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Majority of Epilepsy Mutations are in Genes with Therapeutic Associations

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BACKGROUND

- Specific genetic epilepsy syndromes may be more or less responsive to certain types of therapy (Tab. 1).
- Genetic testing via a targeted panel of genes with therapeutic associations may expedite diagnosis and tailor management, such as use of clobazam and valproic acid as first-line medications and avoidance of sodium channel-blocking anticonvulsants for *SCN1A*-related seizure disorder[1], a common genetic cause of epileptic encephalopathy.

METHODS

- Reviewed 493 cases tested for panel of 16 therapy-associated epilepsy genes or for comprehensive panel of 100 epilepsy-related genes.
- Determined mutation and VUS rates per panel and gene.

RESULTS

- 55 total mutations were distributed among 20 genes, 7 of which were on therapy-associated panel (Fig. 1).
- 467 VUS were detected in 82 genes (Fig. 3).

Figure 1. Mutation Distribution Among Genes (n=55 mutations)

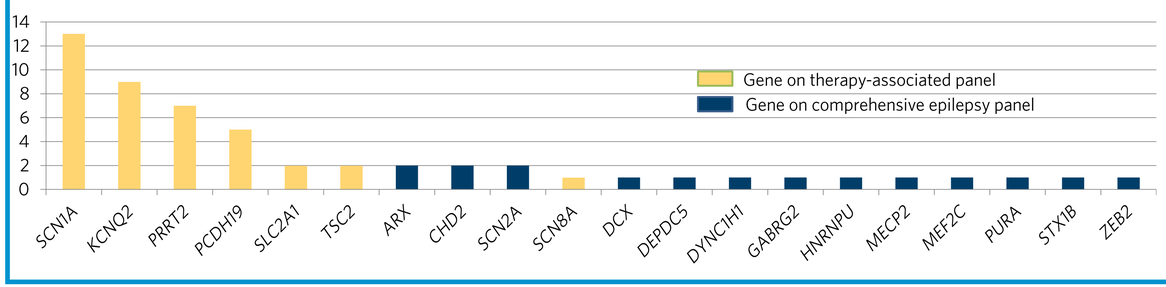


Table 1. Genes and Associated Therapies

Gene	Therapy	Reference(s)
ALDH7A1	Pyridoxine (vitamin B6), folinic acid	Mills PB, et al. *Brain.* 2010; 133:2148-2159.
FOLR1	Folinic acid	Delmelle F, et al. *Eur J Paediatr Neurol.* 2016;20(5):709-713.
KCNQ2	Carbamazepine, phenytoin, ezogabine	Bellini G, et al. *KCNQ2*-Related Disorders. GeneReviews® [Internet]. Hani AJ, et al. *Pediatr Clin North Am.* 2015;62(3): 703-722.
KCNQ3	Phenobarbitol, phenytoin, carbamazepine, valproate	Bellini G, et al. KCNQ3-Related Disorders. GeneReviews® [Internet].
KCNT1	Quinidine	Mikati MA, et al. *Ann Neurol.* 2015; Sep 15.
MECP2	Memantine	Bello O, et al. *Front Neurosci.* 2013;7(245):1-3
PCDH19	Stiripentol	Trivisano M, et al. *Eur J Paediatr Neurol.* 2015; 19(2):248-50.
PNPO	Pyridoxine (vitamin B6)	Riikonen R, et al. *Eur J Paediatr Neurol.* 2015;19(6):647-651.
POLG	Avoid: valproic acid	Saneto RP, et al. *Seizure.* 2010;19(3):140-146
PRRT2	Carbamazepine	Dale RC, et al. *Dev Med Child Neurol.* 2014; 56(9):910. Chou IC, et al. *Biomedicine.* 2014;4:15.
SCN1A	Consider: diazepam, clonazepam, levetiracetam, topiramate, stiripentol, valproate, clobazam, ketogenic diet; Avoid: carbamazepine, lamotrigine, vigabatrin	Wallace A, et al. *Paediatr Drugs.* 2016 Jun;18(3):197-208. Miller IO, et al . *SCN1A*-Related Seizure Disorder. GeneReviews® [Internet].
SCN8A	Phenytoin	Boerma RS, et al. *Neurotherapeutics.* 2015; Aug 9.
SLC2A1	Ketogenic diet	Ramm-Pettersen A, et al. *Dev Med Child Neurol.* 2013;55(5):440-447.
STXBP1	Levetiracetam	Dilena R, et al. *Brain Dev.* 2015; Jul 23.
TSC1	Vigabatrin	Wang S, et al. *Neuropsychiatr Dis Treat.* 2014; 10: 2021-2030.
TSC2	Vigabatrin	Wang S, et al. *Neuropsychiatr Dis Treat.* 2014; 10: 2021-2030.

Fig. 2. Mutation Distribution Between Panels

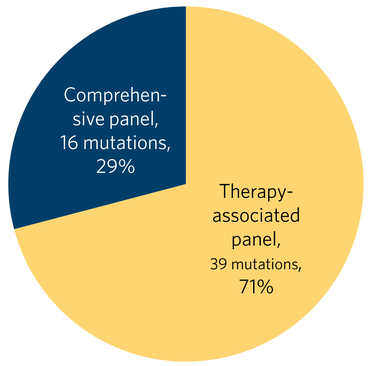
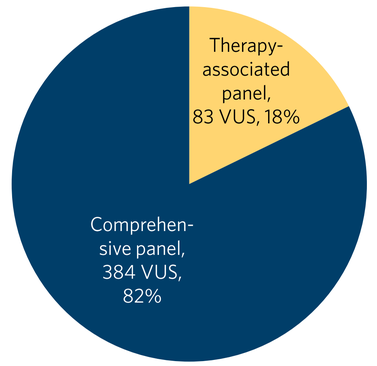


Figure 3. VUS Distribution Between Panels



TAKE-HOME POINTS

- Majority (39/55; 71%) of epilepsy mutations were found in 16 genes with therapeutic associations (Fig. 2).
- Additional 84 genes on the comprehensive 100-gene panel were responsible for nearly 30% of mutations and patient diagnoses, but also responsible for the majority (384/467; 82%) of VUS (Fig. 3).
- Starting with management-associated genes then reflexing to a comprehensive panel may be efficient for many patients.

REFERENCES

1. Wallace A et al. Paediatr Drugs. 2016 Jun;18(3):197-208

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