrum alongside detailed clinical phenotyping in such a population may refine differential diagnosis across overlapping neurodegenerative syndromes and help prioritise variants for segregation analysis and reclassification.

Objective

To describe the clinical phenotypes and *LRRK2* variant spectrum identified in a real-world cohort enriched for dementia and mixed dementia–parkinsonism presentations.

Methods

We retrospectively reviewed consecutive patients in whom *LRRK2* variants were reported during routine clinical genetic testing. Referral clinical labels were categorised as dementia, PD, or PD with comorbid dementia. Variant nomenclature is reported as provided in laboratory reports

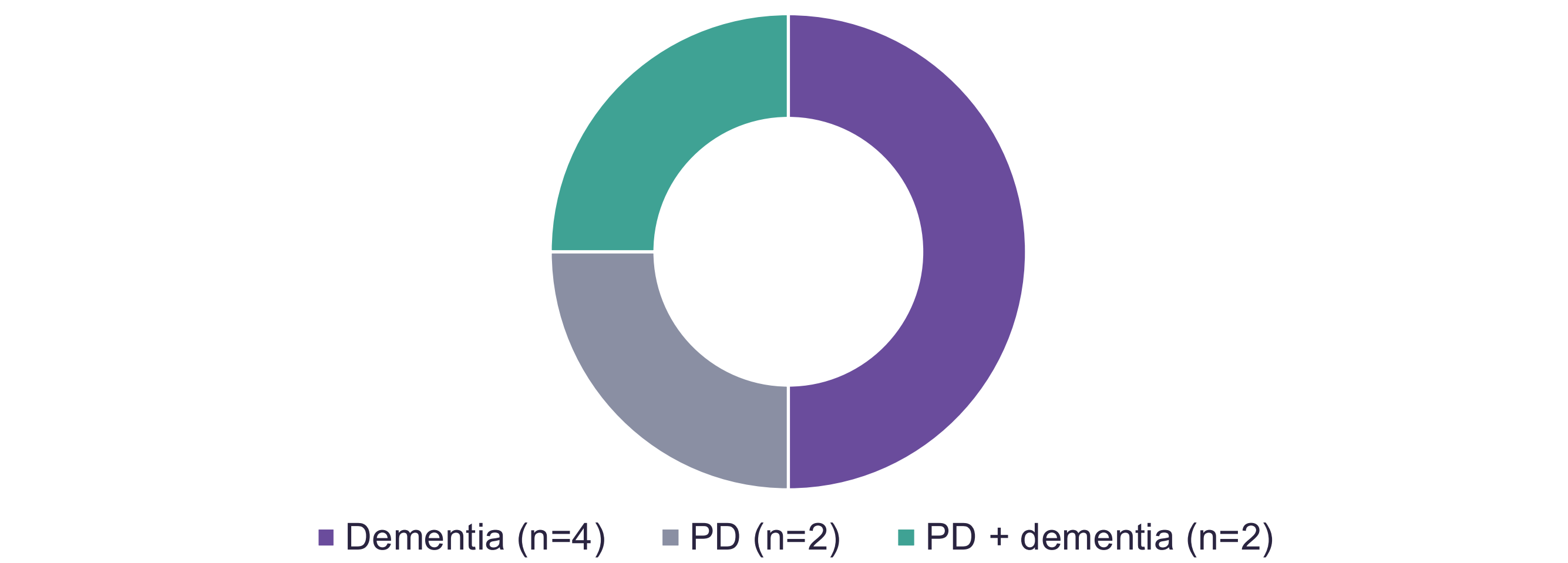
Clinical caveat

The predominance of dementia-spectrum presentations underscores the need for careful phenotyping and biomarker-based clarification of Alzheimer biomarkers, dopaminergic imaging, and/or synucleinopathy markers before causal attribution of any VUS.

Study population



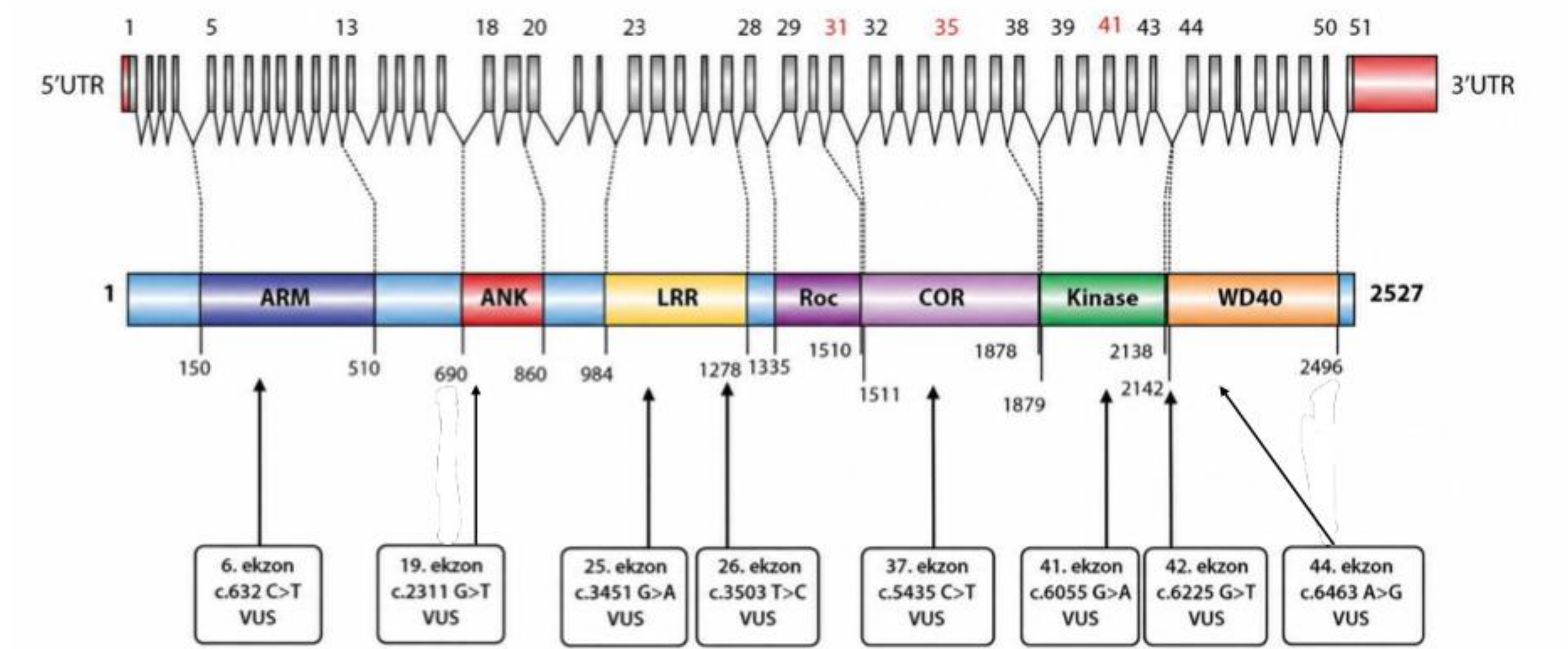
Phenotype distribution



A dementia component (dementia or PD with dementia) was present in 6 of 8 patients (75%).

Variant spectrum

Eight patients carrying *LRRK2* variants were identified. Referral phenotypes were dementia (n = 4), PD (n = 2), and PD with dementia (n = 2) a dementia component in 6 of 8 cases. One PD patient carried the likely pathogenic G2019S variant; the remaining seven carried variants reported as VUS, distributed across multiple protein domains and including one intronic change.



VUS, variant of unknown significance. Domain localisation derived from residue position; the splice-region variant is listed separately.

#	Reported variant	Domain	Classification
1	p.Gly2019Ser (c.6055G>A)	Kinase	Likely pathogenic
2	p.Ala211Val	ARM	VUS
3	p.Ala1151Thr	LRR	VUS
4	p.Met1168Thr	LRR	VUS
5	p.Ala1812Val	COR	VUS
6	p.Glu2075Asp	Kinase	VUS
7	p.Met2155Val	WD40	VUS
8	c.5510-9A>G (intronic)	Splice region	VUS

Conclusion & take-home

One actionable pathogenic variant, plus multiple VUS distributed across the *LRRK2* gene.

- G2019S (p.Gly2019Ser) was the only clearly actionable likely pathogenic variant identified in a patient with PD.
- The remaining seven variants were VUS spread across the ARM, LRR, COR, kinase and WD40 domains, plus one intronic change.
- Findings support standardised dementia/Parkinsonism phenotyping, segregation analysis and longitudinal follow-up to enable future variant reclassification and clarify the contribution of *LRRK2* to dementia-spectrum presentations.

Next steps

- Biomarker confirmation, Alzheimer, dopaminergic imaging, synucleinopathy
- Segregation analysis within families
- Longitudinal clinical follow-up
- Periodic variant reclassification