Parkinsonism and Related Disorders 123 (2024) 106973

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

The p.Val234Met *LRP10* likely pathogenic variant associated with Parkinson's disease: Possible molecular implications

Dear Editor,

The *LRP10* gene has been associated with Lewy Body Diseases, including PD, Parkinson's Disease Dementia (PDD) and Dementia with Lewy Bodies (DLB) and it is characterised by autosomal dominant inheritance. In recent years, multiple studies have linked *LRP10* pathogenic variants to PD, but the role played by the protein in the pathogenetic process is still unclear [1,2]. Studies on patients carrying LRP10 pathological variants showed co-staining between LRP10 and α-synuclein in Levi's Bodies present Substantia nigra pars compacta and in the core of brainstem type, but functional significance of this interaction remains difficult to interpret [3,4].

A wide genetic screening including 24 movement disorder-associated genes was applied to sixty consecutive PD patients, in our Institution. A very rare *LRP10* heterozygos likely pathogenic variant c.700G > A (NM_014045.5) p.Val234Met (GRCh37.p13 chr 14, NC_000014.8:g.23344857G > A, dbSNP, rs371755191; GnomAD: minor allele frequency/MAF = 0.0003) (Fig. 1) was detected in a 53-onset tremor-dominant PD patient with a positive family history (brother, unfortunately not available for assessment). Brain MRI at diagnosis was normal, whereas the dopaminergic imaging showed both putaminal and caudate deficits prominent on the right side. At clinical presentation, the patient showed a classical asymmetric parkinsonism and no atypical motor feature (such as dystonia, early freezing of gait or postural instability). At time of diagnosis he already complained about night sialorrhea, anxiety and insomnia, along with a mild urinary urgency; constipation was not reported. The patient was classified as benignant phenotype according to the lack of presence of REM sleep behavioural disorder, orthostatic hypotension and mild cognitive impairment at time of diagnosis [5]. The patient displayed levodopa responsiveness in a L-dopa challenging test, but considering the young age he was first prescribed rasagiline as monotherapy. During the following years, due to incomplete efficacy of the therapy, pramipexole was added up to the dosage of 2.1 mg per day. L-DOPA was prescribed in September 2016, progressively increased up to 650 mg per day distributed in four administrations. The patient developed motor fluctuations with OFF-related dystonia around eight years into the disease, but only mild and rare dyskinesias were reported (Supplemental Tables 1 and 2).

Regarding non motor symptoms, urinary urgency and sialorrhea remained stable during the years, while insomnia improved with clonazepam. The patient developed early onset dysphagia (from 2016), mainly for solids, and severe dysphonia (from 2017), both treated with logopedia. No behavioural or cognitive changes or hallucinations were reported until follow-up in 2023, confirming the benign PD phenotype after nine years of disease (Fig. 1).

In order to elucidate a possible molecular mechanism, the LRP10 protein was simulated by an online 3D program (Uniprot) and its structure showed to be characterized by 2 extracellular CUB domains and large intracellular tails containing acidic dileucine motif. The CUB domains (derived from for complement C1r/C1s, Uegf, Bmp1) are structural motifs conserved in evolution mainly found in the extracellular part of protein associated with membrane. Valine 234 was identified in the internal and hydrophobic portion of the CUB2 domain β-strand and exhibited an essential role in constituting a totally hydrophobic core in its motif. The β-sheet was composed additionally by Leu232, Phe236, Val276, Val274 on one side and Val249, Val285, Leu224, Ala283 and Val285 on the opposite side.

The novel likely pathogenic variant changed the branched, hydrophobic amino acid Valine in position 234 with the linear, non-polar amino acid Methionine. This Valine is demonstrated to be highly conserved in mammals during the evolution. It is only in zebrafish (*Danio Rerio*) that the amino acid is substituted with a Leucine which is a similar branched amino acid. Therefore, the substitution with a linear Methionine could impair the function of the protein by deforming the structure of its extracellular CUB2 domain probably due to the different steric hindrance of the side chains of the two amino acids, while maintaining the non-polarity of the core (Supplemental Fig. 1).

The role of the CUB2 domain in the protein disfunction is supported by the evidence that the same protein region is affected by the adjacent pathogenic variants p.Arg230Trp and p.Arg235Cys reported in literature as potentially damaging in relation to PD.

The heterozygous pathogenic variant c.703C > T (NM_014045.5) p.Arg235Cys (GRCh37.p13 chr 14, NC_000014.8:g.23344860C > T, dbSNP, rs374479224) was found in a patient diagnosed with PD evolving in a rapidly progressive cognitive impairment and a positive familial history of PDD. Further neuro-biological tests showed that the patient was probably affected by a mixed form of dementia with similarities to DLB and mild signs of an Alzheimer's disease co-pathology. In his family, three relatives were affected by similar neurodegenerative pathologies and the p.Arg235Cys pathogenic variant was found in only two of them while the third tested negative and was characterized by a slower evolution of the disease. A fourth relative tested positive for the variation but manifested no signs or symptoms of the disease probably due to an incomplete penetrance of the pathogenic variant or maybe a late-onset form of the pathology [1].

Further functional studies on the effect of the p.Arg235Cys pathogenic variant were made analyzing brain samples obtained by autopsy from some patients and controls. No particular difference in immunochemistry was found between *LRP10* p.Arg235Cys carriers and controls,

https://doi.org/10.1016/j.parkreldis.2024.106973
Received 12 February 2024; Received in revised form 9 April 2024; Accepted 13 April 2024
Available online 17 April 2024
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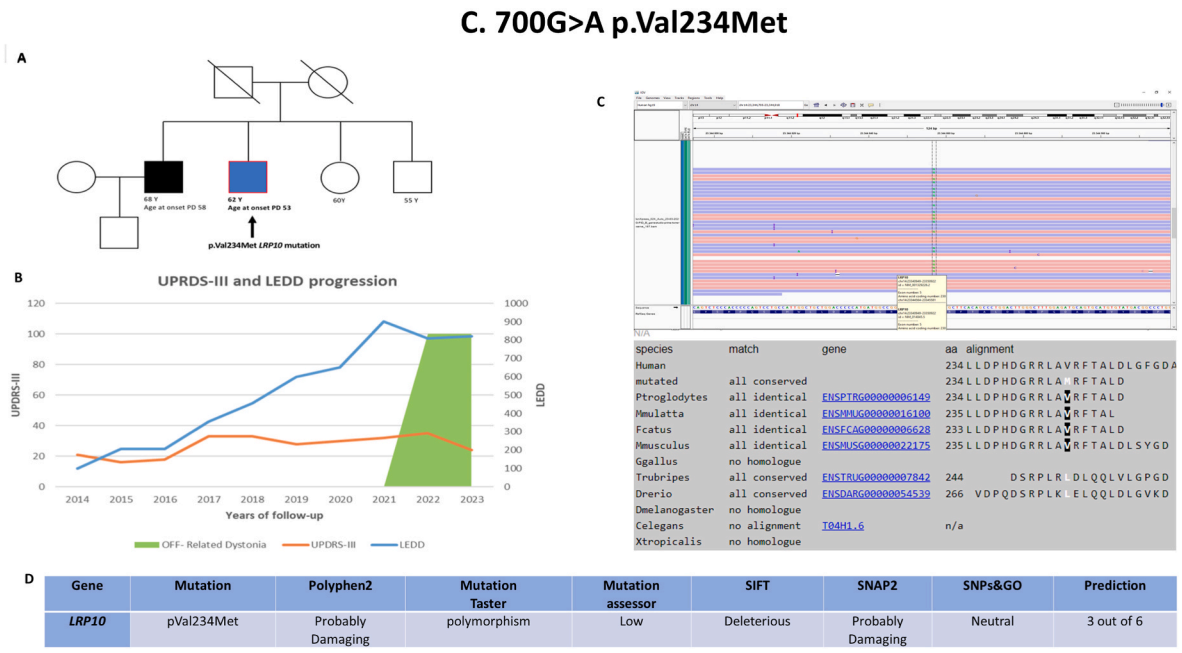

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Gene	Mutation	Polyphen2	Mutation Taster	Mutation assessor	SIFT	SNAP2	SNPs&GO	Prediction
LRP10	pVal234Met	Probably Damaging	polymorphism	Low	Deleterious	Probably Damaging	Neutral	3 out of 6

Fig. 1. Panel A: Family tree (affected brother unfortunately refused testing and assessment). Panel B: motor progression (UPDRS-III) and levodopa equivalent daily dose (LEDD) of the patient; Panel C: Probably pathogenic variant C. 700G > A p.Val234Met. Val 234 is highly conserved in mammals (Site: mutationtaster). Panel D: results of the *in-silico* simulation (sites used: PolyPhen-2, Mutationtaster, MutationAssessor, SIFT, SNAP2, SNPs&GO).

the only anomaly was the finding of clustered and larger LRP10-expressing vesicles in the brainstem tissue of the p.Arg235Cys carriers [1].

At the confocal microscopy imaging, these vesicles showed a peculiar donut-shaped morphology and were characterized by an increased lumen volume resembling those of damaged lysosomes [3].

The deleterious effect of the amino acid change in the p.Arg235Cys pathogenic variant suggests that the affected LRP10 region could be essential to the protein functionality. Expanding on it, since the change of Arg 235 is localized next to that of Val234, the same portion of the extracellular CUB2 domain could be altered and thus interfere with the functionality of the LRP10 receptor. However, the wild-type Arginine 235 is not located in the internal hydrophobic core of the CUB2 domain such as Val 234 but in the external structure responsible for the solvent interface.

Another potentially pathogenetic *LRP10* mutation was described in a 58-year-old Chinese patient affected by PD and suffering from resting tremor, bradykinesia and muscle stiffness but responsive to levodopa therapy. The patient tested positive for the heterozygous pathogenic variant c.688C > T (NM_014045.5) p.Arg230Trp (GRCh37.p13 chr 14, NC_000014.8:g.23344845C > T, dbSNP, rs568860898) that caused the substitution of the positive-charged Arginine with the aromatic, non-polar amino acid Tryptophan in the loop region connecting two β-strands of the CUB2 domain [6].

Since Arg230 belongs to the same β-strand as Val234 and Arg235, we have hypothesized that the CUB2 domain may play a fundamental role in the functionality of the LRP10 protein. Even if further studies are needed, these observations may shed some light on the biochemical mechanism that could impair the mutated protein in patients affected by LPR10-associated PD.

In conclusion, the case described a LRP-10 rare variant associated with a benignant PD familial phenotype. The report highlight the need for larger propective studies focused on familial neurodegenerative disorders in order to disentangle the role of *LRP10* gene within the wide spectrum of α-synucleinucleinopathies.

CRediT authorship contribution statement

Andrea Pilotto: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Mattia Carini:** Writing – review & editing, Formal analysis, Conceptualization. **Alessandro Lupini:** Writing – review & editing, Conceptualization. **Alessio di Fonzo:** Writing – review & editing, Data curation, Conceptualization. **Eugenio Monti:** Writing – review & editing, Data curation, Conceptualization. **Roberto Bresciani:** Writing – review & editing, Data curation, Conceptualization. **Alessandro Padovani:** Writing – review & editing, Data curation, Conceptualization. **Giorgio Biasiotto:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

Declaration of competing interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andrea Pilotto reports a relationship with Roche Diagnostics GmbH that includes: speaking and lecture fees. Andrea Pilotto reports a relationship with Zambon SpA that includes: speaking and lecture fees. Andrea Pilotto reports a relationship with BioMarin Pharmaceutical Inc that includes: speaking and lecture fees. Andrea Pilotto reports a relationship with Nutricia SRL that includes: speaking and lecture fees. Andrea Pilotto reports a relationship with Chiesi Pharmaceuticals Inc that includes: speaking and lecture fees.

Alessandro Padovani reports a relationship with GE Healthcare that includes: consulting or advisory. Alessandro Padovani reports a relationship with Eli Lilly and Company that includes: consulting or advisory. Alessandro Padovani reports a relationship with Actelion Ltd that includes: consulting or advisory. Alessandro Padovani reports a relationship with Nutricia SRL that includes: speaking and lecture fees. Alessandro Padovani reports a relationship with Piam Pharmaceuticals that includes: speaking and lecture fees. Alessandro Padovani reports a relationship with GE Healthcare that includes: speaking and lecture fees. Alessandro Padovani reports a relationship with Langstone Technology that includes: speaking and lecture fees. Alessandro Padovani reports a relationship with UCB Pharma SpA that includes: speaking and lecture

fees. Alessandro Padovani reports a relationship with Chiesi Farmaceutici SpA that includes: speaking and lecture fees. Andrea Pilotto reports a relationship with Italian Association of Alzheimer Research that includes: funding grants. "Segala grant" funding from Italian Parkinson's Disease Society, Italy (Andrea Pilotto, co-author). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The other Authors declare that there are no conflicts of interest relevant to this work.

Acknowledgments

This work was partially supported by grant: "Ex60 % Biasiotto, University of Brescia, Italy. G.B. would like to thank God for enabling him to work for those people who suffer from health problems.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2024.106973.

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