



SOLVING THE RIDDLE OF A SLOW LEARNER WITH SUDDEN DECLINE IN ACADEMIC PERFORMANCE

Dr. P. Jasmine Kalyani

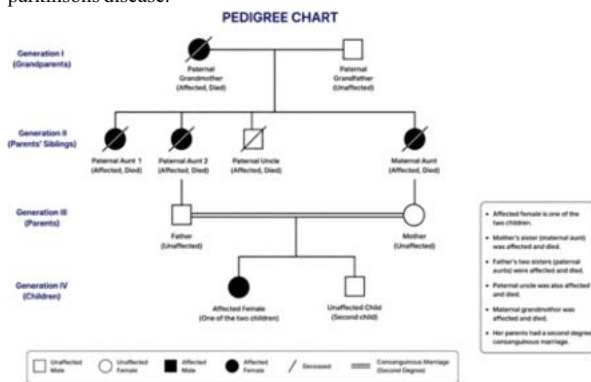
MD.,DM., {Neurology}

KEYWORDS :

16 Year old female referred from school health programme with a decline in academic performance which made the scene even worse due to her mask like facies and the resting tremor made her handwriting illegible. Hence she was fitting into the classical PD Criteria of TRAP which means tremor, rigidity, akinesia and postural instability. Infact the bradykinesia made her appear to be a slow learner. She had a strong genetic background with six of her family members had parkinsons disease. This was quite unique which made us to do genetic work up

Interestingly genetic test showed a homozygous missense variant in exon 10 of MAPT gene on chromosome 17 exon 10.

She was thoroughly investigated for the secondary causes of parkinsons disease.



GENOME LABS

WGA TEST REPORT (REVISION): MEDGENOME LABS

Sample Name: V. ANUSUYA
 Age: 16 years
 Sex: Female
 Date of Sample Collection: 14th March 2025
 Date of Report: 27th April 2025
 Date of Revision: 27th May 2025

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Ms. V. Anusuya, born of a non-consanguineous marriage, presented with clinical indications of rigidity, bradykinesia, and resting tremor (right-left), cervical and arm dystonia, mask like facies and no R/R ring. Ms. V. Anusuya has been evaluated for pathogenic gene variants.

RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Transcript	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
[+]	Exon 10	c.2078C>T (p.Pro693Leu)	Homozygous	Supranuclear palsy, progressive atypical [OMIM8260540]	Autosomal recessive	Pathogenic (P), PS, Moderate, PNL, PNL, PPS

Variant clinically relevant variants were detected in the mitochondrial genome.

NUMBER VARIANTS CNV(s)

nt CNVs for the given clinical indications that warrants to be reported was detected.

INTERPRETATION AND CLINICAL CORRELATION

Interpretation: A homozygous missense variant in exon 10 of the MAPT gene (chr17:g.46010389C>T; Depth: 116x) (The amino acid substitution of Leucine for Proline at codon 693 (p.Pro693Leu; ENST00000262410.10) was observed. The observed variant has previously been reported in patients affected with Semantic variant primary parkinsonism (PMID: 36707905, ClinVar: VCV000014245.45) and lies in the 'Tau and MAP protein, tubulin-binding domain' of the MAPT protein (P00418). Functional study has shown this missense variant can disrupt the normal

APPENDIX

ADDITIONAL VARIANT TABLE:

The table below represents additional variant which is significant but may not be directly relevant to the patient's phenotype. The clinical association may be evident in the future in case the disease phenotype evolves or more information about this variant. The classification of this variant may change over time, and it is to be noted that this table does not provide complete list of all possible significant variants detected. The phenotype-genotype correlation needs to be interpreted and evaluated by the clinician.

Gene, Variant details	Zygosity Depth (Alt. allele %)	In silico tools	MAF	Literature	OMIM Disease	Inheritance	Classification
PNKD (+) c.1043T>A p.Leu348Gln ST00000273077.9	Heterozygous 166x(47.6%)	SIFT - T LRT - N PolyPhen BN MT2 - NA	1000 G - NA gnomAD (V2.1.1) - NA gnomAD (V3.1.1) - NA MedVar - 0.0009%		Paroxysmal nonkinetic dyskinesia 1 [OMIM9118800]	Autosomal dominant	Uncertain Significance

Legend: D: Damaging; Prd: Probably damaging; BN: Benign; T: Tolerated; MAF: minor allele frequency; N: Not in internal database; MT2: MutationTaster2

Interpretation and classification of the variant may change based on segregation analysis.

METHODOLOGY

Sequencing: Selective capture and sequencing of the protein coding regions of the genome.

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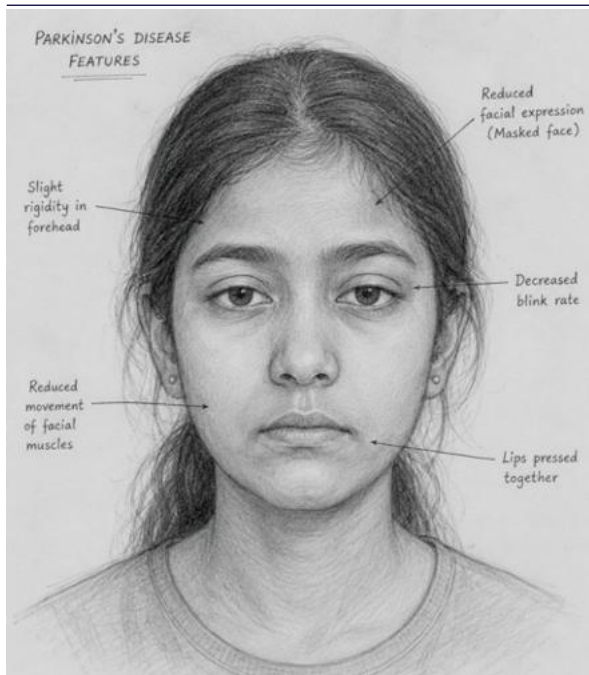
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The MAPT Gene encodes the microtubule-associated protein tau. While classic Parkinson's Disease (PD) is characterized by alpha-synuclein pathology, common variations and haplotypes (specifically the H1 lineage) at the MAPT locus on chromosome 17q21 act as established susceptibility risk factors for developing PD and related movement disorders. [1, 2, 3, 4]

Key Genetic and Pathological Concepts

H1 vs. H2 Haplotypes: An ancient chromosomal inversion divides the MAPT locus into two primary structural variants: H1 and H2. The H1 haplotype is widely replicated as a significant genetic risk factor for Parkinson's disease and other tauopathies like progressive supranuclear palsy (PSP). [1, 2, 3]

Protein Interaction: Although tau accumulation is the hallmark of frontotemporal lobar degeneration (tauopathies), tau pathology frequently co-occurs alongside alpha-synuclein in secondary pathways of PD, suggesting a synergistic molecular interplay between the two proteins. [1, 2]

Risk Factor vs. Direct Mutation: Unlike monogenic forms of Parkinson's driven by genes like *SNCA* or *LRRK2*, variations in *MAPT* typically modulate individual susceptibility rather than directly causing autosomal dominant disease on their own. [1, 2, 3]



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