



PRKN-Linked Parkinsonism: Diagnostic Insights from Clinical Exome Sequencing

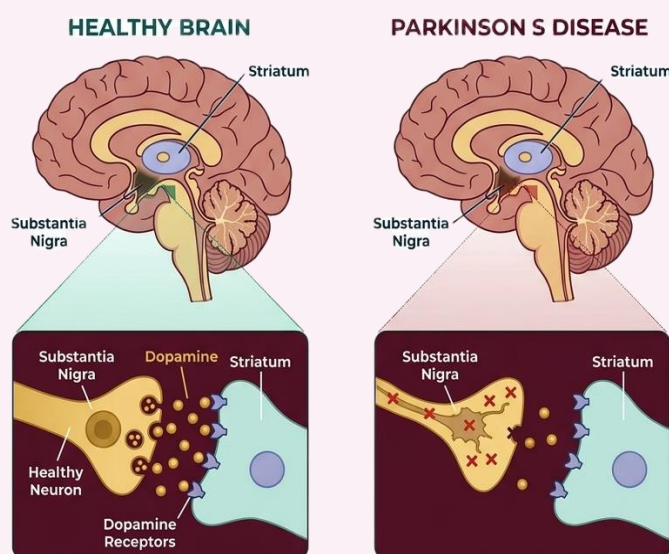
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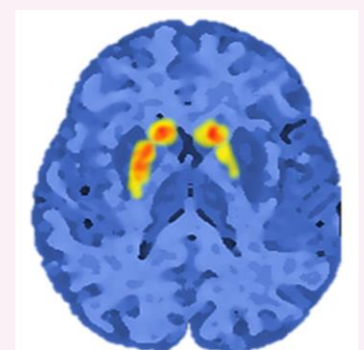
1 OBJECTIVES

Parkinson's disease (PD) is a neurodegenerative disorder that stems from the progressive loss of dopaminergic neurons in the *substantia nigra*, whose most common symptoms include tremor, rigidity, bradykinesia and postural instability. Although the vast majority of cases are sporadic, around 10–15% of cases have a genetic cause. They are found primarily in young-onset PD patients (<50 years old).

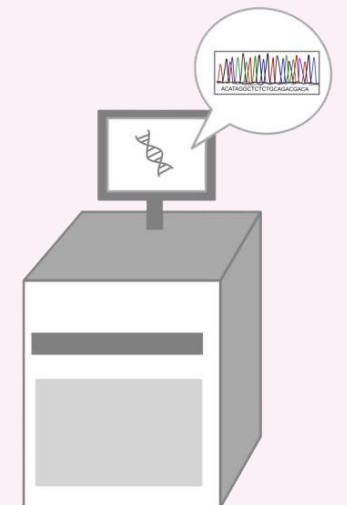


2 METHODS

In the spring of 2023, a 56-year-old female patient came to our clinic, presenting with clumsiness, slowness, hand tremor and tingling in both feet, which she claimed began approximately 10 years ago. Her father experienced head tremors and ptosis, suggesting a genetic cause, and so clinical exome sequencing (CES) was commissioned. The patient showed significant improvement after levodopa treatment, and subsequent DaTscan results (dopamine transporter SPECT imaging) were indicative of neurodegenerative parkinsonism.



Example DaTscan of a person with Parkinson's



3 RESULTS

This was further corroborated by CES analysis, which identified **two heterozygous variants in the PRKN gene** – c.101_102del (p.Gln34ArgfsTer5) and c.1301T>C (p.Met434Thr) (NM_004562.3). The deletion results in a premature STOP codon and is one of the most common pathogenic variants reported in the *PRKN* gene. The other, missense variant, has not been described in the literature so far, although it would be classified as likely pathogenic according to the ACMG Guidelines, and pathogenic by two software predictors (EVE, AlphaMissense).

Variant	Zygosity	ClinVar classification	ACMG classification	ClinVarID	LOVD	Status
c.1301T>C p.(Met434Thr)	hetero	likely pathogenic	PM1, PM2, PP3, PP5	810783	not present	novel
c.101_102del p.(Gln34ArgfsTer5)	hetero	pathogenic	PVS1, PP5, PM2	425403	present	published

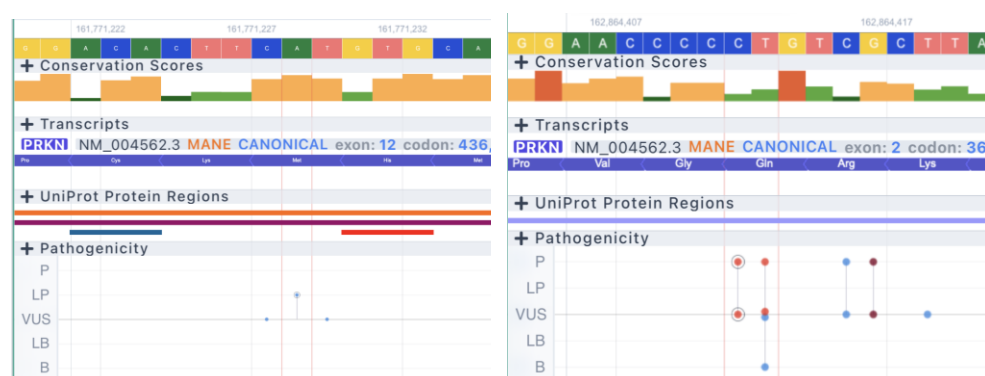


Figure 1. Met434Thr

Figure 2. Gln34ArgfsTer5

4 CONCLUSION

Despite both variants being heterozygous and PD monogenic mutations typically displaying autosomal-recessive pattern of inheritance, this finding would indicate that **there is no functional copy of the gene present** – the deletion in one copy of the gene yielding a dysfunctional 38-residue product and the other copy containing a likely pathogenic Met434Thr substitution. Further analysis should include functional testing, which could confirm the effects of the c.1301T>C variant in the *PRKN* gene.

Keywords: Parkinson's disease, parkinsonism, CES, *PRKN*