Epileptic encephalopathy

The term epileptic encephalopathy describes a heterogeneous group of epilepsy syndromes associated with severe cognitive and behavioral disturbances. These disorders vary in their age of onset, developmental outcome, etiologies, neuropsychological deficits, electroencephalographic (EEG) patterns, seizure types, and prognosis, but all may have a significant impact on neurological development.

Kothur et al., retrospectively analysed the yield of targeted epileptic encephalopathy (EE) panel of 71 known EE genes in patients with epilepsy of unknown cause, who underwent clinical triage by a group of neurologists prior to the testing. We compared cost of the EE panel approach compared to traditional evaluation in patients with identified pathogenic variants.

The yield of pathogenic variants was 28.5% (n = 30/105), highest in early onset EE <3 months including Ohtahara syndrome (52%, n = 10/19) and lowest in generalized epilepsy (0/17). Patients identified with pathogenic variants had earlier onset of seizures (median 3.6 m vs 1.1y, $p < 0.001$, OR 0.6/year, $P < 0.02$) compared to those without pathogenic variants. Pathogenic/likely pathogenic variants were found in ALDH7A1 (2), CACNA1A (1), CDKL5 (3), FOXG1 (2), GABRB3 (1), GRIN2A (1), KCNQ2 (4), KCNQ3 (1), PRRT2 (1), SCN1A (6), SCN2A (2), SCN8A (2), SYNGAP1 (1), UBE3A (2) and WWOX (1) genes. This study expands the inheritance pattern caused by KCNQ3 mutations to include an autosomal recessive severe phenotype with neonatal seizures and severe developmental delay. The average cost of etiological evaluation was less with early use of EE panel compared to the traditional investigation approach ($5990 Australian dollars (AUD) vs $13069 AUD ; $p = 0.02$) among the patients with identified pathogenic variants.

Targeted MPS testing is a comprehensive and economical investigation that enables early genetic diagnosis in children with EE. Careful clinical triage and selection of patients with young onset EE may maximize the yield of EE panel testing [1].

Hypothalamic hamartoma may be associated with gelastic seizures, focal seizures, and a generalized epileptic encephalopathy, with severe seizures and cognitive and behavior decline. Despite earlier views to the contrary, good evidence now exists that all these clinical features are caused, directly or indirectly, by the hamartoma.

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Kothur K, Holman K, Farnsworth E, Ho G, Lorentzos M, Troedson C, Gupta S, Webster R, Procopis PG, Menezes MP, Antony J, Ardern-Holmes S, Dale RC, Christodoulou J, Gill D, Bennetts B. Diagnostic yield of targeted massively parallel sequencing in children with epileptic encephalopathy. Seizure. 2018 May 28;59:132-140. doi: 10.1016/j.seizure.2018.05.005. [Epub ahead of print] PubMed PMID: 29852413.