PTPN11 and SOS1 Gene Analysis in Indonesian Noonan syndrome Patients with Cardiovascular Abnormalities

ABSTRACT

Introduction: Noonan syndrome (NS) is an autosomal dominant disorder with a wide spectrum of symptoms and clinical phenotypes, including short stature, congenital heart defects (CHD), and distinctive facial features. A pathogenic variant in the *PTPN11* gene is the major cause of NS.

Goal: identify the pathogenic variants of *PTPN11* and *SOS1* gene and phenotype in Indonesian Noonan syndrome patients with cardiovascular abnormalities

Method: This study involving 29 patients with clinical features of NS. Detailed clinical and echocardiography data were collected. Genomic DNA was extracted from a peripheral blood sample. Exome sequencing or PCR followed by Sanger DNA sequencing was done. Variant pathogenicity was assessed using the ClinVar database, while the novel variant was analyzed in silico using PolyPhen, Rare Exome Variant Ensemble Learner (REVEL), SIFT, FATHMM Pred, and MutationTaster.

Result: Twenty-nine patients were examined using sequencing, 18 of them were found to have pathogenic variants in the *PTPN11* gene. The clinical findings in these 18 patients showed craniofacial features characteristic of NS., including low-posteriorly rotated ear (83.3%), microcephaly, downslanted palpebral fissures, and a short-webbed neck in 50%, and hypertelorism and a depressed nasal bridge in 44.4%. Other clinical variabilities included CHD (83.3%), thoracic and musculoskeletal deformities (77.8%), short stature (72.2%), and intellectual disability (ID) (50%). A novel variant in exon 3 of *PTPN11* was found in one patient: c.140G>A (p.Arg47Lys), which was predicted to be probably damaging. A variant in exon 8, the c.907G>A (p.Asp303Asn), was found in 11 patients. This variant is not in the ClinVar database yet; however, it was reported in a case report and predicted to be probably damaging. One patient has a variant c.184T>G (p.Tyr62Asp), 1 patient has c.854T>C (p.Phe285Ser), 1 patient has c.922A>G (p.Asn308Asp), 2 patients have c.1510A>G (p.Met504Val), and 1 patient has c.1517A>C (p.Gln506Pro), those variants have been previously reported.

Conclusion: NS patients with *PTPN11* variants demonstrate diverse clinical manifestations. Clinicians' awareness of suspecting NS is essential for early diagnosis, particularly in children with short stature, ID, and CHD who have a distinctive facial dysmorphism at any age.

Keywords: *PTPN11*; *SOS1;* Noonan syndrome; clinical variability; short stature; intellectual disability; congenital heart disease.