Mechanisms of *SLC6A1* dysfunction

SLC6A1 Connect Roundtable
November 29th, 2018

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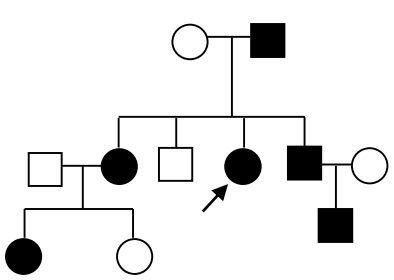
Our Research Strategy



Human Disease

Epilepsy

Novel treatments
New phenotypes

Mouse model

Disease mechanisms
Co-morbidities
Genetic modifiers
Seizure triggers
Therapies

Human Gene

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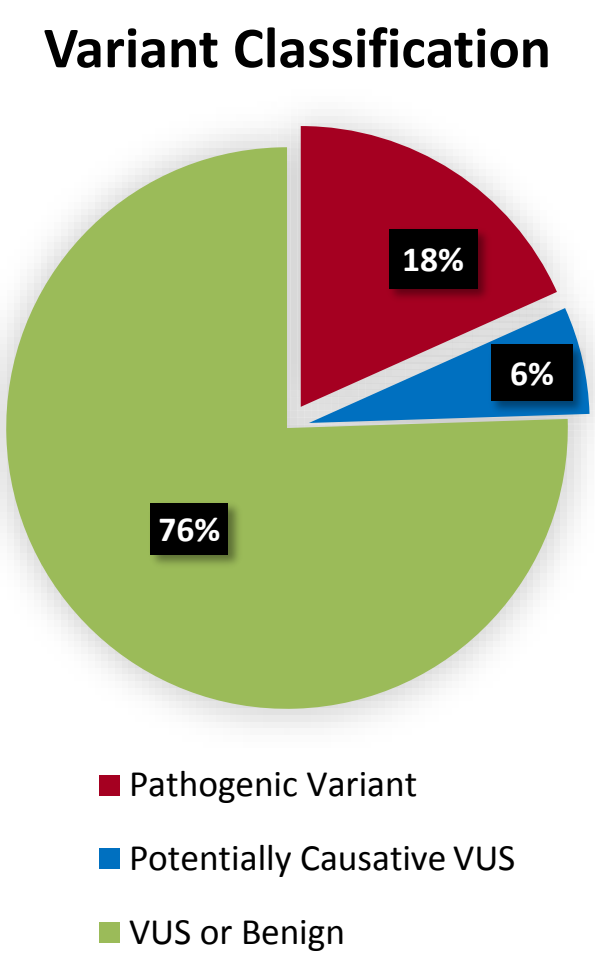
Most referrals are children with severe epilepsy

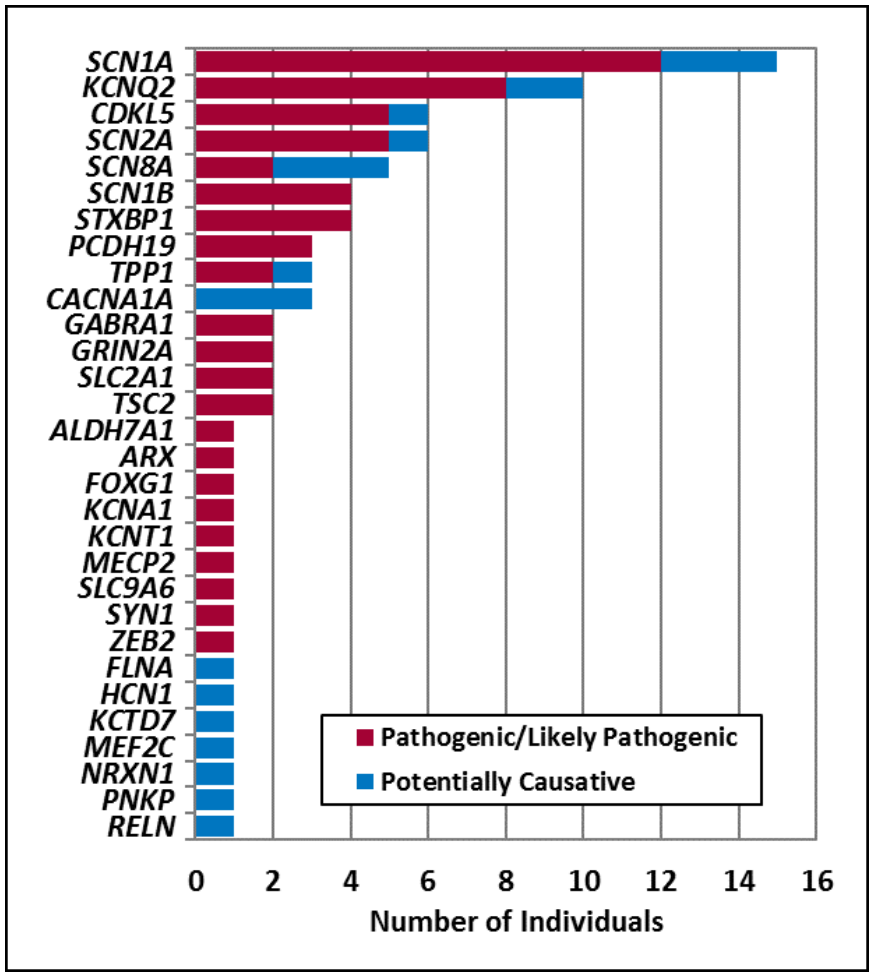
Demographics	
Average Age	7.53 yrs
Median Age	5.6 yrs
Maximum	74 yrs
Minimum	0.2 yrs

Phenotype listed	%
Developmental delay	31.2
Movement disorders	14.4
Hypotonia	13.0
Epileptic encephalopathy	12.6
Intellectual disability	7.4
Autism	5.6
Developmental regression	4.7
Microcephaly	4.7
Family History	4.2

Diagnostic yield of the ESD panel

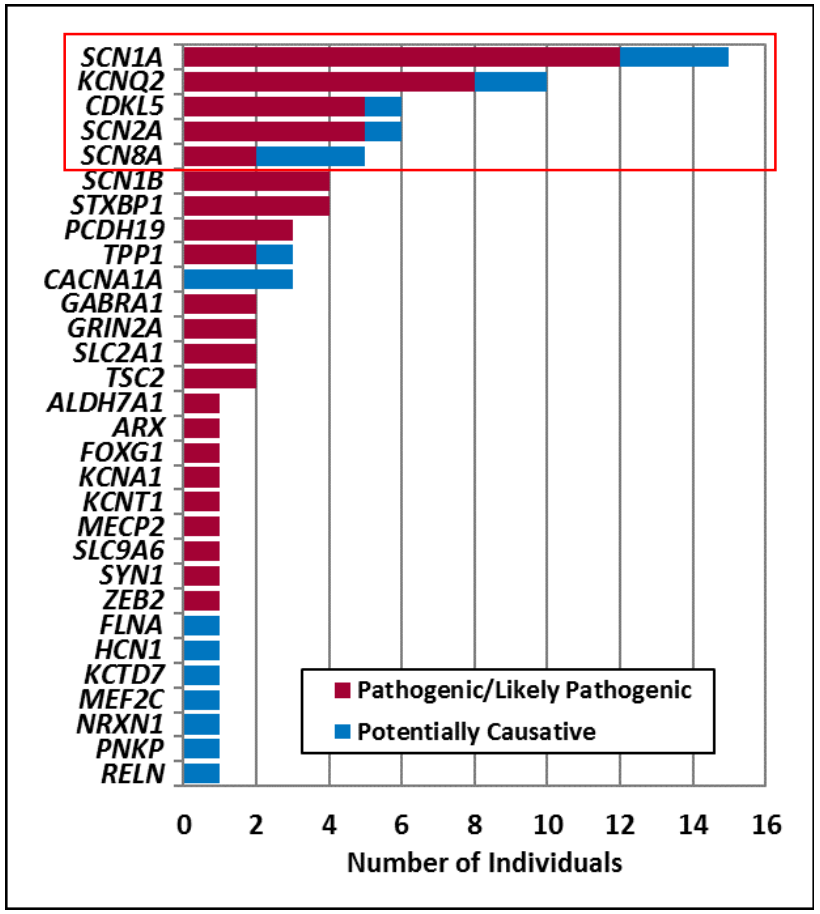
339 consecutive patients screened at EGL on the epilepsy panel





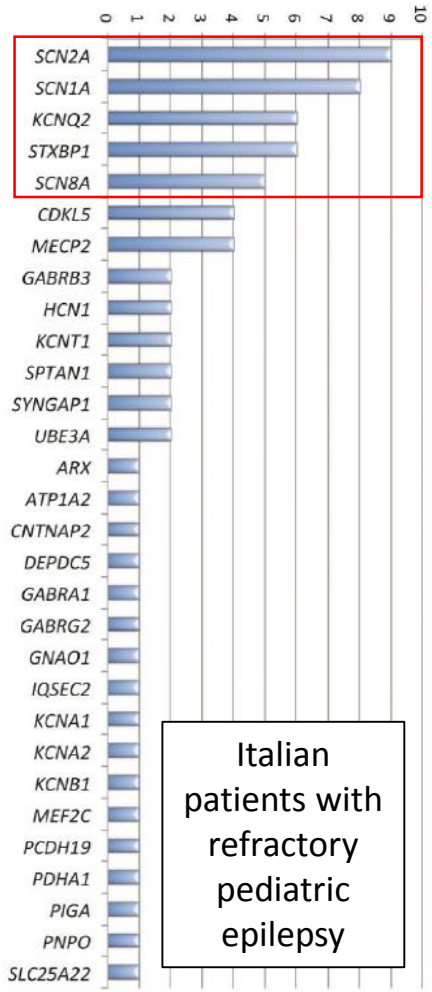
Butler *et al.* (2017) *Ped. Neurol.*

Comparable diagnostic yield of the ESD panel



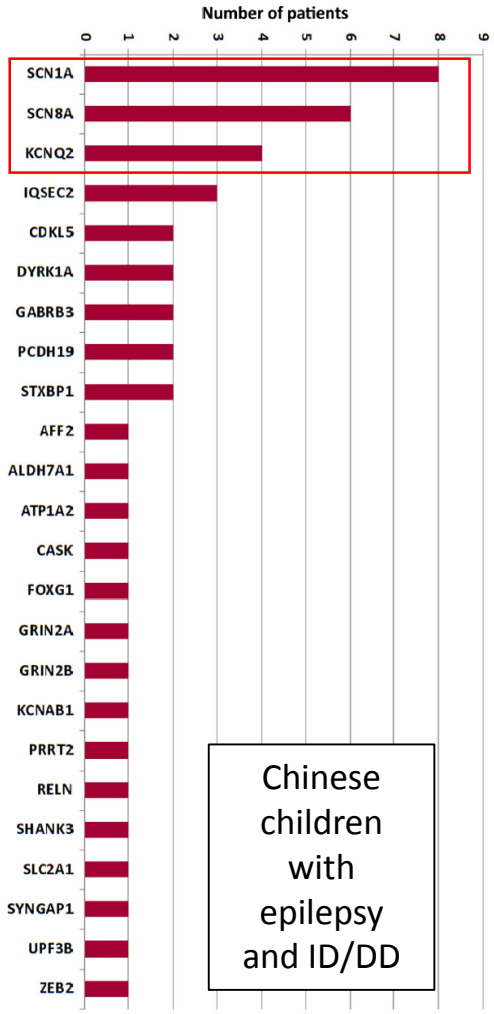
Butler *et al.* (2017) *Ped. Neurol.*

N = 339



Parrini *et al.* (2017) *Hum Mutat.*

N = 349



Zhang *et al.* (2015) *PLoSOne*

N = 253

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BRIEF COMMUNICATION

Epilepsia

SLC6A1 variants identified in epilepsy patients reduce γ-aminobutyric acid transport

8 mutations from 460 referrals

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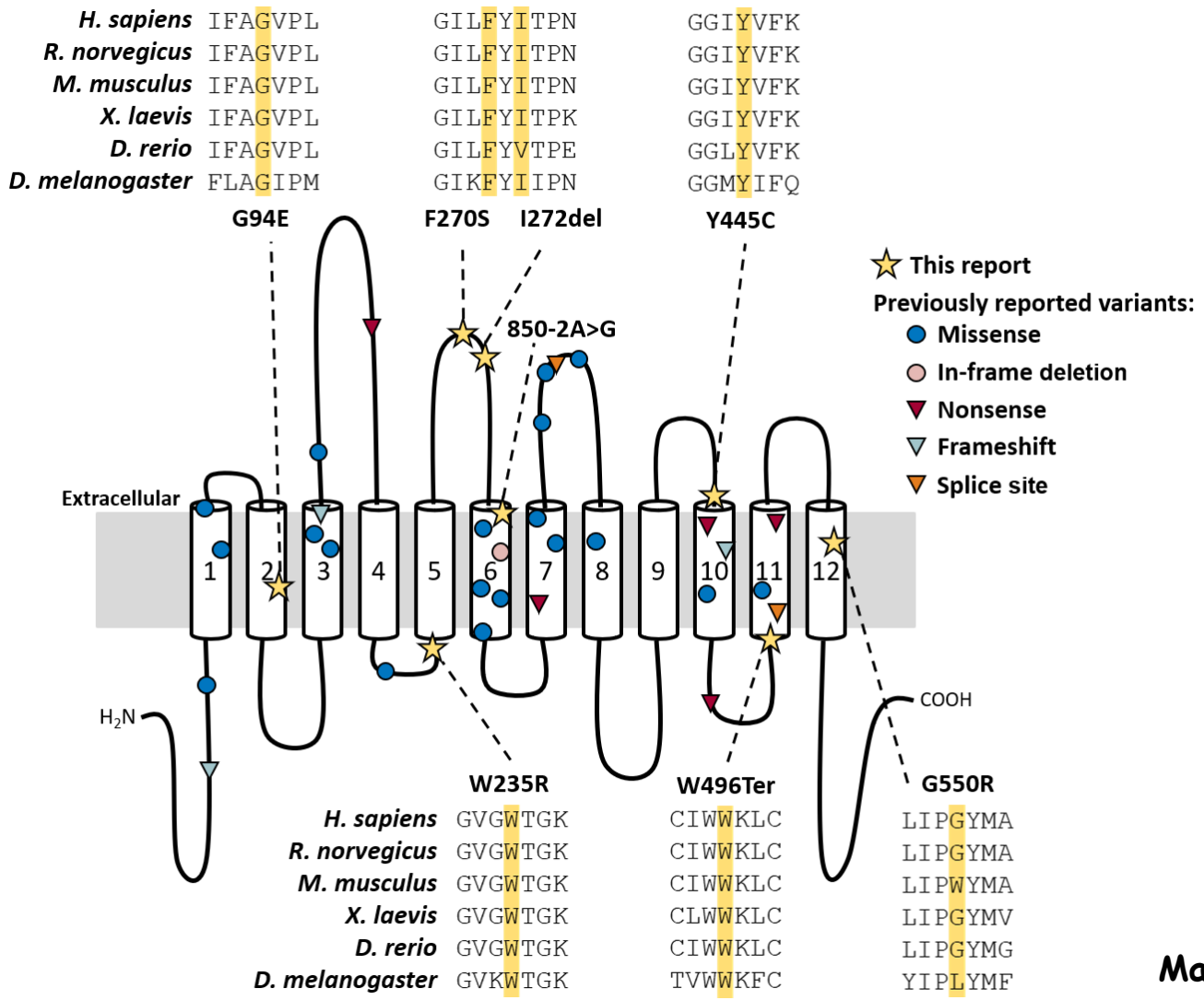
Summary

Previous reports have identified *SLC6A1* variants in patients with generalized epilepsies, such as myoclonic-atonic epilepsy and childhood absence epilepsy. However, to date, none of the identified *SLC6A1* variants has been functionally tested for an effect on GAT-1 transporter activity. The purpose of this study was to determine the incidence of *SLC6A1* variants in 460 unselected epilepsy patients and to evaluate the impact of the identified variants on γ-aminobutyric acid (GABA) transport. Targeted resequencing was used to screen 460 unselected epilepsy patients for variants in *SLC6A1*. Five missense variants, one in-frame deletion, one nonsense variant, and one intronic splice-site variant were identified, representing a 1.7% diagnostic yield. Using a [^{3}H]-GABA transport assay, the seven identified exonic variants were found to reduce GABA transport activity. A minigene splicing assay revealed that the splice-site variant disrupted canonical

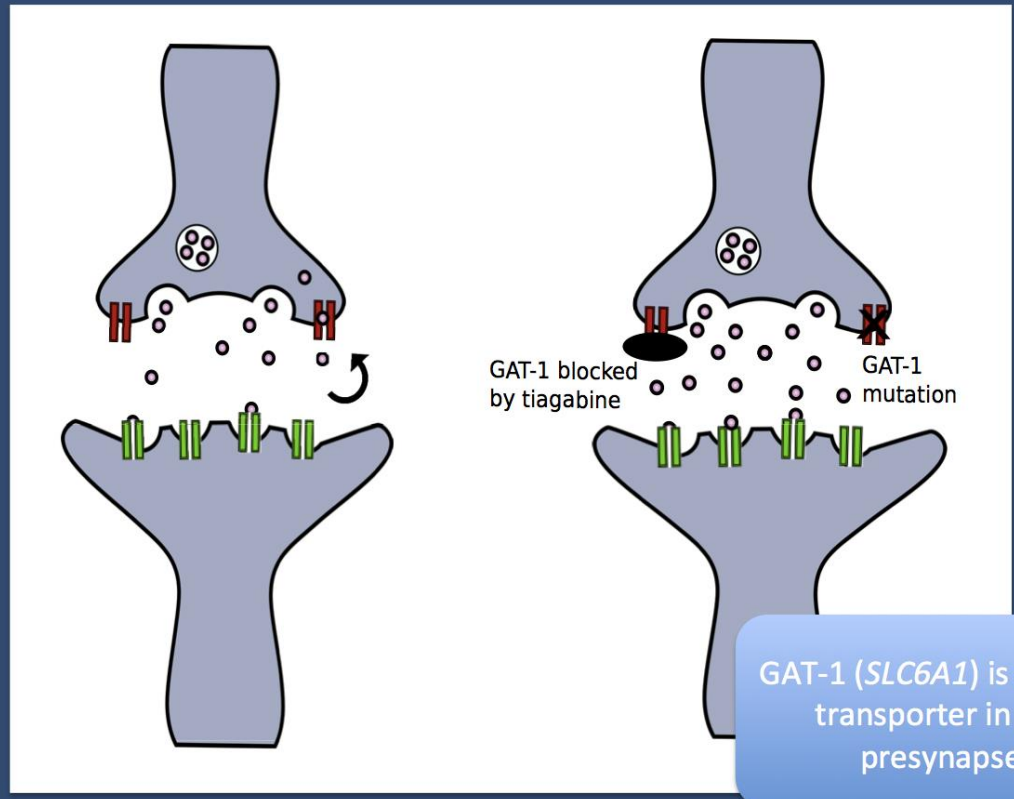
SLC6A1 Variants Identified in Epilepsy Patients



Mattison and Butler *et al*[8] (2018)

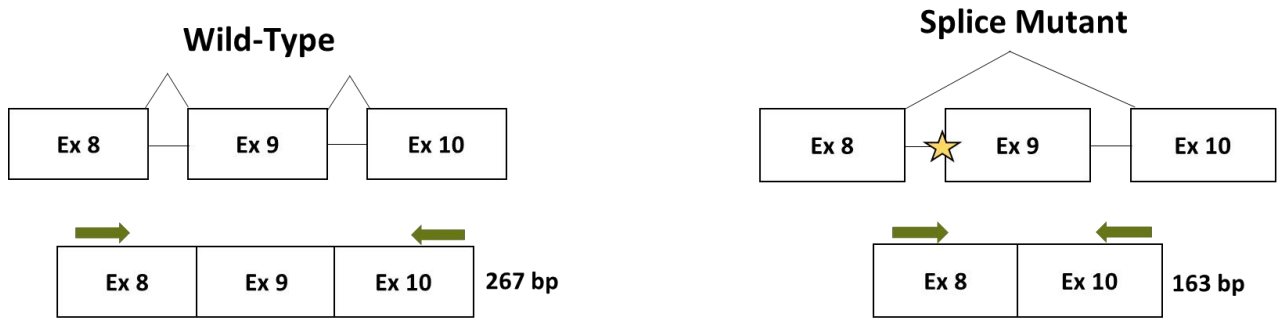
SLC6A1 Encodes the GAT 1 GABA Transporter

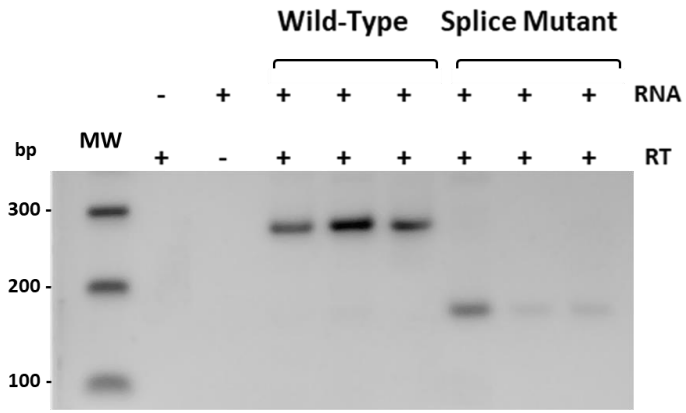
SLC6A1 mutations in Myoclonic Astatic Epilepsy
(Carvill et al., 2015)

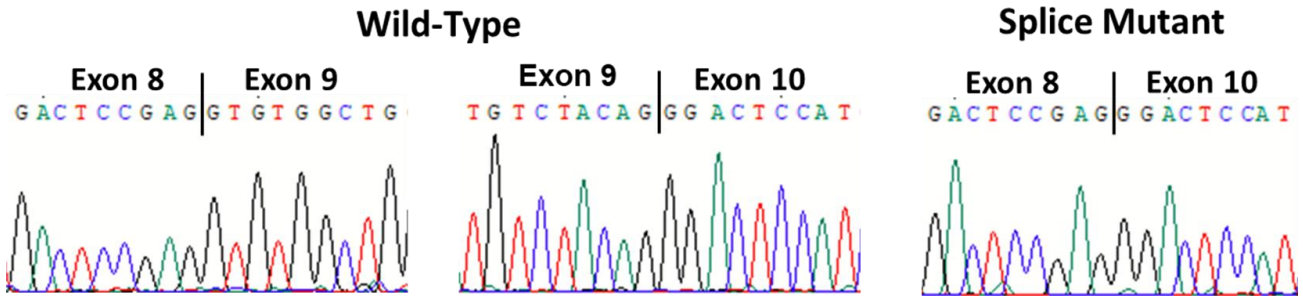


GAT-1 (*SLC6A1*) is a GABA transporter in the presynapse

SLC6A1 c.850-2A>G variant causes exon skipping

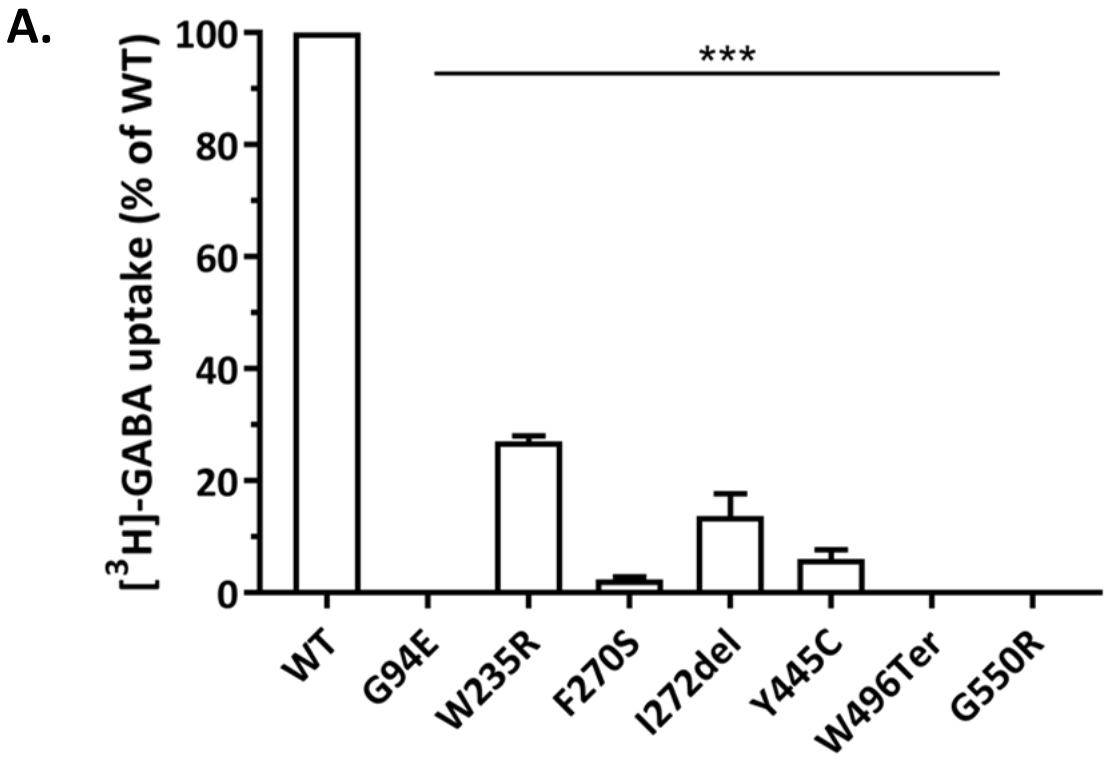






Mattison and Butler *et al.* (2018)

GAT 1 mutations reduce GABA transport



No obvious genotype/phenotype correlation

Mattison and Butler *et al.* (2018)

Summary

- GAT 1 mutations reduce GABA clearance.
- Likely to affect neuronal excitability via multiple mechanisms.
- No obvious genotype/phenotype correlation at this time.

Escayg Laboratory

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