

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 avoided¹; 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)
<i>ALDH7A1</i>	Pyridoxine (vitamin B6), folinic acid	Mills PB, et al. <i>Brain</i> . 2010; 133:2148-2159.
<i>FOLR1</i>	Folinic acid	Delmelle F, et al. <i>Eur J Paediatr Neurol</i> . 2016;20(5):709-713.
<i>KCNQ2</i>	Carbamazepine, phenytoin, ezogabine	Bellini G, et al. <i>KCNQ2</i> -Related Disorders. GeneReviews® [Internet]. Hani AJ, et al. <i>Pediatr Clin North Am</i> . 2015;62(3): 703-722.
<i>KCNQ3</i>	Phenobarbitol, phenytoin, carbamazepine, valproate	Bellini G, et al. <i>KCNQ3</i> -Related Disorders. GeneReviews® [Internet].
<i>KCNT1</i>	Quinidine	Mikati MA, et al. <i>Ann Neurol</i> . 2015; Sep 15.
<i>MECP2</i>	Memantine	Bello O, et al. <i>Front Neurosci</i> . 2013;7(245):1-3
<i>PCDH19</i>	Stiripentol	Trivisano M, et al. <i>Eur J Paediatr Neurol</i> . 2015; 19(2):248-50.
<i>PNPO</i>	Pyridoxine (vitamin B6)	Riikonen R, et al. <i>Eur J Paediatr Neurol</i> . 2015;19(6):647-651.
<i>POLG</i>	<u>Avoid:</u> valproic acid	Saneto RP, et al. <i>Seizure</i> . 2010;19(3):140-146
<i>PRRT2</i>	Carbamazepine	Dale RC, et al. <i>Dev Med Child Neurol</i> . 2014; 56(9):910. Chou IC, et al. <i>Biomedicine</i> . 2014;4:15.
<i>SCN1A</i>	<u>Consider:</u> diazepam, clonazepam, levetiracetam, topiramate, stiripentol, valproate, clobazam, ketogenic diet <u>Avoid:</u> carbamazepine, lamotrigine, and vigabatrin	Wallace A, et al. <i>Paediatr Drugs</i> . 2016 Jun;18(3):197-208 Miller IO, et al. <i>SCN1A</i> -Related Seizure Disorder. GeneReviews® [Internet].
<i>SCN8A</i>	Phenytoin	Boerma RS, et al. <i>Neurotherapeutics</i> . 2015; Aug 9.
<i>SLC2A1</i>	Ketogenic diet	Ramm-Petersen A, et al. <i>Dev Med Child Neurol</i> . 2013;55(5):440-447.
<i>STXBP1</i>	Levetiracetam	Dilena R, et al. <i>Brain Dev</i> . 2015; Jul 23.
<i>TSC1</i>	Vigabatrin	Wang S, et al. <i>Neuropsychiatr Dis Treat</i> . 2014; 10: 2021-2030.
<i>TSC2</i>	Vigabatrin	Wang S, et al. <i>Neuropsychiatr Dis Treat</i> . 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)

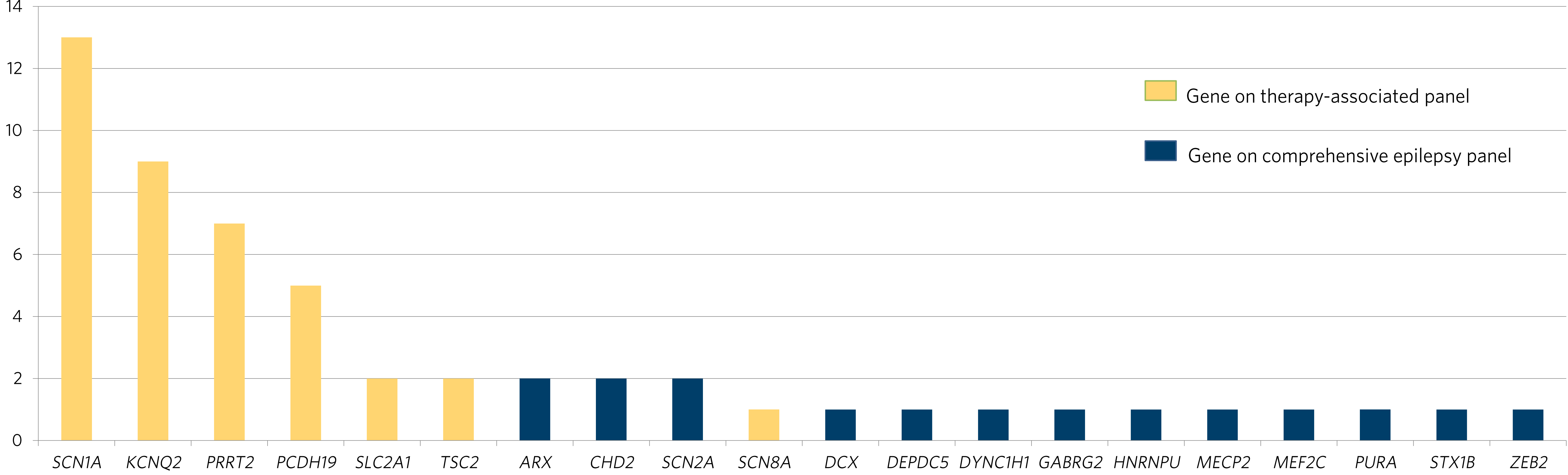


Figure 2. Mutation Distribution Between Panels

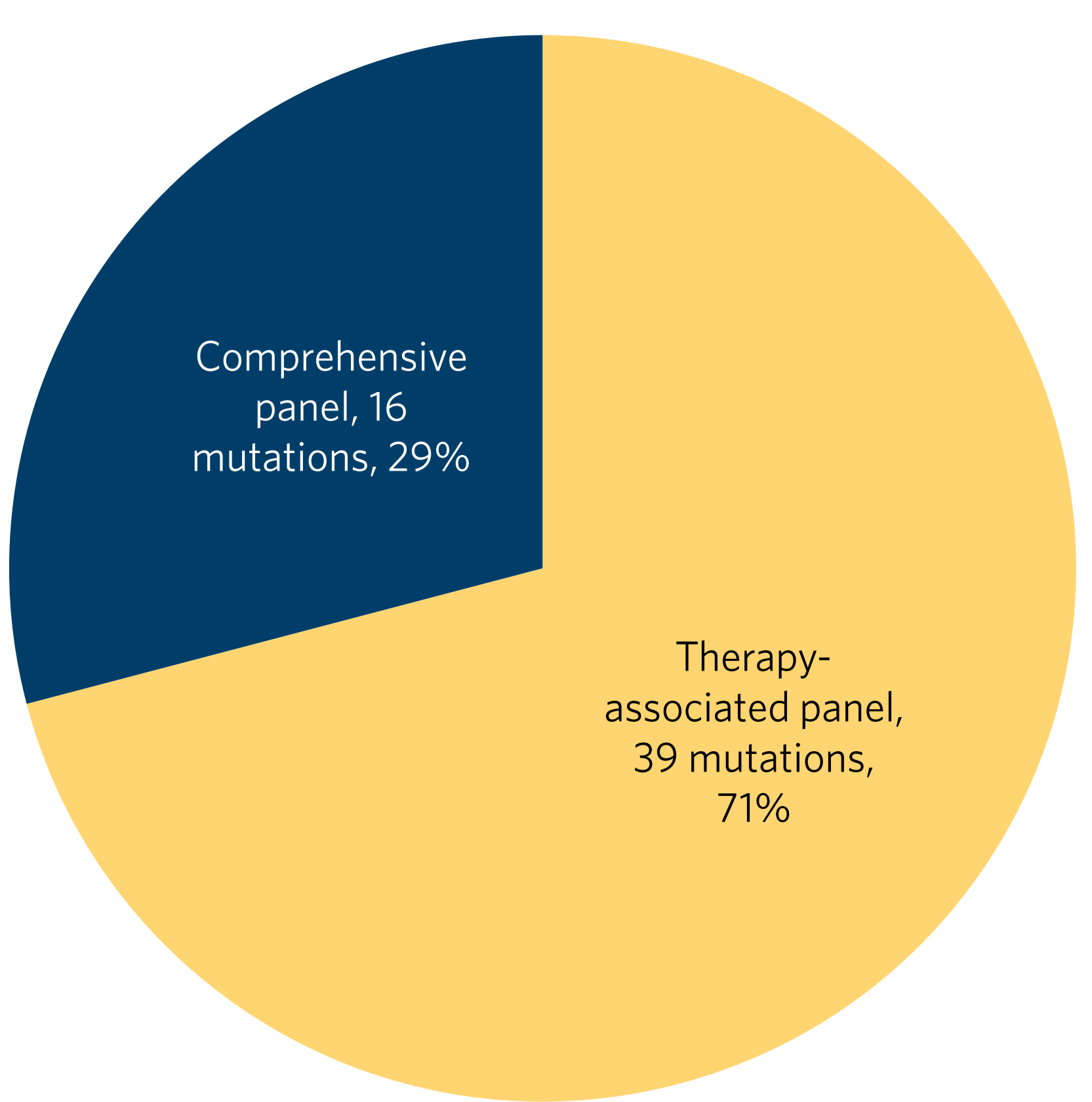


Figure 3. VUS Distribution Between Panels

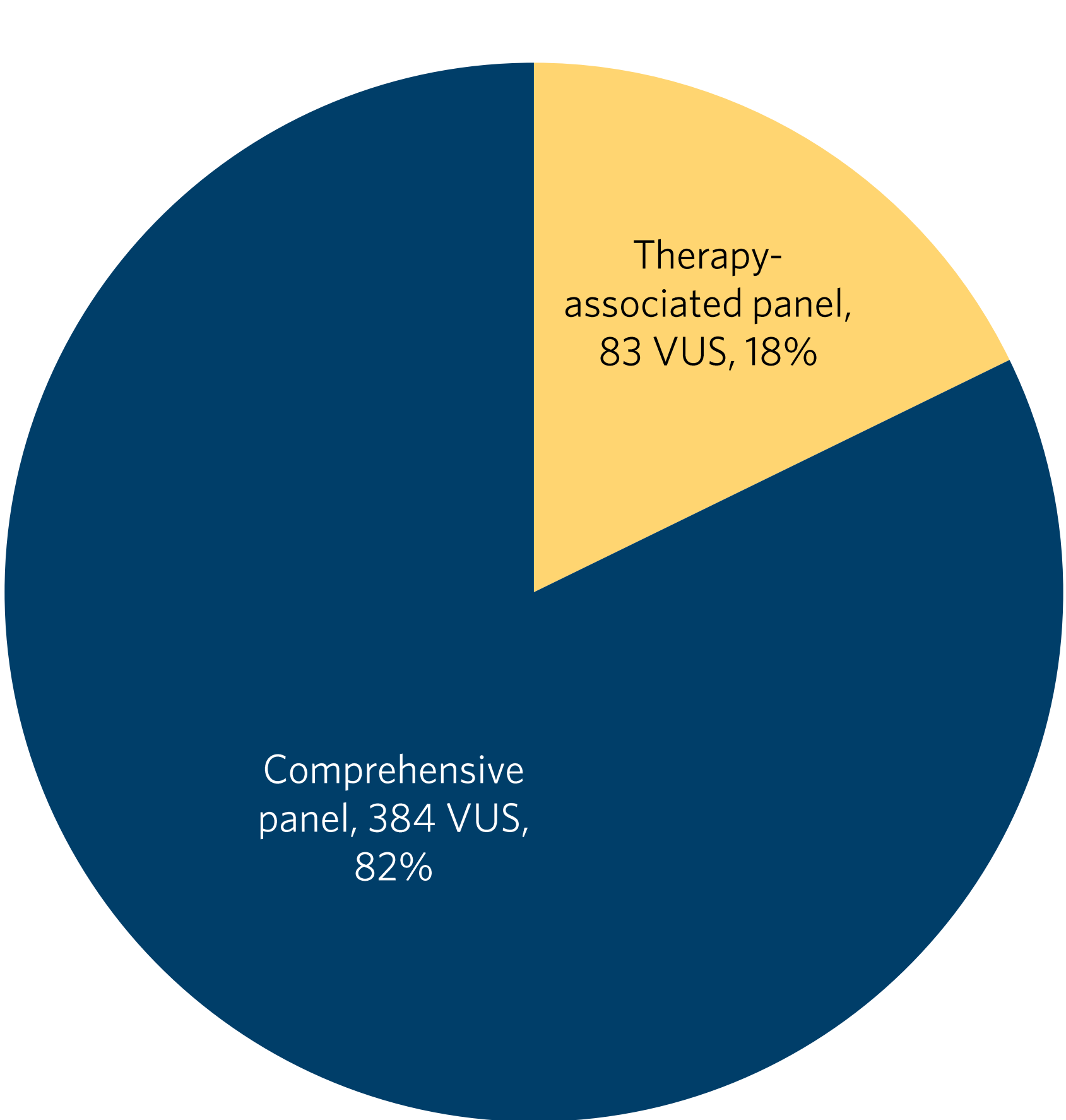
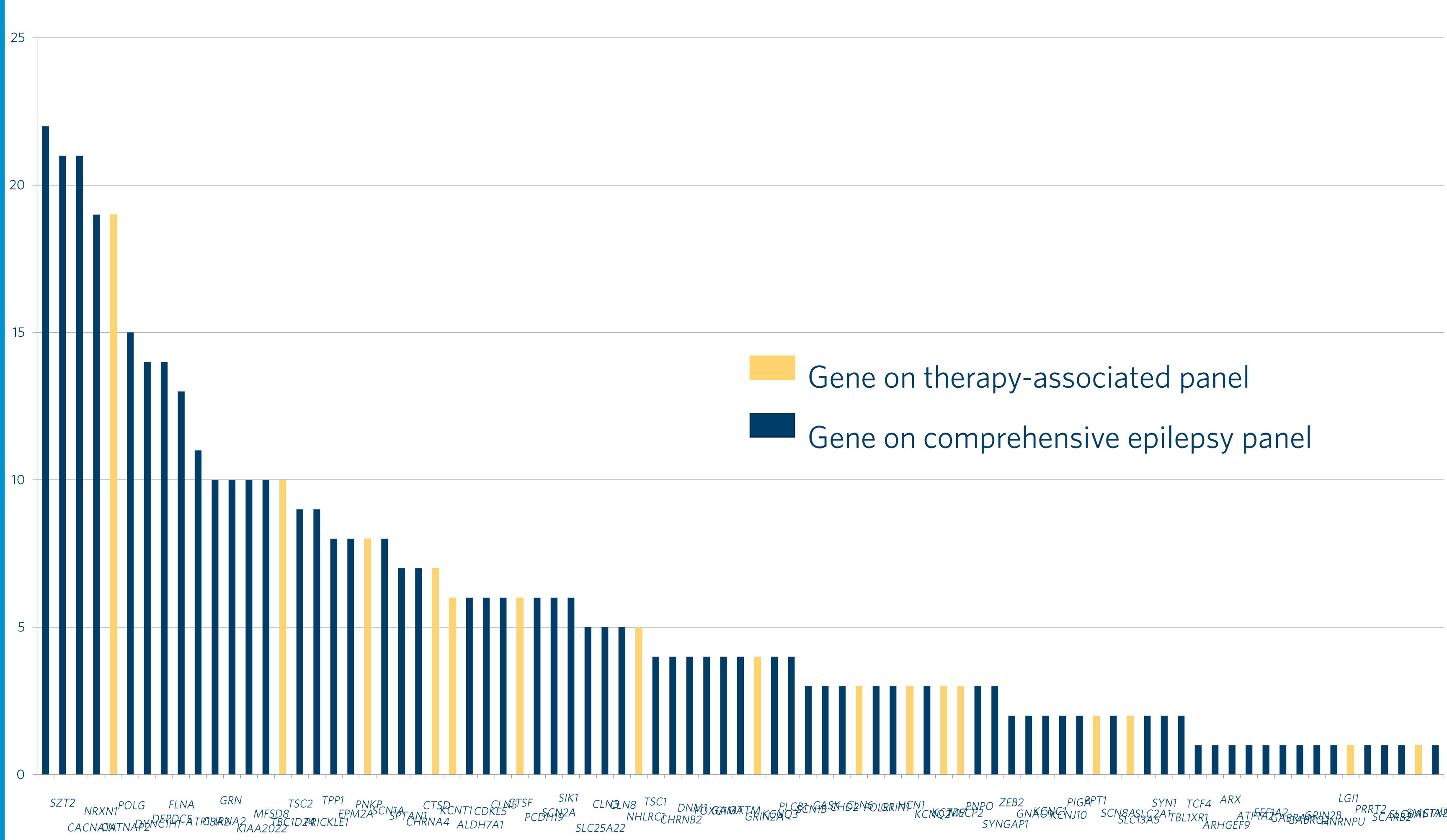


Figure 4. VUS Distribution Among Genes (n=467 VUS)



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