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CLINICAL REASONING: CASE REPORT

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Expanding the clinical and geographical spectrum of PARK-LRRK2 p.(Asn1437His): first report in a Swiss family

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Summary

INTRODUCTION: Pathogenic variants in the *LRRK2* gene represent the most common monogenic cause of Parkinson's disease. Individual variants differ in frequency, geographical distribution and genotype-phenotype associations. Here, we report a Swiss family with multiple affected individuals carrying a very rare ROC-domain variant and provide a comprehensive characterisation of their clinical phenotype.

CLINICAL FINDINGS: Age at onset was earlier than typically reported for PARK-*LRRK2*. Leg tremor was frequently the initial presenting symptom, followed by the development of an asymmetric akinetic-rigid syndrome with a clear dopaminergic response. Constipation was commonly reported, whereas significant cognitive symptoms were not evident. Notably, despite the high penetrance of the variant, disease progression was relatively mild.

PRIMARY DIAGNOSIS: Genetic testing identified a heterozygous missense variant in the LRRK2 gene (c.4309A>C, p.(Asn1437His)), classified as likely pathogenic according to ACMG criteria.

CONCLUSION: The present work expands both the geographical distribution of this rare ROC-domain variant and suggests that it may be associated with earlier onset but not necessarily greater disease severity. Continued characterisation of rare LRRK2 variants is essential for refining genotype-phenotype correlations and supporting emerging targeted therapies.

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Introduction

Pathogenic variants in the LRRK2 gene are the most common monogenic causes of Parkinson's disease, accounting for about 3% of all cases [1]. Over 25 pathogenic LRRK2 variants, usually missense mutations, have been described, most of which affect the kinase or the ROC domain [2, 3]. Park-LRRK2 closely resembles idiopathic Parkinson's disease, typically presenting with similar age of onset, asymmetry at onset, resting tremor, good levodopa response and slow progression [2–4]. However, the clinical penetrance and severity can vary significantly depending on the specific variant, with certain variants being associated with atypical features. Moreover, recent evidence shows that *LRRK2* mutations are even associated with Lewy body dementia in patients with North African ancestry [2–5]. The most prevalent variant is p.(Gly2019Ser) in the kinase domain, characterised by incomplete and age-dependent penetrance with estimates of approximately 50% at age 80 and a notably high frequency in Ashkenazi Jewish and North African Arab-Berber populations [6, 7]. In contrast, variants in the ROC domain are considered more deleterious and penetrant, but are less frequent and less well characterised both clinically and geographically [7, 8]. Here, we report a Swiss family with Park-*LRRK2* carrying the rare p.(Asn1437His) variant and present detailed clinical phenotyping of affected family members.

ABBREVIATIONS
LRRK2 leucine-rich-repeat-kinase 2
ROC-DOMAIN ras of complex protein domain
GTPASE guanosine triphosphatase
DAT-SCAN dopamine transporter scan
MDS Movement Disorder Society
UPDRS Unified Parkinson Disease Rating Scale

Cases

This Swiss family has been established in Switzerland for multiple generations with no known connection to other countries or populations. There is no history of consanguinity. The pedigree spans three generations with nine individuals affected by Parkinson's disease. Based on clinical records and historical data, the mean age at disease onset was 50.4 years (range: 39–70 years) (figure 1). Four affected family members underwent comprehensive clinical and genetic evaluation at the University Hospital of Bern. Clinical history and examination were aligned with the Movement Disorders Society (MDS)-Gene framework (figure 2). All four patients provided informed consent for further scientific use of their clinical data.

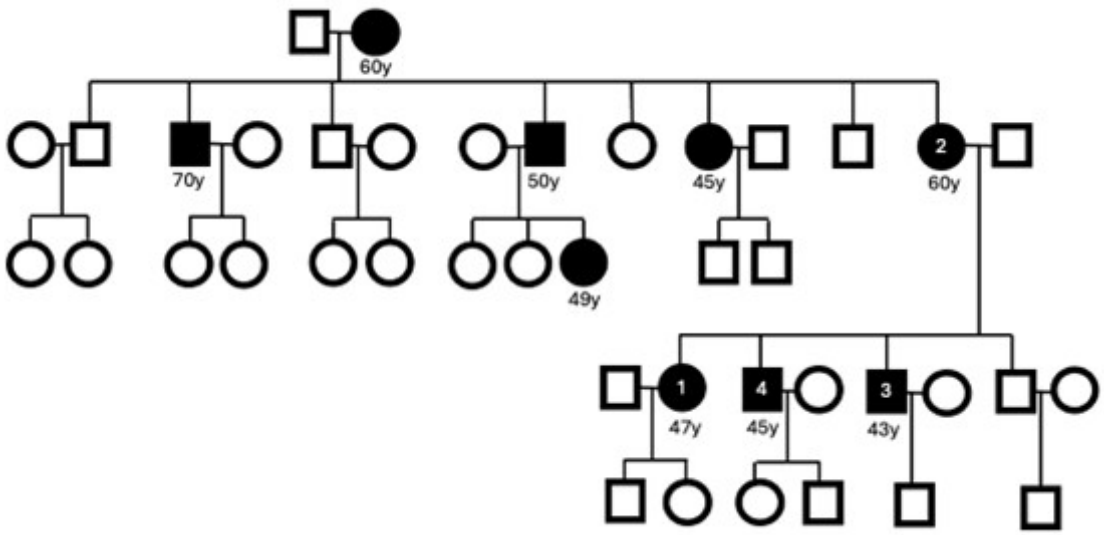


Figure 1: Pedigree of the Swiss family depicted over three generations with 9 affected members. The age at diagnosis of Parkinson's disease for each patient is indicated. The four patients available for genetic analysis and clinical examination are indicated (1–4). All four carry the LRRK2 variant p.(Asn1437His).

	Patient 1	Patient 2	Patient 3	Patient 4
Symptom onset (years)	42	60	39	43
Bradykinesia	+	+	+	+
Rigor	+	+	+	+
Resting tremor	+	+	+	+
Postural tremor	+	+	+	+
Action tremor	-	-	-	-
Motor fluctuations	-	+	-	-
Dyskinesia	-	-	-	-
Dystonia	-	-	-	-
Gait difficulty	-	-	-	-
Freezing of gait	-	-	-	-
Postural instability	-	-	-	-
Dysarthria	-	-	-	-
Lateralisation	+	+	+	+
Atypical parkinsonian signs	-	-	-	-
Hyperreflexia	-	-	-	-
Depression	+	-	-	-
Anxiety	-	-	-	-
Psychotic symptoms	-	-	-	-
Sleep disorder	-	-	-	-
Apathia	-	-	-	-
Impulse control disorder	-	-	-	-
Constipation	-	+	+	+
Urinay dysfunction	-	-	-	-
Orthostatic hypotension	-	-	-	-
Pain	-	-	-	+
Hyposmia	-	-	-	-
Cognitive decline	-	-	-	-
MRI	●	●	●	○
Dat scan	○	●	●	○
Clear favourable response to levodopa	●	●	●*	○

+ present - absent ● available ○ not available

Figure 2: Motor and non-motor symptoms in the four examined patients, reported according to the MDS-Gene framework (https://www.mdsgene.org/genes/PARK-LRRK2). Patient 1 presented with depression, Patients 2 and 4 with constipation and Patient 4 with shoulder pain as pre-motor symptom. * In Patient 3, the response to levodopa is unclear, because of low baseline symptom severity.

Patient 1

The index patient is a 47-year-old female who first developed motor symptoms at the age of 42. The initial presentation included cramping of the right hand, followed by the emergence of a resting tremor affecting the right hand and leg. Her past medical history is notable for a depressive episode at the age of 26, which may represent a prodromal symptom. Her brain MRI was unremarkable. She responded well to treatment with pramipexole 1.5mg/d. On current neurological examination, while on regular medication, she presents with a mild right-sided akinetic-rigid syndrome and intermittent resting tremor of the right hand with an MDS-Unified Parkinson's Disease Rating Scale (UPDRS)-III of 14/132 points.

Patient 2

A 74-year-old female and biological mother of the index patient. She developed motor symptoms at the age of 60, presenting with a resting tremor of the left leg. The only reported non-motor symptom is constipation. A DAT scan performed six years after symptom onset confirmed absent uptake in the right putamen, possible slight residual uptake on the left side and reduced uptake in both caudate heads. Her brain MRI was unremarkable. Treatment with levodopa/benserazide

200/50mg (currently 4 times daily) resulted in a marked and sustained improvement with so far no evidence of motor fluctuations or dyskinesias. On neurological examination, there is slight bradykinesia and rigidity of the left hand, as well as a subtle resting tremor of the left leg. The motor assessment yielded an MDS-UPDRS-III of 14/132 points.

Patient 3

A 43-year-old male patient and younger brother of the index patient. He developed a resting tremor of the right leg at the age of 39 years. The only non-motor symptom reported is constipation. The MRI scan was unremarkable and a DAT scan performed one year after symptom onset revealed a mildly asymmetric reduction in uptake in the left putamen, consistent with the clinical presentation. Over 4 years of clinical observation, disease progression has been mild. At the time of assessment, he was on rasagiline monotherapy. Neurological examination revealed slight bradykinesia and rigidity on the right side and an intermittent resting tremor with an MDS-UPDRS-III score of 7/132 points.

Patient 4

A 45-year-old male and younger brother of the index patient. He developed a slight resting and postural tremor of the left leg at the age of 43 years. A few years prior, he complained of a left-sided shoulder pain. Neuroimaging was not performed. Over 2 years of clinical observation, he only had a very mild disease progression and medical treatment was not yet started. Neurological examination revealed a slight intermittent resting tremor of the left leg and a slight bradykinesia and rigidity on the left side corresponding to an MDS-UPDRS Part III score of 11/132 points.

Genetic testing

Due to the positive family history for Parkinson's disease and young disease onset, we conducted genetic testing. Our centre-specific approach includes exome sequencing with subsequent evaluation of variants in Parkinson's disease-related genes according to the Genomics England Panel App [2]. For the index patient, this analysis identified a heterozygous missense variant in the LRRK2 gene (c.4309A>C, p.(Asn1437His)), which was classified as likely pathogenic according to ACMG criteria [9], and then confirmed in the other three affected individuals.

Discussion

This is the first report of a Swiss family carrying the rare *LRRK2* p.(Asn1437His), N1437H variant, which expands the geographical distribution and the clinical phenotype associated with this rare missense variant.

The *LRRK2* p.(Asn1437His) variant, located in the ROC domain, reduces GTPase activity and indirectly increases kinase function, a mechanism distinct from kinase-domain variants, which directly enhance enzymatic activity. This leads to elevated kinase signalling implicated in dopaminergic neurodegeneration via disrupted autophagy, cytoskeletal instability and alpha-synuclein accumulation [7, 8] . This variant has previously only been reported in a large Norwegian and Polish family and in one Swedish patient [10-12]. A recent population-based screening study in Sweden failed to detect this variant in another Scandinavian region [13], underscoring its low prevalence. All affected individuals in the reported family exhibit a clinical profile similar to idiopathic Parkinson's disease, characterised by a dopamine-responsive, asymmetric akinetic-rigid syndrome with resting tremor as well as a non-motor symptom such as constipation, depression or pain [14] (table 1). Interestingly, in all four patients tremor was the first symptom and in three patients tremor onset was first noted in the legs. From a phenomenological perspective, this is noteworthy, as a leg tremor has been reported as an initial symptom in about 9% of *LRRK2*-associated Parkinson's disease in earlier series, compared to only 2% in idiopathic Parkinson's disease [15]. Notably, symptom onset in 3 of the 4 cases is earlier than typically seen in *LRRK2*-associated (~54 years) or idiopathic (~55 years) Parkinson's disease [3, 7, 14, 16]. Moreover, the age of onset appears to be earlier in the third generation, compared to the previous two generations, which could suggest an anticipation phenomenon. This has previously been described only once in *LRRK2*-associated Parkinson's disease [17]. A more severe phenotype, including psychotic symptoms and dysarthria in a Polish patient and severe depression in a Swedish patient, has previously been reported [10-12]. In the family described here, disease severity appears to be mild, with slow progression over the observed period and no major psychiatric features. Our findings suggest that although ROC domain variants may show higher penetrance and earlier disease onset [12], they do not necessar-

ily lead to a more severe clinical course. The role of other genetic or epigenetic factors contributing to the phenotype can however not be excluded. Interpretation of the findings is further limited by the small proportion of family members who underwent genetic testing, the lack of information on potential asymptomatic carriers and the limited duration of longitudinal clinical follow-up.

In conclusion, the comprehensive evaluation of the assessed individuals broadens the clinical spectrum of the rare *LRRK2* p.(Asn1437His) variant by showing relatively early disease onset in some affected family members and a generally mild phenotype with slow progression during the observed period, despite apparent high familial penetrance. In addition, this report expands the geographical distribution of this specific variant. Continued reporting and functional analysis of such rare variants are essential for refining genotype-phenotype correlations, informing clinical and genetic counselling and guiding emerging *LRRK2*-targeted therapies [18].

Notes

Informed consent: Written informed consent was obtained from the patients for the publication of the case report and the accompanying images.

Use of AI: Large language models (LLMs) were used during the preparation of this manuscript to assist with rephrasing and improving the wording of parts of the text, as well as to correct some linguistic and grammatical formulations. The authors reviewed and edited all AI-assisted suggestions and take full responsibility for the content and accuracy of the manuscript.

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Potential competing interests

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