# CONCOMITANT HETEROZYGOUS VARIANTS IN PINK1 AND EIF4G1 IN PARKINSON'S DISEASE: A CASE REPORT

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**BACKGROUND:** Parkinson's disease (PD) is the second most common neurodegenerative disorder in Western populations. Although most cases are idiopathic, a subset arises from genetic mutations. Homozygous *PINK1* mutations are among the most frequent genetic causes, whereas the pathogenic role of heterozygous *PINK1* variants remains controversial. Novel mutations, including those in *EIF4G1*, have been implicated in PD risk.

**OBJECTIVE:** To describe a PD patient carrying a heterozygous *PINK1* mutation and an *EIF4G1* variant.

**METHODS:** A 62-year-old male with a history of epilepsy managed with valproate, behavioral alterations, and mild intellectual disability, developed resting tremor and rigidity, first becoming clinically evident at age 54. His clinical course began with a long-standing postural tremor, followed two decades later by resting tremor, mild rigidity, and bradykinesia, with subsequent progressive deterioration. Levodopa/carbidopa provided transient benefit but induced early dyskinesia. Over time, the patient experienced loss of ambulation, multidomain mild cognitive impairment, and ultimately required institutional care.

***FIG.1*** *The video illustrates the clinical presentation of the patient in its advanced stages. A pronounced global bradykinesia is evident, with marked hypomimia and bradykinesia*

**RESULTS:** Brain MRI showed mild leukoencephalopathy, while DaTSCAN revealed bilateral presynaptic nigrostriatal dysfunction, more pronounced on the right. Given the patient's clinical history, the exact onset of parkinsonian features remains uncertain, and early-onset PD could not be excluded.

Comprehensive next-generation sequencing panels for movement disorders, epilepsy, and rare neurological diseases identified a likely pathogenic heterozygous *PINK1* variant, along with two variants of uncertain significance in *CACNA1H* and *EIF4G1*.

| Gene | Nucleotide | Amino acid | Zygosity | Clinical relevance | Inheritance |
|---|---|---|---|---|---|
| PINK1 | c.1226G>T | p.(Gly409Val) | Heterozygous | Likely pathogenic | AR |
| CACNA1H | C.3779C>T | p.(Pro1260Leu) | Heterozygous | VUS | AD |
| EIF4G1 | c.2962A>G | p.(Ser988Gly) | Heterozygous | VUS | AD |

Reference sequences: PINK1 NM_032409.3; CACNA1H NM_021098.2; EIF4G1 NM_198241.3

***TABLE 1.*** *Heterozygous variants detected through the genetic panelan alysis*

**CONCLUSIONS**: Current hypothesis suggest that heterozygous *PINK1* variants may not independently cause PD but rather increase susceptibility through genetic and environmental interactions. In this patient, the presence of a heterozygous missense *EIF4G1* variant—previously implicated in familial PD—together with chronic valproate therapy may have contributed to disease onset, potentially exacerbating the effects of the *PINK1* variant via mitochondrial dysfunction.

***MAJOR REFERENCES:***

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