ABSTRAK

Latar Belakang : Penelitian genetik pada mikrotia hingga saat ini masih terbatas pada populasi dan keluarga tertentu, tanpa adanya eksplorasi menyeluruh terhadap spektrum genetik yang lebih luas. Pada populasi Indonesia belum tersedia data genetik terkait mikrotia. Identifikasi varian genetik melalui pendekatan *Whole Exome Sequencing* (WES) dapat memberikan gambaran menyeluruh mengenai varian yang berpotensi berperan dalam patogenesis mikrotia. Penelitian ini bertujuan untuk mengetahui frekuensi serta hubungan antara genotipe dan fenotipe pada pasien mikrotia sindromik, non-sindromik, familial, dan sporadik.

Metode : Sebanyak 26 pasien mikrotia direkrut antara tahun 2018 hingga 2023 dari dua rumah sakit di Indonesia. Setelah persetujuan tertulis diperoleh dari seluruh partisipan, DNA genomik diekstraksi dan dianalisis menggunakan *Whole Exome Sequencing* berbasis teknologi *Next-Generation Sequencing* (NGS). Varian jarang dengan *minor allele frequency* (MAF) <1% diidentifikasi melalui *bioinformatics pipeline*. Patogenisitas varian dievaluasi dengan menggunakan alat prediksi *in silico*, seperti phyloP, CADD score, dan Grantham score. Hubungan genotipe-fenotipe ditentukan berdasarkan pedoman ACMG (*American College of Medical Genetics and Genomics*).

Hasil : Analisis genetik dengan metode WES menunjukkan hasil positif pada 12 pasien. Berdasarkan pedoman ACMG, ditemukan 2 pasien dengan varian patogenik, 1 pasien dengan varian *likely pathogenic*, dan 9 pasien dengan *variant of uncertain significance* (VUS). Dari total 26 pasien yang diperiksa, 12 pasien (46%) menunjukkan hasil genetik positif, sementara 14 pasien (54%) lainnya negatif. Penelitian ini juga menemukan varian dan gen baru pada 11 pasien (42%) dengan mikrotia sindromik, 1 pasien (4%) dengan mikrotia non-sindromik, 3 pasien (12%) dengan mikrotia familial, serta 9 pasien (35%) dengan mikrotia sporadik.

Kesimpulan : Hasil penelitian ini menunjukkan adanya hubungan antara varian genetik (genotipe) dengan fenotipe pada pasien mikrotia sindromik, non-sindromik, familial, maupun sporadik.

Kata kunci: Genetik mikrotia, *Whole Exome Sequencing*, Fenotip, Kelainan kongenital

ABSTRACT

Background: *Genetic studies on microtia remain limited to specific populations and families, without comprehensive exploration of the broader genetic spectrum. In Indonesia, no genetic data related to microtia are currently available. Identification of genetic variants in this condition can be performed using Whole Exome Sequencing (WES), which provides a comprehensive overview of rare variants potentially involved in the pathogenesis of microtia. This study aimed to determine the frequency and genotype–phenotype correlation in patients with syndromic, non-syndromic, familial, and sporadic microtia.*

Methods: *A total of 26 microtia patients were recruited between 2018 and 2023 from two hospitals in Indonesia. After obtaining informed consent, genomic DNA was extracted and analyzed using WES based on Next-Generation Sequencing (NGS) technology. Rare variants with a minor allele frequency (MAF) <1% were identified through a bioinformatics pipeline. Variant pathogenicity was evaluated using* in silico *prediction tools, including phyloP, CADD score, and Grantham score. Genotype–phenotype correlations were assessed according to ACMG (American College of Medical Genetics and Genomics) guidelines.*

Results: *Genetic analysis using WES revealed positive findings in 12 patients. According to ACMG guidelines, 2 patients carried pathogenic variants, 1 patient carried a likely pathogenic variant, and 9 patients had variants of uncertain significance (VUS). Of the 26 patients examined, 12 (46%) showed positive genetic findings, while 14 (54%) were negative. This study also identified novel variants and genes in 11 patients (42%) with syndromic microtia, 1 patient (4%) with non-syndromic microtia, 3 patients (12%) with familial microtia, and 9 patients (35%) with sporadic microtia.*

Conclusion: *The findings of this study demonstrate a correlation between genetic variants (genotype) and phenotypic presentation in syndromic, non-syndromic, familial, and sporadic microtia patients.*

Keywords*: Microtia genetics, Whole Exome Sequencing, Phenotype, Congenital anomaly*