**SLC6A1 GENE**

- Encodes instructions for GABA transporter 1 (GAT1)
- Removes GABA from synaptic cleft
  - Major inhibitory neurotransmitter in the brain

Credit: studyblue.com
SLC6A1 DEFICIENCY DISORDER

• First implicated in neurological disease by Carvill et al. 2015
  ▪ 6 individuals with Epilepsy with Myoclonic-Atonic Seizures (MAE; Doose syndrome) with pathogenic SLC6A1 variants
  ▪ 4% of individuals with EMAS explained by SLC6A1

Mutations in the GABA Transporter SLC6A1 Cause Epilepsy with Myoclonic-Atonic Seizures

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The American Journal of Human Genetics 96, 808–815, May 7, 2015
SLC6A1 DEFICIENCY DISORDER

• Follow up study by Johannesen et al. 2018
SLC6A1 DEFICIENCY DISORDER

• As of December 2019:
  ▪ >50 individuals published in the literature
  ▪ 70 unique SLC6A1 variants reported in HGMD
  ▪ 60 (likely) pathogenic SLC6A1 variants in ClinVar

  ▪ Phenotypic spectrum has expanded beyond Epilepsy with Myoclonic-Atonic Seizures (MAE/Doose syndrome)

  ▪ What does SLC6A1 Deficiency Disorder look like now?
PHENOTYPIC FEATURES: EPILEPSY

- Epilepsy is present in 81% of individuals
  - Median age of onset 24 months (range 5 months – 7 years)
  - 65% of individuals become seizure free

![Pie chart showing percentage of different types of epilepsy](image-url)
PHENOTYPIC FEATURES: EPILEPSY

• Generalized seizure types predominate

Percentage of pts w/seizure type

Seizure types

Typical Absence 50.0%
Atonic 44.1%
Atypical absence 29.4%
Myoclonic 20.6%
Myoclonic-atonic 20.6%
GTCS 14.7%
Eyelid myoclonia 8.8%
Focal-onset 5.9%
Tonic 2.9%
PHENOTYPIC FEATURES: DEVELOPMENT

• Developmental delays in 91% of individuals
• No correlation between seizure control and developmental outcome

3% Age Appropriate
9% Specific Learning Disability
35% Mild ID
6% Moderate ID
47% Severe ID
OTHER NEUROLOGICAL FEATURES

- Aggression: 11.8%
- Hypotonia: 8.8%
- Ataxia/Tremor: 29.4%
- ADHD: 17.6%
- Autism/Autistic features: 23.5%
SLC6A1 GENETIC SPECTRUM

• 60 (likely) pathogenic variants reported in ClinVar

• 70 variants reported in HGMD

• Most commonly reported variant c.863C>T; p.(Ala288Val)
**SLC6A1 GENETIC SPECTRUM**

**Variant Type**
- Missense: 57%
- PTV: 30%
- Splice: 10%
- In-Frame Deletion: 3%

**Inheritance of SLC6A1 Variant**
- de novo: 75%
- Inherited (affected parent): 16%
- Inherited (unaffected mosaic parent): 9%
TREATMENT OF SLC6A1 DEFICIENCY DISORDER

• 65% of individuals become seizure free
  ▪ Developmental concerns unrelated to seizure control

• Sodium valproate may be effective
  ▪ May not be specific to SLC6A1
  ▪ Standard treatment for Epilepsy with Myoclonic-Atonic Seizures

• Ketogenic diet?
  ▪ One published report (Palmer et al. 2016 Pediatr Neurol)
HOW COMMON IS SLC6A1 DEFICIENCY DISORDER?

• ~2% of all epilepsies in unselected cohort (Mattison et al. 2018 Epilepsia)

• 4% of all Epilepsy with Myoclonic-Atonic Seizures (Carvill et al. 2015 AJHG)

• 1.5% of adults with epilepsy and ID (Borlot et al. 2019 Epilepsia)

• ~1% of children with epilepsy onset <36 months (Symonds et al. 2019 Brain)
  - Prospective, population-based study
  - 5th most common genetic diagnosis
  - 8 children with EMAS (1 with SLC6A1)
GENOTYPE-PHENOTYPE CORRELATIONS?

• Not explored in the published literature

• Based on available data, no correlation between genotype and phenotype
  ▪ Systematic studies of genotype-phenotype correlations needed
SUMMARY

• Childhood-onset generalized epilepsy in 80%
  ▪ Median onset 24 months
  ▪ Most common seizure types: absence (typical and atypical), atonic
  ▪ >60% Epilepsy with Myoclonic-Atonic Seizures (MAE, Doose syndrome)
  ▪ Seizures can usually be well-controlled (VPA, Ketogenic Diet)

• Developmental delay in >90%
  ▪ Often apparent before seizure onset
  ▪ Most often mild to moderate developmental impairment

• Ataxia and coordination difficulties in 30%

• Autism spectrum disorders in 25%

• No clear genotype-phenotype correlations
CHOP EPILEPSY NEUROGENETICS INITIATIVE TEAM

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