

## INTISARI

**Latar Belakang:** Epilepsi ensefalopati mengacu pada sekelompok gangguan dimana aktivitas epilepsi yang terus menerus berkontribusi terhadap disfungsi otak progresif dan proses degeneratif, yang etiologinya tidak dapat dijelaskan secara spesifik. Identifikasi dari dasar genetik epilepsi ensefalopati dapat memberikan tambahan informasi mengenai patofisiologi, prognosis, pilihan terapi, *personalized precision medicine*, termasuk peluang terapi genetik di masa depan.

**Tujuan:** Mengidentifikasi karakteristik genetik dan hubungannya dengan fenotip *developmental and epileptic encephalopathy* (DEE) yang diperiksa dengan *Next Generation Sequencing* (NGS)

**Metode penelitian:** Subjek penelitian adalah pasien dengan kecurigaan ke arah *developmental and epileptic encephalopathy* di bawah usia 18 tahun di RS Sardjito dari tahun 2023-2024, yang bersedia mengikuti penelitian dan menandatangani *informed consent*. Subjek penelitian 35 pasien. Isolasi DNA akan dilakukan di Laboratorium Riset Terpadu FK-KMK UGM. Identifikasi molekuler akan menggunakan *Whole Exome Sequencing* (WES) dilanjutkan dengan *sanger sequencing*. Hasil bioinformatika akan diolah untuk mencari varian patogenik yang sesuai dengan data klinis pasien. Pembahasan difokuskan pada hubungan genotip yang didapat dan fenotip dari pasien DEE.

**Hasil penelitian:** Sebanyak 49 pasien dengan diagnosis klinis DEE, didapatkan 11 pasien dengan hasil genetik pemeriksaan WES termasuk sindrom DEE menurut ILAE; 4 (36,7%) Sindrom West (*ARX*, *TSC2*, dan *GABRB3*), 3 (27,3%) Sindrom Ohtahara (*STXBPI*, *KCNQ2*, dan *GABRB3*), 2 (18,2%) Sindrom Dravet (*SCN1A* dan *SCN9A*), dan 2 (18,2%) Sindrom Lennox Gastaut (*YWHAG*, *GABRB3*). Korelasi genotip dan fenotip DEE ditemukan pada beberapa gen, diantaranya letak varian *KCNQ2* berpengaruh pada fenotip berat seperti DEE maupun ringan seperti BFNS, varian delesi *STXBPI* menyebabkan ataksia dan IEES, sedangkan varian *missense* sering berhubungan dengan EIEE/DEE, frekuensi epilepsi lebih tinggi pada varian *TSC2* di domain fungsional, jenis varian *SCN1A* menentukan fenotip pasien dari yang berat seperti Dravet maupun ringan seperti GEFS+, dan jenis varian *GABRB3* menentukan onset kejang, gangguan neurologis, dan gangguan intelektual.

**Kesimpulan:** Hubungan genotip dan fenotip pasien DEE dengan menggunakan WES dapat ditemukan pada 11/49 (22,4%) pasien dengan varian gen *ARX*, *TSC2*, *GABRB3* pada Sindrom West, *STXBPI*, *KCNQ2*, *GABRB3* pada Sindrom Ohtahara, *SCN1A*, *SCN9A* pada Sindrom Dravet, dan *YWHAG*, *GABRB3* pada Sindrom Lennox Gastaut. Korelasi genotip dan fenotip DEE terdapat pada beberapa gen, diantaranya *KCNQ2*, *STXBPI*, *TSC2*, *SCN1A*, *GABRB3*, dan sebagainya

**Saran:** Penelitian selanjutnya dapat menggunakan *long read* NGS, pemberdayaan fasilitas pemeriksaan genetik baik WES maupun WGS dengan harga terjangkau, serta pembuatan algoritma mulai dari fenotip DEE sampai dengan pemeriksaan *targeted panel sequencing* masing-masing klasifikasi DEE.

Kata kunci: *developmental and epileptic encephalopathy*, anak, genetik, *next generation sequencing*.

## ABSTRACT

**Background:** Epileptic encephalopathy refers to a group of disorders in which persistent epileptic activity contributes to progressive brain dysfunction and degenerative processes, the etiology of which cannot be specifically explained. Identification of the genetic basis of epileptic encephalopathy can provide additional information regarding pathophysiology, prognosis, therapeutic options, personalized medicine precision, including opportunities for future genetic therapy.

**Objective:** To identify genetic characteristics and their relationship to developmental and epileptic encephalopathy phenotypes examined by Next Generation Sequencing (NGS) Research methods: The subjects of the study were patients with suspicion of developmental and epileptic encephalopathy under the age of 18 years at Sardjito Hospital from 2023-2024, who were willing to participate in the study and signed an informed consent. The subjects of the study were 35 patients. DNA isolation will be carried out at the Integrated Research Laboratory of Faculty of Medicine Public Health and Nursing UGM. Molecular identification will use *Whole-Exome Sequencing* (WES) followed by *sanger sequencing*. The bioinformatics results will be processed to find pathogenic variants that match the patient's clinical data. The discussion focuses on the relationship between the obtained genotip and phenotype of developmental and epileptic encephalopathy patients.

**Results:** A total of 49 patients with a clinical diagnosis of DEE, 11 patients were found with genetic results of WES examination including DEE syndrome according to ILAE; 4 (36.7%) West Syndrome (*ARX*, *TSC2*, and *GABRB3*), 3 (27.3%) Ohtahara Syndrome (*STXBPI*, *KCNQ2*, and *GABRB3*), 2 (18.2%) Dravet Syndrome (*SCN1A* and *SCN9A*), and 2 (18.2%) Lennox Gastaut Syndrome (*YWHAG*, *GABRB3*). The correlation between DEE genotype and phenotype was found in several genes, among which the location of *KCNQ2* mutations affects severe phenotypes such as DEE and mild phenotypes such as BFNS, *STXBPI* deletion variants cause ataxia and IEES, while *missense* variants are often associated with EIEE/DEE, the frequency of epilepsy is higher in *TSC2* variants in the functional domain, the type of *SCN1A* mutation variant determines the patient's phenotype from severe such as Dravet to mild such as GEFS+, and the type of *GABRB3* variant determines the onset of seizures, neurological disorders, and intellectual disabilities.

**Conclusion:** The relationship between genotype and phenotype of DEE patients using WES can be found in 11/49 patients with variants of *ARX*, *TSC2*, *GABRB3* genes in Sindrom West, *STXBPI*, *KCNQ2*, *GABRB3* in Sindrom Ohtahara, *SCN1A*, *SCN9A* in Dravet Syndrome, and *YWHAG*, *GABRB3* in Lennox Gastaut Syndrome. The correlation between genotype and phenotype of DEE is found in several genes, including *KCNQ2*, *STXBPI*, *TSC2*, *SCN1A*, *GABRB3*, and so on.

**Suggestion:** Further research can use long read WES, empowerment of genetic examination facilities both WES and WGS at affordable prices, and the creation of algorithms starting from DEE phenotypes to examination of the target sequencing panels for each DEE classification.

**Keywords:** developmental and epileptic encephalopathy, children, genetics, next generation sequencing.