Genetic landscape of malformations of cortical development with refractory epilepsy in Taiwan

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Abstract

Malformations of cortical development (MCD) are a group of developmental disorders frequently causing epilepsy. Although next generation sequencing can help identify substantial genetic variants, a correct genetic diagnosis of MCD relies on the correlations with neuropathology. I will report the genetic landscape of MCD with refractory epilepsy (RE) whose diagnosis were firmly established in a multidisciplinary epilepsy team at Taipei Veterans General Hospital in Taiwan. Sixty-six patients were recruited. Their MCD types include: FCD (51, 77.3%), heterotopia (4, 6.06%), polymicrogyri, Dandy-Walker malformation and lissencephaly. Tuberous sclerosis complex was not included. These patients were first screened by targeted sequencing (TS) of 66 genes causative for MCD and epilepsy encephalopathy. For those with a potential candidate variant identified, they were submitted to whole exome sequencing to confirm the variant is the best pathogenic candidate. Reported pathogenic variant or novel but potentially disease-causative variants were identified in 28 patients (42%). Among them, nine were familial cases (32%). In the 38 genetic not-assigned individuals, only two had a positive family history (5.3%). Nine variants (32/1%) occurred in the GATOR1 complex genes (DEPDC5/NPRL2/NPRL3). The hit rate was the highest, reaching 78% (7/9), in severe and diffuse MCD, like Dandy-Walker malformation and lissencephaly. For FCD, the hit rate was 55% (28/51). Our results supported that rapid screening by tTS of known disease-causative genes is efficient to enhance genetic diagnosis of MCD, particularly in severe and diffuse MCD and FCD. Brain MRI and neuropathology are essential to determine the pathogenicity of identified variants.