COMPARATIVE ANALYSIS OF THREE PATIENTS WITH *PRKN*-ASSOCIATED PARKINSON´S DISEASE FROM A BRAZILIAN COHORT

Cotrin, JC1; Pereira JS2; Spitz M2; Santos-Rebouças, CB1
1Departamento de Genética, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro
2Serviço de Neurologia, Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro
*cbs@uerj.br
(21) 999154982

INTRODUCTION

Parkinson´s disease (PD) is the second most common neurodegenerative disorder worldwide, being characterized by alfa-synuclein accumulation and progressive loss of dopaminergic neurons in the substantia nigra *pars compacta*, leading to nonmotor and motor symptoms. It is estimated that the hereditary component of PD is around 30%, of which 5-10% correspond to monogenic causes, while the remainder is driven by common variants that confer an increased risk for developing the disease. Massive parallel DNA sequencing have progressively expanded the knowledge about the complex genetic architecture of PD and patients with early-onset PD (EOPD) have provided a valuable opportunity for discovering new genes/variants.

In this study, we performed the Whole Exome Sequencing (WES) in 10 patients diagnosed with PD before the age of 40.

METODOLOGY

National Research Ethics Committee through the Brazil Platform: CAAE 26570919.6.0000.5259

Figure 1: Work flowchart

Legend: AOO: age of onset; ACMG: American College of Medical Genetics

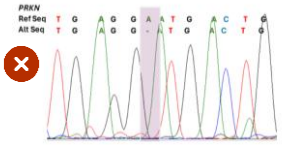
Figure 2: ACMG criteria classification

RESULTS

Patient 1
PRKN
c.155delA + *SYNJ1*

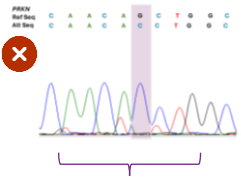
AOO: 29 years old
Initial symptom: tremors in the left hand
Rapid progression and poor response to treatment

Patient 2
PRKN
c.155delA



AOO: 8 years old
Initial symptom: dystonia in the left foot

Patient 3
PRKN
c.872-1G>C



Possible exon exclusion - splicing variant

AOO: 38 years old
Initial symptom: bilateral tremor
Family history of PD: paternal grandfather, father, two brothers, and a nephew
Depression and anxiety

DISCUSSION

Mitochondrial dysfunction can be triggered by the loss of function of proteins such as PINK1, parkin, DJ-1, VPS35, and LRRK2, which are classically associated with PD. Alterations in these proteins overload the autophagy pathway, impairing the ability of neurons to clear dysfunctional mitochondria.

The *PRKN c.155delA* variant, identified in two of our patients, has also been reported in some individuals with PD and is one of the most common *PRKN* variants in EOPD cases. Due to its rarity in population databases and the predicted functional impact of frameshift alterations, *c.155delA* is recognized as pathogenic.

In patient 3, we identified the *PRKN c.872-1G>C* variant in homozygosity, located at the acceptor splice site of exon 8. To date, only a single case has been described in the literature, although no clinical details were provided. In addition, a single submission to ClinVar (November, 2022) classified this variant as pathogenic. This alteration is predicted to cause exon 8 skipping.

CONCLUSIONS

Our results reinforce the complexity of genotype–phenotype correlations in *PRKN*-related EOPD, even among individuals carrying identical pathogenic variants. Furthermore, they highlight the critical role of genetic testing in clinical practice, allowing for more accurate prognostic assessments, family genetic counseling, and more appropriate therapeutic strategies.

FUNDING

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico
FAPERJ Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro
CAPES
InovUerj Departamento de Inovação