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Genes with Therapeutic Associations Responsible for Majority of Epilepsy Mutations

Elaine C. Weltmer, Amal Yussuf, Heather Newman, Tiffiney Carter, Jing Wang

BACKGROUND

- Precision medicine in epilepsy involves identifying a specific genetic epilepsy syndrome and, when available, applying a specific treatment (Tab. 1). For example, clobazam and valproic acid may be used as first-line medications for *SCN1A*-related seizure disorder, while sodium channel-blocking anticonvulsants may be avoided[1]; anti-epileptic drugs may even be avoided all together in favor of the ketogenic diet for *SLC2A1*-related seizure disorder.
- Testing via a targeted panel of genes with therapeutic associations may expedite diagnosis and tailor management.
- In addition, since understanding of these associations is still ongoing, testing via a comprehensive epilepsy gene panel may still provide valuable information in the short term for prognosis and recurrence risk.

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, and 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.

METHODS

- Reviewed the first 65 cases submitted to our laboratory for a standalone panel of 16 epilepsy genes with therapeutic associations or with reflex to a comprehensive 100-gene epilepsy panel, and 428 cases submitted directly for comprehensive epilepsy panel testing.
- 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).
- Most frequently implicated genes were *SCN1A* (13 mutations), *KCNQ2* (9 mutations), *PRRT2* (7 mutations) and *PCDH19* (5 mutations). With the exception of the c.649dupC common mutation in *PRRT2*, which was identified in 5 unrelated patients, each mutation was seen in only one patient.
- 467 VUS in 82 genes were detected among the total cohort of 493 patients (Fig. 4).

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

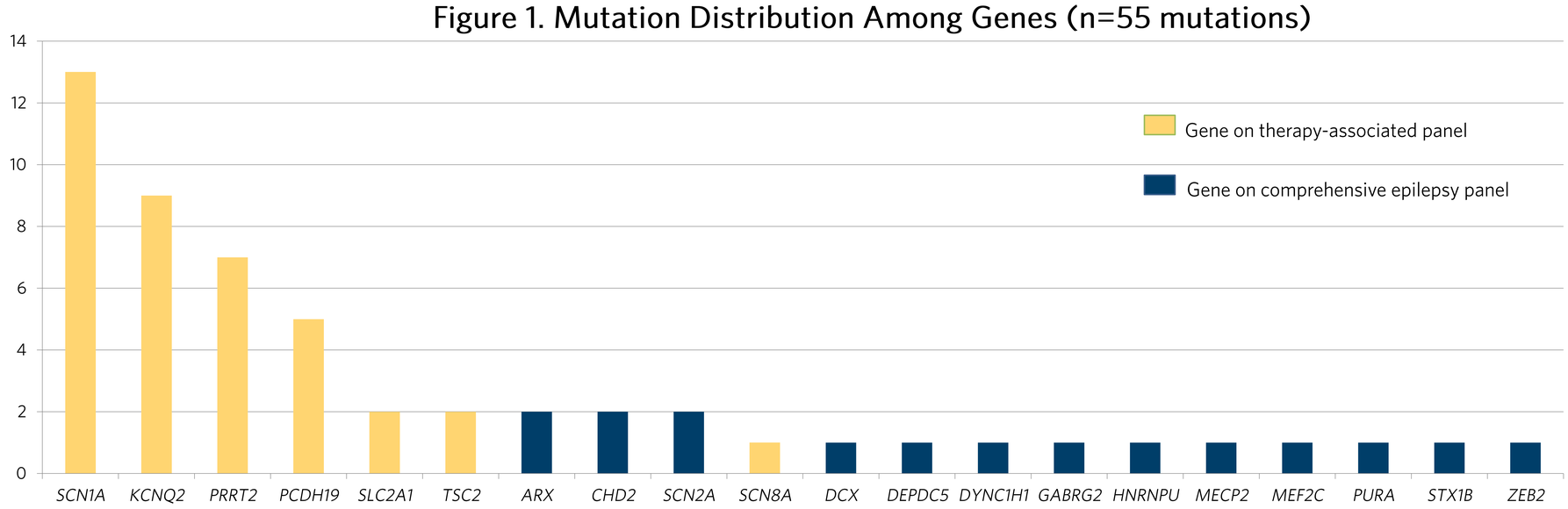


Figure 2. Mutation Distribution Between Panels

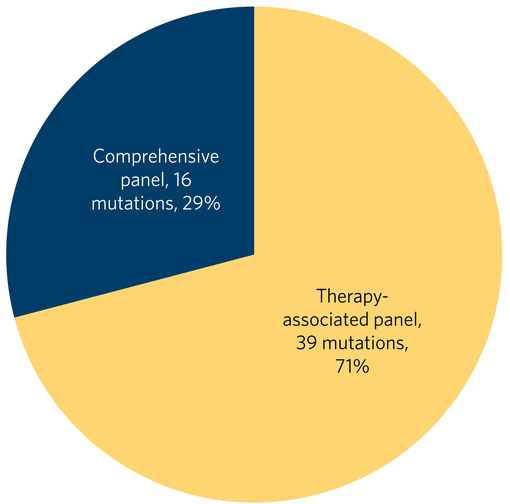


Figure 3. VUS Distribution Between Panels

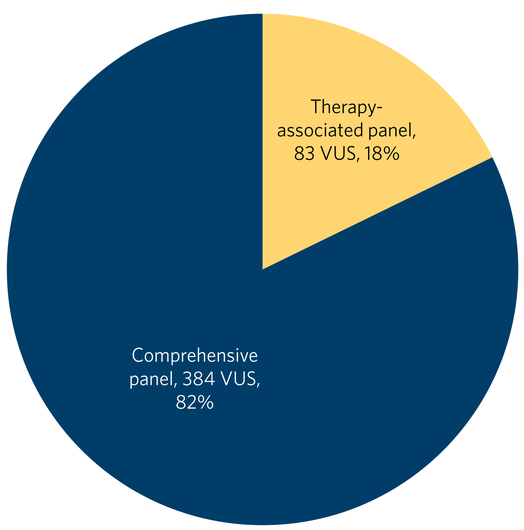
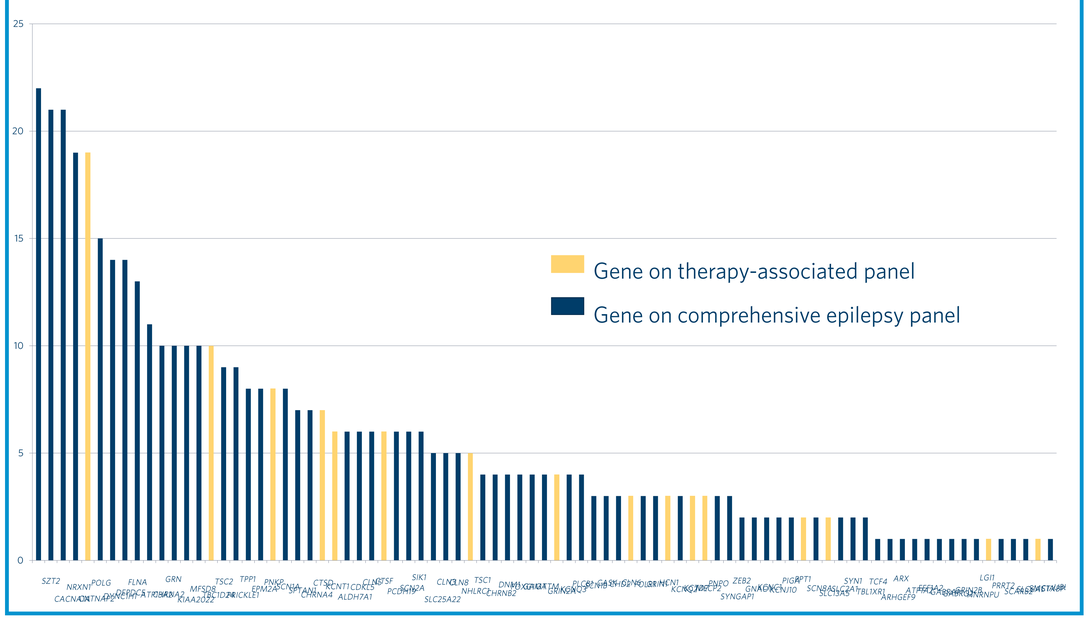


Figure 4. VUS Distribution Among Genes (n=467 VUS)



TAKE-HOME POINTS

- Majority (39/55; 71%) of epilepsy mutations were found in 16 genes with therapeutic associations (Fig. 2).
- Although the additional 84 genes on the comprehensive 100-gene panel were responsible for nearly 30% of mutations and patient diagnoses, these additional genes were also responsible for the majority (384/467; 82%) of VUS (Fig. 3).
- A tiered approach to testing, beginning with a targeted panel of management-associated genes and then reflexing to a more comprehensive panel, may be efficient for many patients.
- Furthermore, the potential for uncertain results is minimized when the management-associated panel is pursued first.
- Continued research into genetic causes of epilepsy and potential targets for therapy are critical to increasing access to precision medicine in epilepsy management.

REFERENCES

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

15 Argonaut, Aliso Viejo, CA 92656 Toll Free 866 262 7943 Fax 949 900 5501 ambrygen.com