CASE STUDY

109. When RASopathies Collide: A Case Highlighting the Continuum between Noonan and LEOPARD Syndromes

Umesh G,[1] Sofia Mondal, Anton Charles,[1] Shaun Nevil,[1] Mansi Kumaraswamy.[2]

[1] ESIC- Medical College and Post Graduate Institute of Medical Science and Research , India

[2] Senior Resident, ESIC Medical College & PGIMSR, Banglore, India

LEOPARD syndrome and Noonan syndrome are clinically overlapping RASopathies, both frequently associated with pathogenic variants in the PTPN11 gene, which encodes the SHP-2 tyrosine phosphatase. Typically, Noonan syndrome arises from gain-of-function variants, while LEOPARD syndrome results from loss-of-function alterations, most often distinguished by the presence of lentigines and cardiac anomalies. We report a diagnostically challenging case of a 17-year-old male who presented with behavioural disturbances, seizure disorder, visual and auditory hallucinations, and history of right orchidectomy and left-eye cataract. Physical examination revealed hypertelorism, low-set ears, high-arched palate, and dental overcrowding, but notably lacked lentigines or cardiac findings. Genetic analysis identified a heterozygous PTPN11 variant, p.Phe285Ser in exon 8, previously described in both LEOPARD syndrome 1 and Noonan syndrome 1. Ancillary investigations confirmed seizure activity on EEG but showed no abnormalities on ECG or MRI. This case highlights the diagnostic ambiguity inherent to RASopathies, where identical PTPN11 variants may underlie divergent phenotypes. The absence of cutaneous and cardiac manifestations traditionally considered pathognomonic for LEOPARD syndrome underscores the limitations of relying solely on phenotype for classification. Instead, this case supports a genotype-first diagnostic framework, where molecular findings refine and sometimes challenge clinical labels. Recognition of such overlap is critical for genetic counselling, prognostic assessment, and surveillance planning, as patients may deviate from usually documented syndrome descriptions. Our report adds to the growing body of evidence that PTPN11 p.Phe285Ser represents a mutational hotspot bridging Noonan and LEOPARD syndromes, reinforcing the continuum model of RASopathies.

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