The spectrum of developmental and epileptic encephalopathies and their genetic heterogeneity are much broader than previously thought

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Letter to the Editor

We read with interest the article by Triono et al., on a review using the PRISMA guidelines on the genetic causes of developmental and epileptic encephalopathy (DEE) and the phenotypes of these genetic disorders.[1] A total of 18 studies were included in the review, and the most frequently reported mutated genes were STXBP1 in Ohtahara syndrome, SLC1A2 in early myoclonic encephalopathy (EME), CDKL5 in West syndrome, SCN1A in Dravet syndrome, and KCNT1 in infantile epilepsy with migrating focal seizures (EIMFS) [1]. Each mutation was associated with different electroclinical features, including differences in age of onset, seizure type, EEG patterns, and developmental outcomes.[1] The overview is remarkable, but some points should be discussed.

The first point is that it is incomprehensible why patients with congenital mitochondrial disorders that manifest themselves in seizures and subsequently worsen due to epilepsy that is often difficult to treat were not included in the overview. In particular, patients with Leigh syndrome should have been included in the overview, as these patients are relatively common, the syndrome results from a broad spectrum of >100 mutated genes, progresses with the duration of the disease, often manifests itself through therapy-resistant seizures, and progresses with the number of seizures. Particularly, Alpers-Huttenlocher syndrome, POLG-associated mitochondrial syndromes, MERRF syndrome, and patients with MEGDEL syndrome should be included. It is also unclear why no patients with non-syndromic or syndromic microdeletion or microduplication disorders were included in the overview. This patient group includes, for example, 15q13.3 microdeletion syndrome or 3q29 microdeletion syndrome. It is also unclear why Lennox-Gastaux syndrome, myoclonic atonic epilepsy (Doose syndrome), Landau-Kleffner syndrome, epileptic encephalopathy with continuous spike-and-wave seizures during sleep, and fever-induced epilepsy syndrome (FIRES) are not mentioned.[2,3]

The second point concerns the discrepancy between the statement in the summary that the causes of DEE and the causes of variations are unknown, and the statement in the introduction that recent studies have shown that genetic causes have been identified in various epileptic encephalopathies and that various previously unknown genes have emerged.[1] The review itself has shown that the causes of DEE and the causes of variations are no longer unknown.

In summary, the review by Triono et al. is incomplete, as the spectrum of DEE is much broader than assumed. Expanding the review to include the many DEEs that were not considered could significantly increase reader interest and enhance the review's significance.

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