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EDITORIAL

Precision genetics for precision medicine in epilepsy: toward optimizing treatment

Brahim Tabarki[1*]

Editorial

Precision Genetics for Precision Medicine in Epilepsy: towards optimizing treatment

Epilepsy affects 65 million people worldwide; the incidence is higher in Arab population. Epilepsy has a major burden in seizure-related quality of life, disability, mortality, social, stigma, and costs. Although the number of available antiepileptic drugs has increased substantially during the past 20 years, 30%–40% of patients will continue to have uncontrolled seizures. Moreover, the main purpose of the most antiepileptic medications is reducing the likelihood of seizure occurrence rather than influencing the underlying disease process. In the past decade, fundamental advances have been made in the understanding of the pathophysiological mechanisms of epilepsy. Molecular genetics research in epilepsy began more than 20 years ago. Findings from traditional heritability studies and more recent genomic heritability analysis unequivocally show the important role of genetics in epilepsy risk and deepened understanding of disease biology (1–3).

Precision genetics for precision medicine approach in the epilepsies is facilitating: first, find the genetic cause; second, establish a therapy addressing the pathophysiology mechanism revealed; and finally, avoidance of adverse reactions of antiepileptic medications.

1. Genetic cause of epilepsy

   Significant progress has been made in genetic discovery in epilepsies, particularly in monogenic epilepsies. As of 2019, more than 140 epilepsy-associated genes or loci are listed in the Online Mendelian Inheritance in Man database. Diverse genetic causes and molecular pathways have been implicated, involving ion channels, and proteins needed for synaptic, regulatory, and developmental functions. Advances in genetic technologies such as next generation sequencing can identify up to 40% causative gene mutations in developmental and epileptic encephalopathies. The most common genes identified are: SCN1A, SLC13A5, CDKL5, WWOX, STXBP1, SCN8A, and KCNQ2 (1).

2. Establish a therapy addressing the pathophysiology mechanism

   Precision medicine strategies using vitamins, metabolites, or enzyme replacements in deficiency syndromes can be strikingly effective, especially if started early. Classical examples include the use of pyridoxine and L-arginine in ALDH7A1-related pyridoxine-dependent epilepsy, ketogenic diet in glucose transporter 1 deficiency, Folinic acid in folic acid-responsive seizures, cerliponase alpha in neuroral ceroid lipofuscinosis type 2. Other successful strategies include the use of quinidine in KCNT1-related epilepsy, Acetazolamide in KCNA2-related epilepsy, sodium channel blockers in gain-of-function SCN8A-related epilepsy, or memantine in gain-of-function GRIN2A-related epilepsy.

3. Avoidance of adverse reactions of antiepileptic medications

   Precision medicine in the epilepsies also has an important role in the prevention or minimizing adverse reactions of antiepileptic medications. In POLG1-related epilepsy, patients might develop fatal hepatic failure when treated with sodium valproate. In SCNA1-related epilepsy, sodium-channel blocking antiepileptics may aggravate seizures. In other cases the risk factors for a severe adverse reaction will be independent of factors responsible for the disease; for example, the HLA-B*15:02 allele is highly predictive of carbamazepine-induced Stevens Johnson syndrome, a severe hypersensitivity reaction, in patients of Asian origin.

Epilepsy genetics is moving quickly from gene discovery to clinical practice. Precision medicine in epilepsy is beginning to emerge and hold great promise for future therapeutic approaches. However, significant challenges remain: moving from successful outcome in anecdotal cases to large scale of the population, and moving from controlling seizures to improving comorbidities particularly neuropsychological deficits.

Correspondence to: Brahim Tabarki
*Prince Sultan Military Medical City, Riyadh 11159, Saudi Arabia.
Email: btabarki@hotmail.com
Full list of author information is available at the end of the article.
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Author details
Brahim Tabarki[1]
1. Division of Neurology, Department of Pediatrics, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

References

1. Nashabat M, Al Qahtani XS, Almakdob S, Altwaijri W, Ba-Armah DM, Hundallah K, et al. The landscape of early infantile epileptic encephalopathy in a consanguineous population. Seizure. 2019;69:154–72. https://doi.org/10.1016/j.seizure.2019.04.018
2. Ellis CA, Petrovski S, Berkovic SF. Epilepsy genetics: clinical impacts and biological insights. Lancet Neurol. 2020;19:93–100. https://doi.org/10.1016/S1474-4422(19)30269-8
3. Symonds JD, Zuberi SM, Johnson MR. Advances in epilepsy gene discovery and implications for epilepsy diagnosis and treatment. Curr Opin Neurol. 2017;30:193–9. https://doi.org/10.1097/WCO.0000000000000433