

PSEN1 pathogenic variants in Alzheimer's Disease: Insights from the Serbian Population

Ana Marjanovic¹, Milena Jankovic¹, Lenka Stojadinovic¹, Gorana Mandic^{1,2}, Tanja Stojkovic^{1,2}, Predrag Aleksic¹, Valerija Dobricic¹, Ivana Novakovic², Elka Stefanova^{1,2}

1 Neurology Clinic, University Clinical Center of Serbia, Belgrade, Serbia;

2 School of Medicine, University of Belgrade, Belgrade, Serbia

Background

Presenilin-1 (*PSEN1*), located on chromosome 14, is the most common genetic cause of autosomal dominant early-onset Alzheimer's disease (EOAD). It encodes the essential catalytic subunit of the γ -secretase complex, an intramembrane protease responsible for the proteolytic processing of the amyloid precursor protein (APP). Pathogenic variants in *PSEN1* typically lead to an increased ratio of neurotoxic A β 42 peptides, which promotes rapid amyloid aggregation, synaptic dysfunction, and progressive neurodegeneration.

Materials and Methods

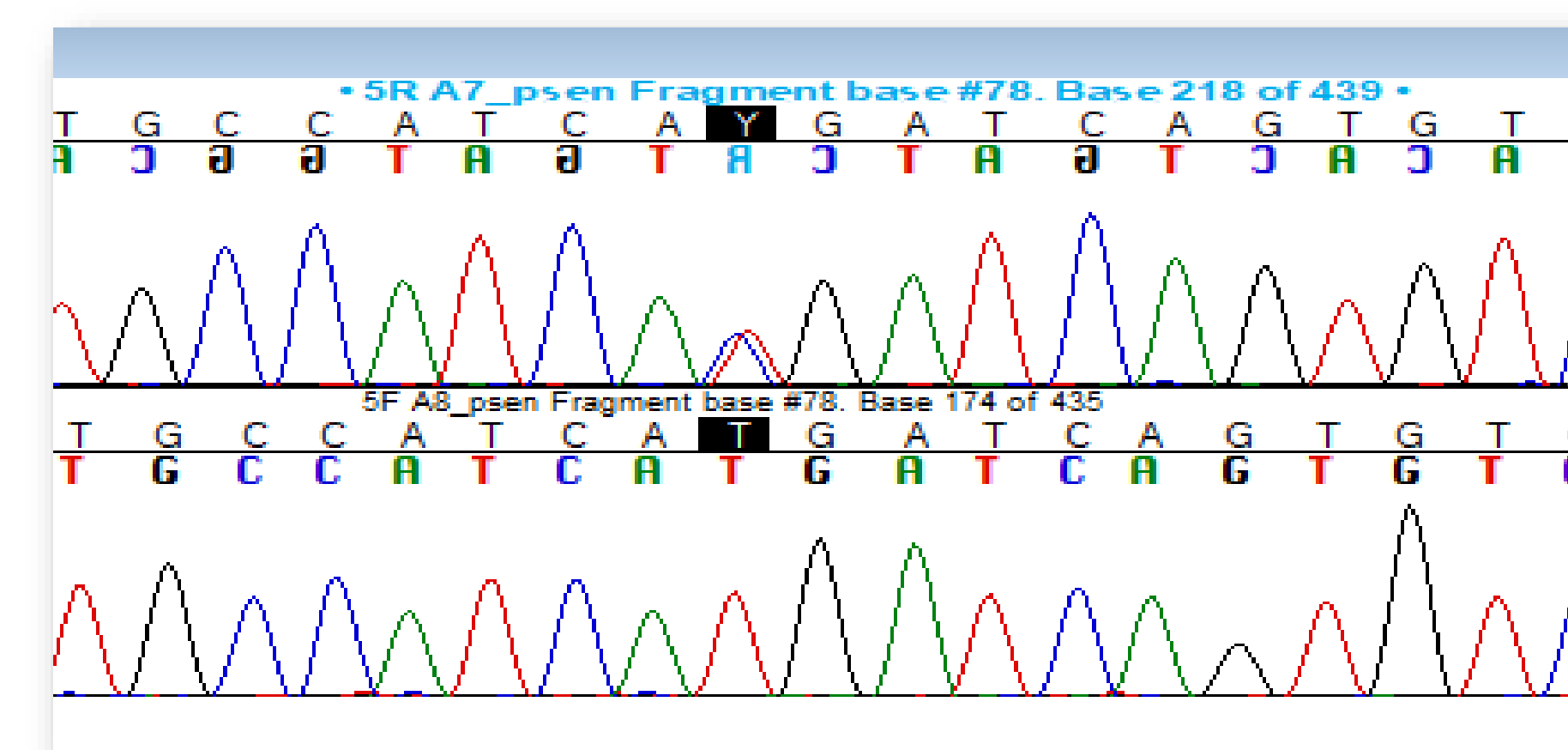
A total of 142 patients were enrolled at the Memory Center of the Neurology Clinic, University Clinical Center of Serbia, between 2010 and 2025. After obtaining informed consent, genomic DNA was extracted using standardized protocols. The analysis of the entire *PSEN1* coding region and flanking intronic boundaries was subsequently performed with Sanger sequencing.

Conclusion

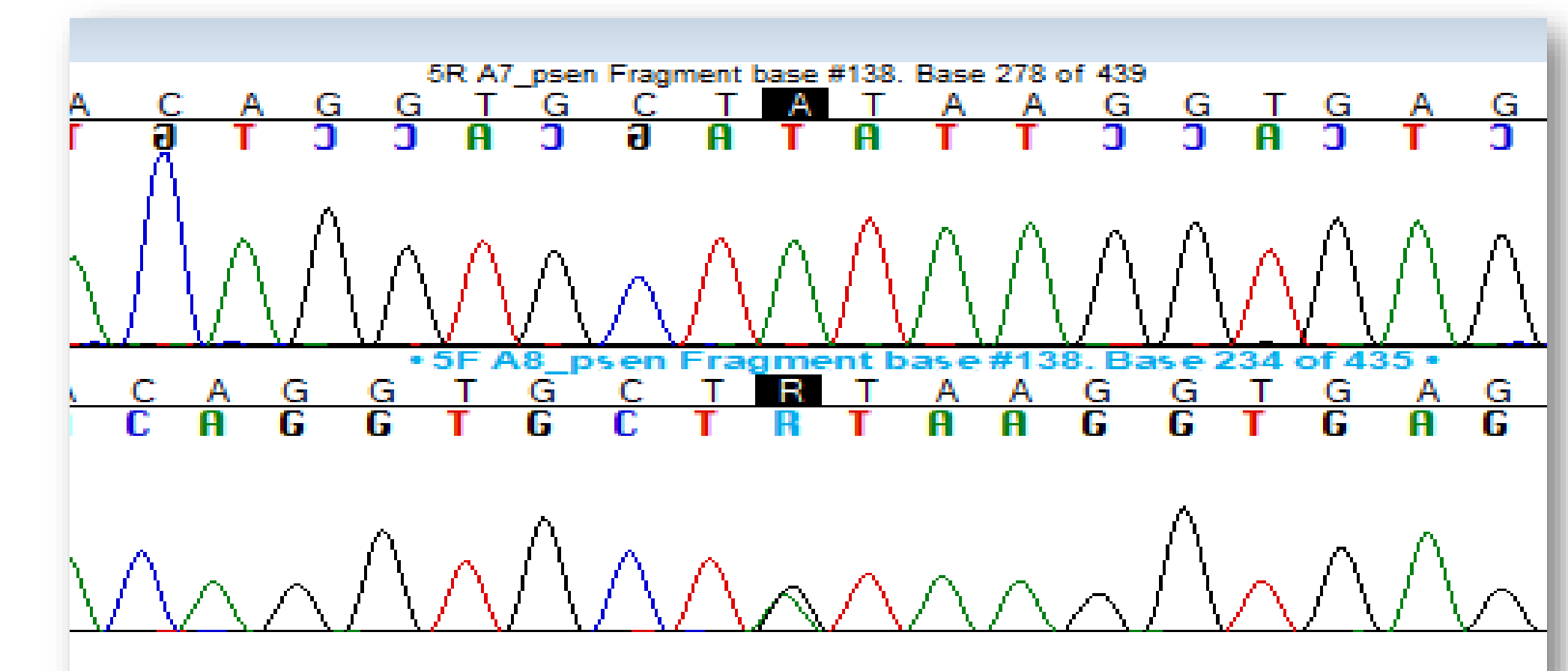
Our data demonstrate that *PSEN1* pathogenic variants contribute significantly to the familial AD burden in Serbia. These results emphasize that genetic testing is a critical component of the diagnostic workup for early-onset cases. Furthermore, understanding population-specific variants is vital for personalized medicine and improving the quality of genetic counseling for families at risk.

Results

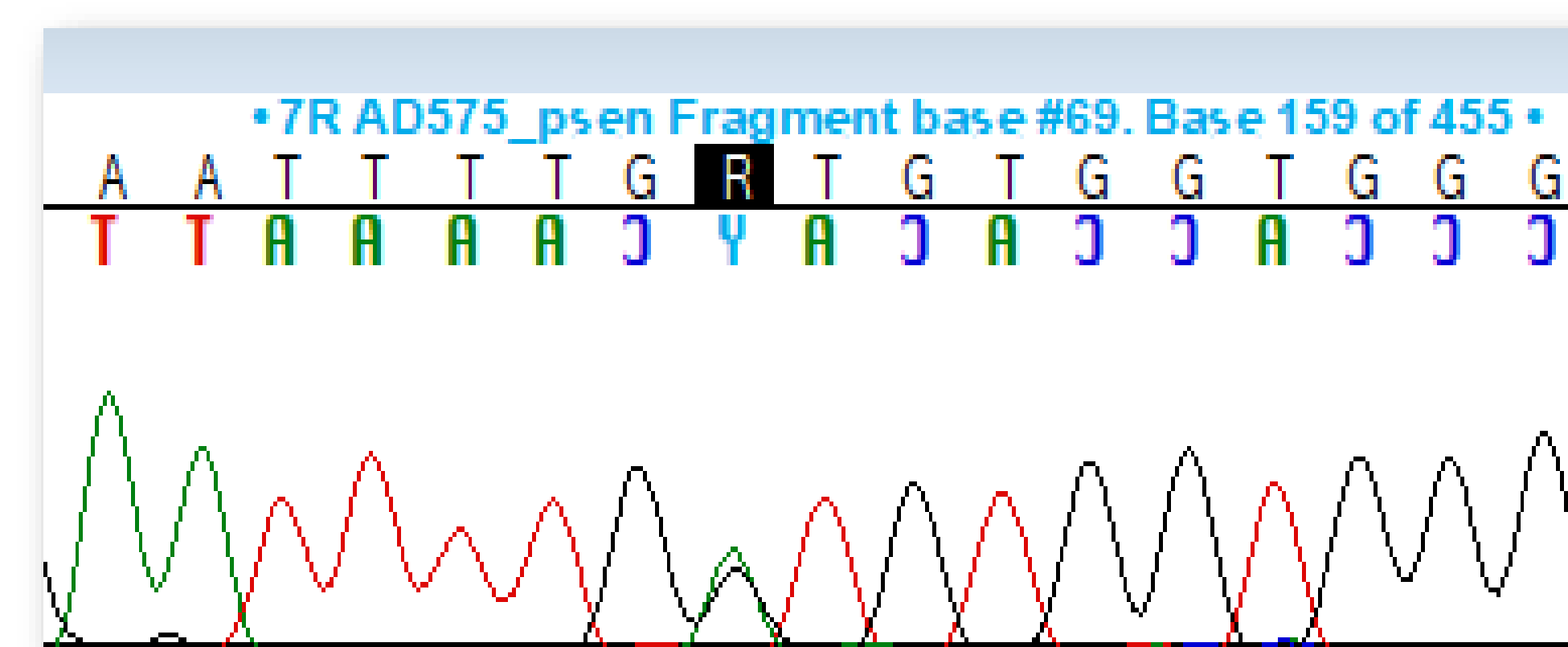
Pathogenic *PSEN1* variants were identified in 5.63% of the cohort, spanning six unrelated families. The detected pathogenic variants included p.M139T, p.Y159C, p.G206D, p.P267T, and p.R269H. All carriers clinically presented with an early onset and a familial form of the disease, characterized by at least two affected relatives with cognitive decline. In addition to core memory deficits, the clinical phenotype in select patients was marked by atypical features, including chorea and hallucinations. All identified variants have been previously documented in literature.



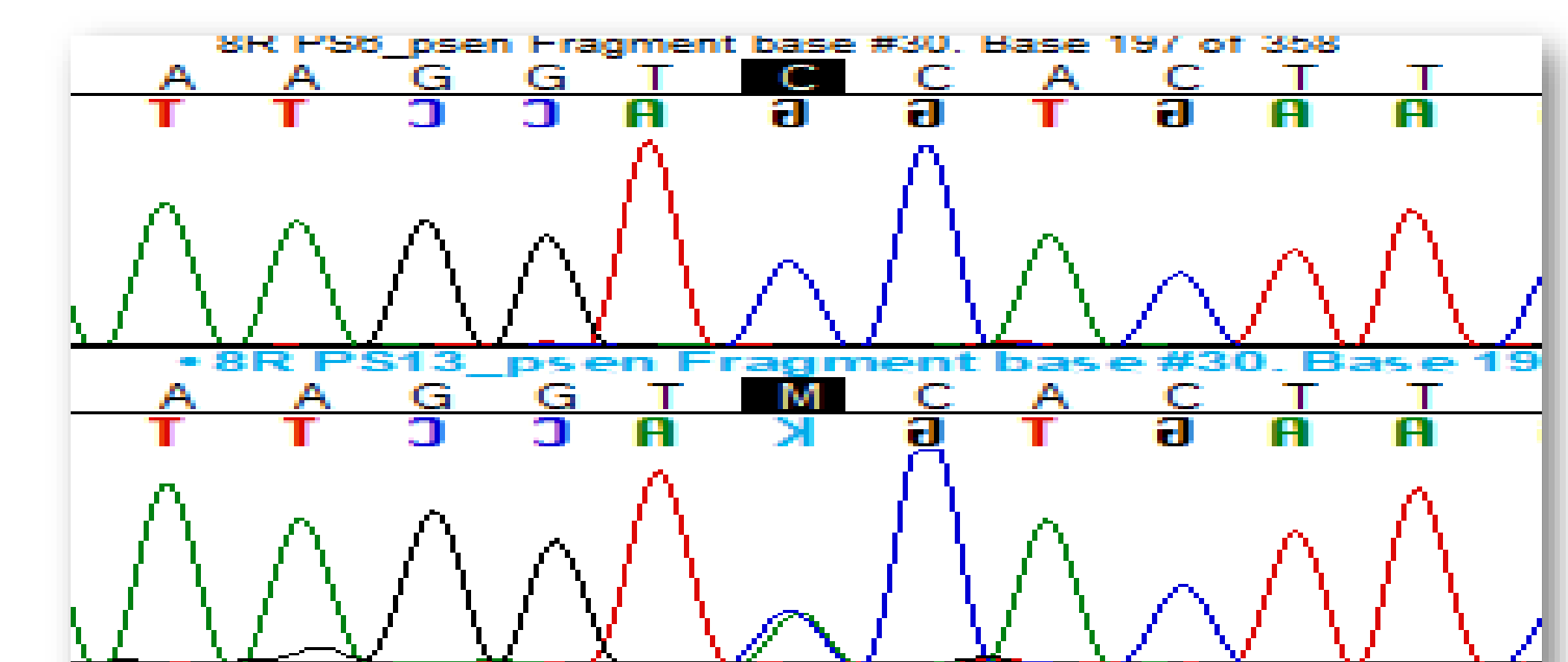
c.416T>C, p.Met139Thr



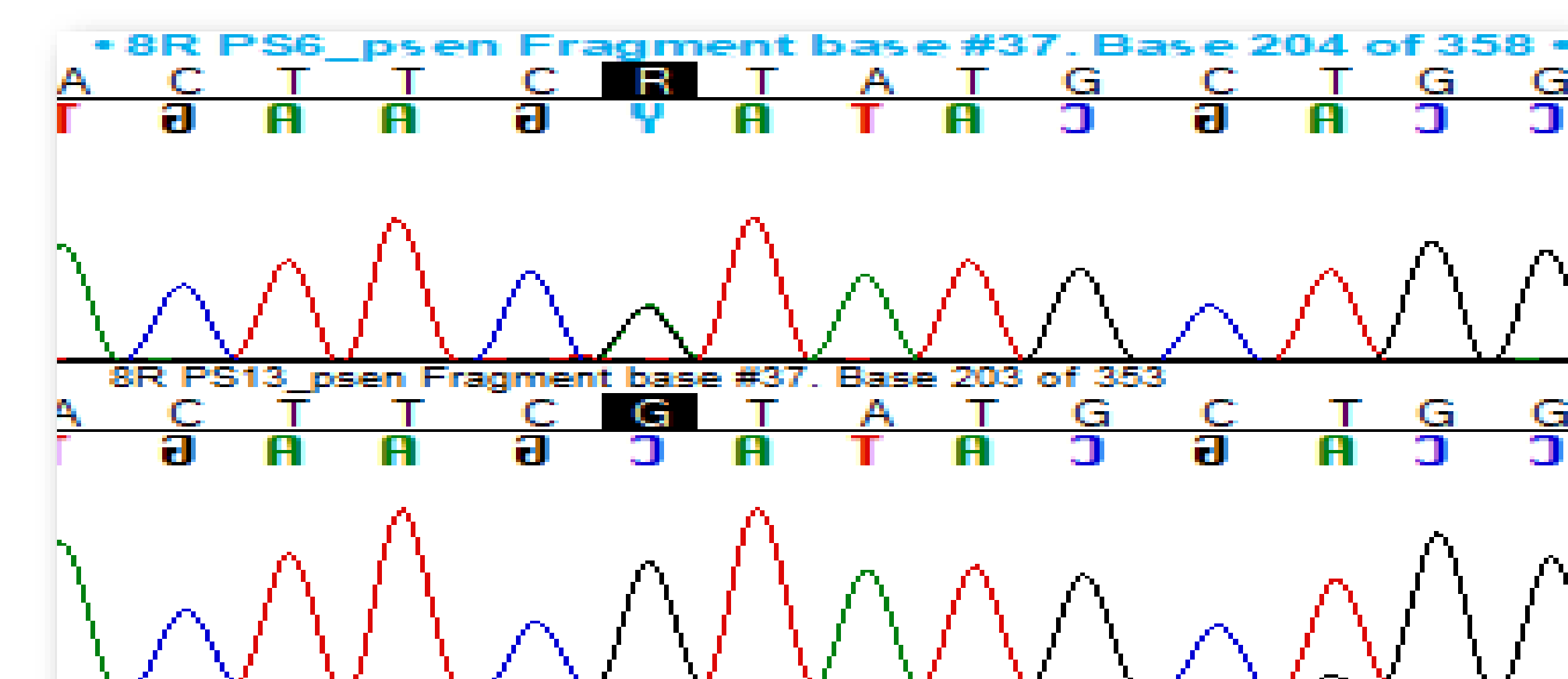
c.476A>G, p.Tyr159Cys



c.617G>A, p.Gly206Asp



c.799C>A, p.Pro267Thr



c.869G>A, p.Arg269His

Notification

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Contact: ana.marjanovic@yahoo.com