Analisis Varian Gen Arylsulfatase B (ARSB) Ekson 1-4 pada Pasien Mukopolisakaridosis (MPS) Tipe VI di Indonesia = Variant Analysis of Arylsulfatase B (ARSB) Gene Exons 1-4 in Indonesian Mucopolysaccharidosis (MPS) Type VI Patients

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Abstrak

Mukopolisakaridosis tipe VI (MPS tipe VI) merupakan gangguan metabolisme yang diakibatkan defisiensi aktivitas enzim pengolah glycosaminoglycan (GAG) jenis dermatan sulfat, yaitu arylsulfatase B (ARSB). Prevalensi MPS tipe VI di dunia tercatat dalam rentang 0,03—7,85 per 100.000 kelahiran. Gejala MPS tipe VI meliputi coarse facies, dysostosis multiplex, gangguan pendengaran, pernapasan, dan penglihatan, serta penebalan katup jantung, tetapi tidak disertai kelainan sistem saraf pusat. Varian pathogenic gen Arylsulfatase B (ARSB) pada ekson 1—4 telah dilaporkan sebagai pemicu manifestasi MPS tipe VI pada pasien dari berbagai belahan dunia, salah satunya dari Thailand. Laporan varian gen ARSB pada ekson 1—4 pasien MPS tipe VI di Indonesia belum ditemukan sehingga penelitian ini bertujuan mengidentifikasi dan mengklasifikasikan tingkat patogenisitas varian gen ARSB pada ekson 1—4 pasien MPS tipe VI di Indonesia. Gen ARSB dua pasien MPS tipe VI dan 10 individu normal diamplifikasi menggunakan polymerase chain reaction (PCR) dan disekuensing menggunakan metode Sanger. Patogenisitas varian gen ARSB yang teridentifikasi diklasifikasikan menurut panduan yang diterbitkan American College of Medical Genetics (ACMG). Identifikasi varian gen ARSB pada ekson 1—4 pasien MPS tipe VI di Indonesia berhasil dilakukan dengan temuan sejumlah delapan varian. Satu varian novel berhasil diklasifikasikan sebagai varian likely pathogenic, yaitu c.235_236delinsCC (p.Gly79Pro) yang ditemukan pada ekson 1 kedua pasien MPS tipe VI. Enam varian reported yang ditemukan pada intron 1 individu-individu normal berhasil diklasifikasikan sebagai varian likely benign, yaitu c.312+167G>A, c.312+229C>A, c.312+304C>T, c.313-81G>A, c.313-77G>A, dan c.313-26T>C. Satu varian reported yang ditemukan pada ekson 1 dua individu normal diklasifikasikan sebagai variant of uncertain significance (VUS), yaitu c.181G>A (p.Gly61Ser). Penelitian lebih lanjut yang melibatkan lebih banyak individu normal diperlukan untuk memperoleh data frekuensi alel kedelapan gen ARSB tersebut dalam populasi normal di Indonesia sehingga spesifisitas klasifikasi varian dapat meningkat menjadi varian pathogenic atau benign.

.....Mucopolysaccharide type VI (MPS tipe VI) is a metabolic disorder caused by deficient activity of arylsulfatase B (ARSB) enzyme, which processes a type of glycosaminoglycan (GAG) known as dermatan sulfate. Worldwide prevalence of MPS tipe VI ranges from 0.03—7.85 per 100,000 live births. Symptoms of MPS tipe VI include coarse facies, dysostosis multiplex, eyes, lungs, and ears disorders, as well as valvular stenosis, but without central nervous system abnormalities. Pathogenic variants of Arylsulfatase B (ARSB) gene in exons 1—4 has been reported to cause MPS tipe VI manifestation in patients from multiple countries, including Thailand. No report of ARSB gene variants in exons 1—4 of Indonesian MPS tipe VI patients have been found. This study aims to identify and classify the pathogenicity of ARSB gene variants in exons 1—4 of Indonesian MPS tipe VI patients. ARSB gene of two patients and 10 healthy individuals were amplified using polymerase chain reaction (PCR) and Sanger sequenced. Pathogenicity of identified ARSB gene variants were classified according to the American College of Medical Genetics (ACMG)

guidelines. Identification of ARSB gene variants in exons 1—4 of MPS type VI patients in Indonesia was successfully carried out with a finding of eight gene variants. A novel variant found in exon 1 of both MPS type VI patients was classified as a likely pathogenic, notated as c.235_236delinsCC (p.Gly79Pro). Six reported variants found in intron 1 of healthy individuals were classified as likely benign, each notated as c.312+167G>A, c.312+229C>A, c.312+304C>T, c.313-81G> A, c.313-77G>A, and c.313-26T>C. One reported variant found in exon 1 of two healthy individuals was classified as a variant of uncertain significance (VUS), notated as c.181G>A (p.Gly61Ser). Further research involving more healthy individuals is required to obtain frequency allele data of the eight ARSB gene variants in the Indonesian normal population, which supports the increase of each variant’s classification specificity into pathogenic or benign.