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The value of genetic testing in epilepsy

Genetic testing presents the opportunity for physicians to potentially identify a causal mutation in their patients. One question remaining in the field is when to prescribe genetic testing for patients with epilepsy. The International League Against Epilepsy (ILAE) — an association of healthcare professionals dedicated to improving epilepsy education and research — has provided some perspective on this topic. This group advises that physicians consider prescribing genetic testing when there is:

- ***Clinical validity*** (the physician has made an informed opinion that their patient has epilepsy or a seizure disorder with a genetic basis), and
- ***Clinical utility*** (the results of the test are likely to positively impact the patient's health or well-being).[1]

It's important to know that if clinical utility and clinical validity can be established for genetic testing, many insurers are likely to cover the cost of testing. To date, the frequency with which genetic testing pinpoints a specific mutation as contributing to epilepsy is estimated to be around 15-20%.[2] These numbers are anticipated to increase over time as new genes are discovered in the field.

While the ultimate decision of whether to order genetic testing — particularly in regard to clinical validity — rests with the treating physician, there are a number of instances where the clinical utility of genetic testing has been demonstrated.

This identification of specific genetic mutations may have implications for clinical management by enabling an earlier diagnosis, informing therapy choice, or preventing unnecessary invasive procedures.

Gene	Clinical utility of testing for mutation
ALDH1A7	A lysine-restricted diet may reduce seizure frequency[3]
DCSDP5	mTOR inhibitors may be of use. Surgery has also been shown to be beneficial.[4]
EMP2A or EMP2B	Targeted therapy with a premature stop codon read-through drug (e.g. gentamicin) may be indicated, while sodium channel blockers and GABAergic drugs should be avoided.[5]
FOLR	Auto-immunity against or mutations in FOLR lead to cerebral folate deficiency, which is treated with folinic acid.[6] Treatment with folic acid should be avoided.[7]
GRIN2A	Memantine has been shown to reduce seizures in those with specific *GRIN2A* mutations.[8]
KCNT1	Treatment with quinidine is indicated for patients with the specific KCNT1 mutations.[9-11]
MTOR	Treatment with mTOR inhibitors may reduce seizures.[12,17]
PNPO	Pyridoxal-5-phosphate treatment can reduce seizure recurrence and may improve cognitive function.[13]
POLG	Treatment with valproic acid should be avoided, as it can induce fatal liver failure in patients with *POLG* deficiency.[14]
PRRT2	Most seizures induced by *PRRT2* mutations respond well to carbamazepine, phenobarbital, valproate, or zonisamide.[15]
SCN1A	Carbamazepine and phenytoin exacerbate seizures and should be avoided.[16]
SLC2A1	A ketogenic diet can reduce seizures and improve cognition in these patients.[2] Steroids and carbonic anhydrase inhibitors may also be useful.[17]
TSC1 or TSC2	Treatment with everolimus reduces seizures.[18]

[1] Ottoman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies- report of the ILAE Genetics Commission. *Epilepsia*. 2010;51(4):655.

[2] EpiPM Consortium. A roadmap for precision medicine in the epilepsies. *Lancet Neurol*. 2015;14:1219.

[3] Van Karnebeek CD, Hartmann H, Jaggumantri S, et al. Lysine restricted diet for pyroxidine-dependent epilepsy: first evidence and future trials. *Mol Genet Metab.* 2012;107:335.

[4] Baulac S, Ishida S, Marsan E, et al. Familial focal epilepsy with focal cortical dysplasia due to DEPDC5 mutations. *Ann Neurol.* 2015;77:675.

[5] Medina MT, Martinez-Juarez IE, Duran RM et al. Treatment of monoclonic epilepsies of childhood adolescence, and adulthood. *Adv Neurol.* 2005;95:307.

[6] Surtes R, Wolf N. Treatable neonatal epilepsy. *Arch Dis Child.* 2007;92:659.

[7] Wu D, Pardridge WM. Blood-brain barrier transport of reduced folic acid. *Pharm Res.* 1999;16:415.

[8] Pierson TM, Yuan H, Marsh ED, et al. GRIN2A mutation and early-onset epileptic encephalopathy: personalized therapy with memantine. Ann Clin Trans Neurol. 2014;1(3):190.

[9] Bearden D, Strong A, Ehnot J, et al. Targeted treatment of migrating partial seizures of infancy with quinidine. *Ann Neurol.* 2014;76:457.

[10] Mikati MA, Jiang Y, Carboni M, et al. Quinidine in the treatment of KCNT1-positive epilepsies. *Ann Neurol.* 2015;78:995.

[11] Milligan CJ, Li M, Gazina EV, et al. KCNT1 gain of function in 2 epilepsy phenotypes is reversed by quinidine. *Ann Neurol.* 2014;75:581.

[12] Lim JS, Kim W, Kang H. Brain somatic mutations in MTOR cause focal cortical dysplasia type II leading to intractable epilepsy. *Nature Medicine.* 2015;21(4):395.

[13] Hoffman GF, Schmitt B, Windfur M, et al. Pyridoxal 5'-phosphate may be curative in early-onset epileptic encephalopathy. *J Inherit Metab Dis.* 2007;30:96.

[14] Saneto RP, Lee IC, Koenig MK, et al. POLG DNA testing as an emerging standard of care before instituting valproic acid therapy for pediatric seizure disorders. *Seizure.* 2010;19(3):140.

[15] Vigevano F. Benighn family infantile seizures. *Brain Dev.* 2005;27:172.

[16] Sheffer IE. Genetic testing in epilepsy: what should you be doing? *Epilepsy Currents.* 2011;11(4):107

[17] Ream MA, Patel AD. Obtaining genetic testing in pediatric epilepsy. *Epilepsia.* 2015;56(10):1505.

[18] Krueger DA, Wilfong AA, Holland-Bouley K, et al. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. *Ann Neurol.* 2013;74(5):679.