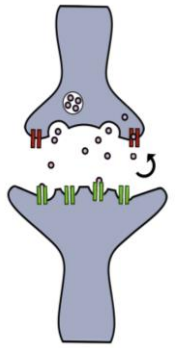
CLINICAL FEATURES OF SLC6A1 DEFICIENCY DISORDER



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Division of Neurology, Children's Hospital of Philadelphia

December 5, 2019

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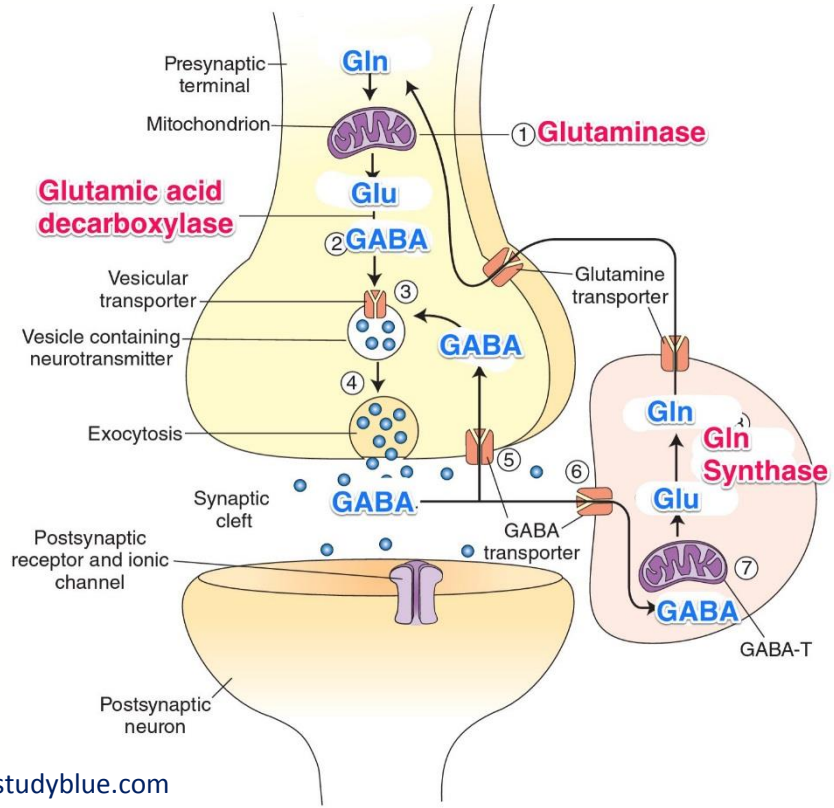
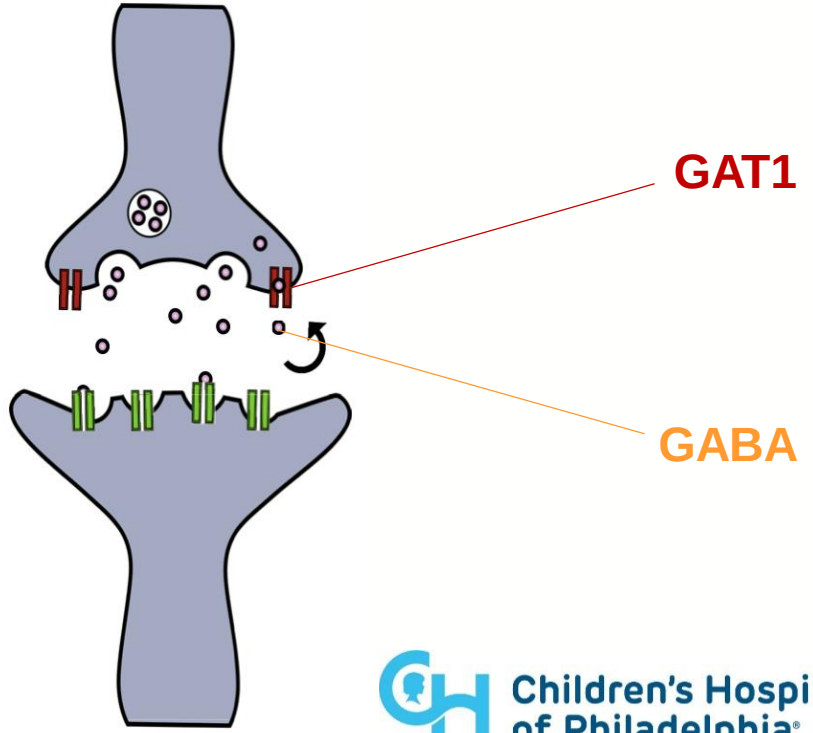
Epilepsy Neurogenetics Initiative

SLC6A1 GENE

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



Credit: studyblue.com



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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

Gemma L. Carvill,[1] Jacinta M. McMahon,[2] Amy Schneider,[2] Matthew Zemel,[1] Candace T. Myers,[1] Julia Saykally,[1] John Nguyen,[1] Angela Robbiano,[3] Federico Zara,[3] Nicola Specchio,[4] Oriano Mecarelli,[5] Robert L. Smith,[6] Richard J. Leventer,[7,8,9] Rikke S. Møller,[10,11] Marina Nikanorova,[10] Petia Dimova,[12] Albena Jordanova,[13,14,15] Steven Petrou,[16] EuroEPINOMICS Rare Epilepsy Syndrome Myoclonic-Astatic Epilepsy & Dravet working group, Ingo Helbig,[17,18] Pasquale Striano,[19] Sarah Weckhuysen,[13,14,20] Samuel F. Berkovic,[2] Ingrid E. Scheffer,[2,7,16,21,*] and Heather C. Mefford[1,21,*]

The American Journal of Human Genetics *96*, 808–815, May 7, 2015

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SLC6A1 DEFICIENCY DISORDER

- Follow up study by Johannesen et al. 2018

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Defining the phenotypic spectrum of *SLC6A1* mutations

Katrine M. Johannesen[1,2] | Elena Gardella[1,2] | Tarja Linnankivi[3] | Carolina Courage[4,5] | Anne de Saint Martin[6,7] | Anna-Elina Lehesjoki[4,5] | Cyril Mignot[8] | Alexandra Afenjar[9] | Gaetan Lesca[10,11,12] | Marie-Thérèse Abi-Warde[6,7] | Jamel Chelly[13,14] | Amélie Piton[13,14] | J. Lawrence Merritt II[15] | Lance H. Rodan[16,17] | Wen-Hann Tan[16,17] | Lynne M. Bird[18] | Mark Nespeca[19] | Joseph G. Gleeson[20] | Yongjin Yoo[21] | Murim Choi[21] | Jong-Hee Chae[22] | Desiree Czapansky-Beilman[23] | Sara Chadwick Reichert[24] | Manuela Pendziwiat[25] | Judith S. Verhoeven[26] | Helenius J. Schelhaas[26] | Orrin Devinsky[27] | Jakob Christensen[28] | Nicola Specchio[29] | Marina Trivisano[29] | Yvonne G. Weber[30] | Caroline Nava[31,32] | Boris Keren[31,32] | Diane Doummar[33] | Elise Schaefer[34] | Sarah Hopkins[35] | Holly Dubbs[36] | Jessica E. Shaw[36] | Laura Pisani[36] | Candace T. Myers[15] | Sha Tang[37] | Shan Tang[38] | Deb K. Pal[38] | John J. Millichap[39,40] | Gemma L. Carvill[40] | Kathrine L. Helbig[37] | Oriano Mecarelli[41] | Pasquale Striano[42] | Ingo Helbig[25,35] | Guido Rubboli[1,43] | Heather C. Mefford[15] | Rikke S. Møller[1,2]

Epilepsia. 2018;59:389–402.

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SLC6A1 DEFICIENCY DISORDER

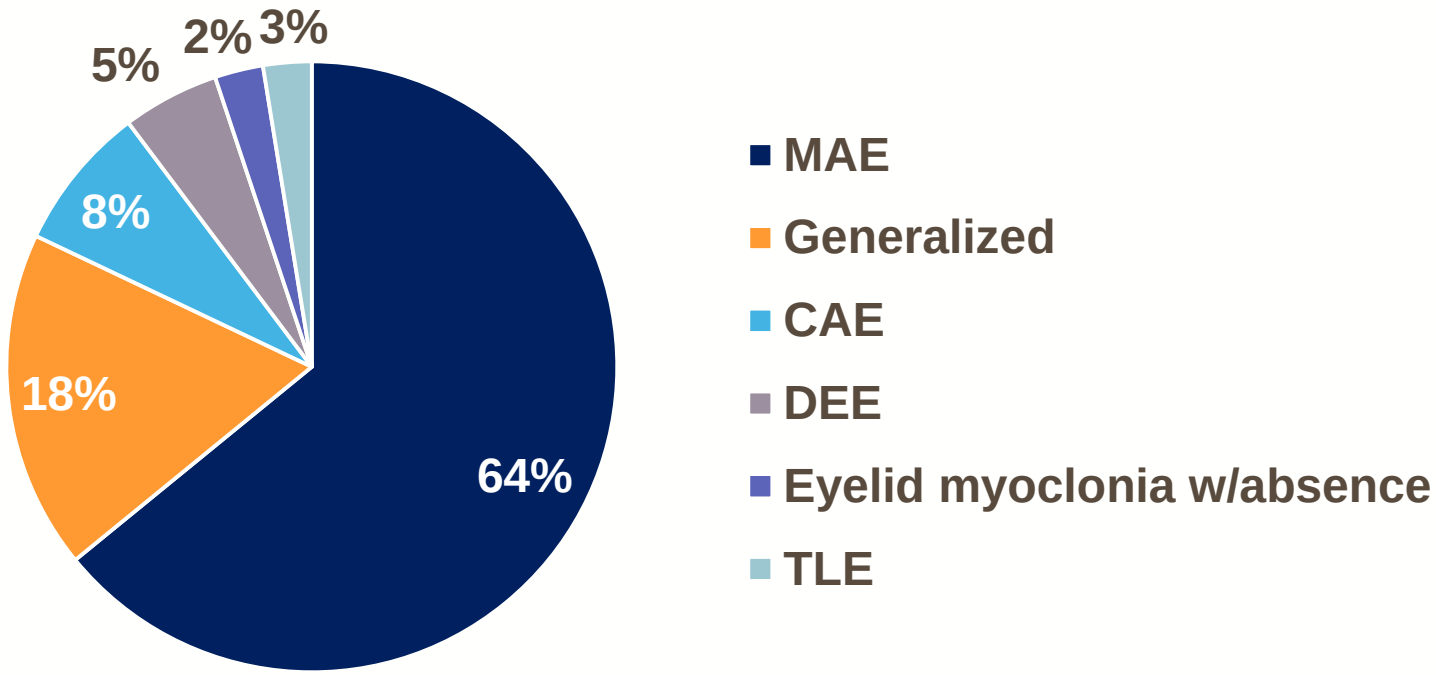
- As of December 2019:
  - >50 individuals published in the literature
  - 70 unique *SLC6A1* variants reported in HGMD
  - 60 (likely) pathogenic *SLC6A1* variants in ClinVar

- 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 5m – 7y)
  - 65% of individuals become seizure free



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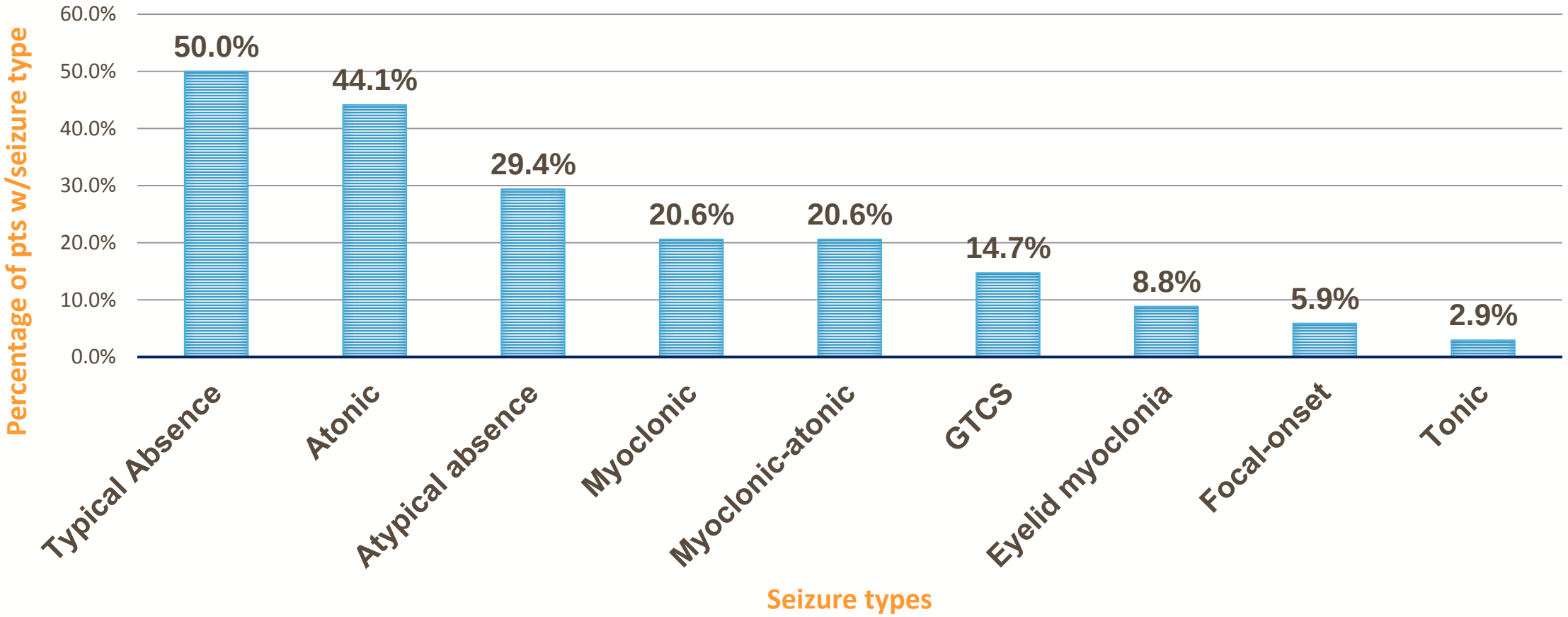
PHENOTYPIC FEATURES: EPILEPSY

- Generalized seizure types predominate



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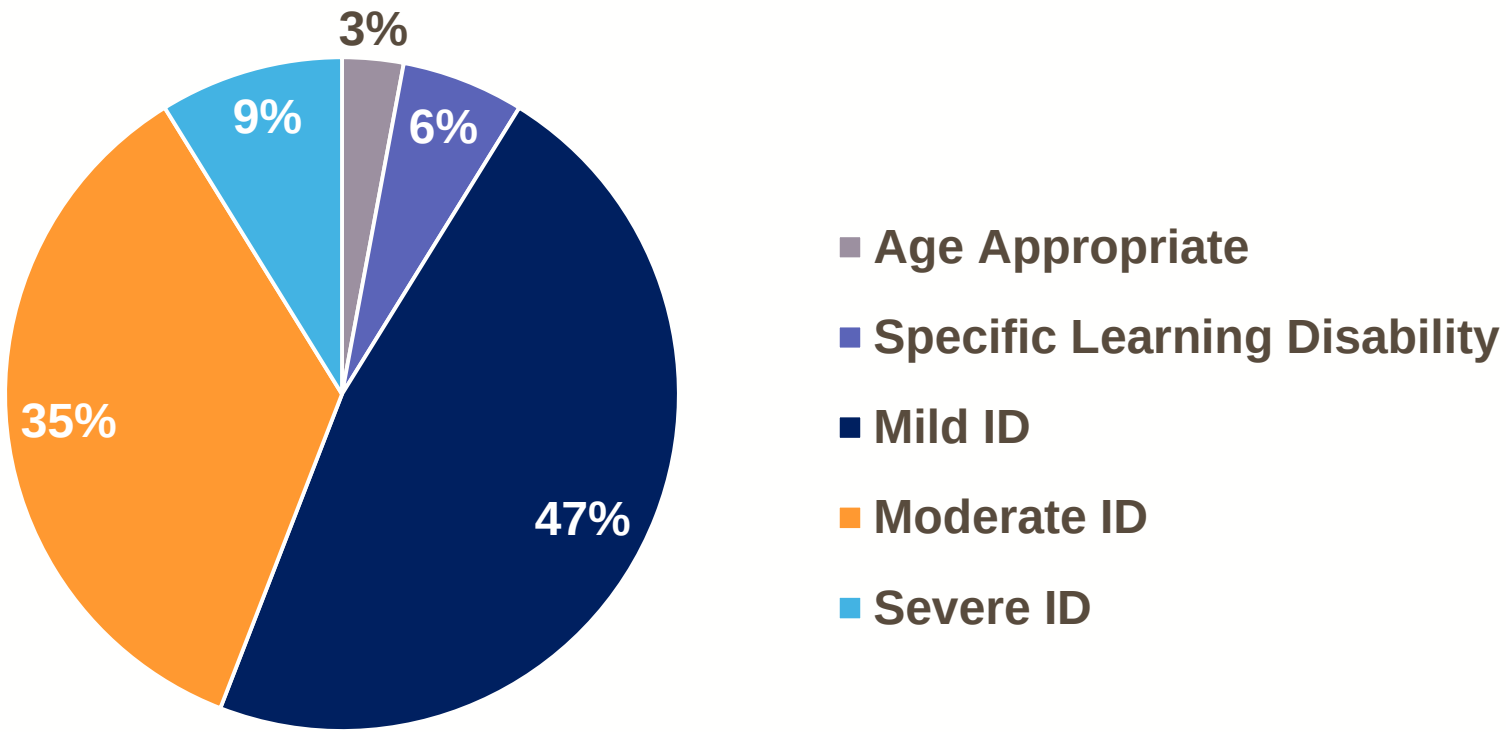
PHENOTYPIC FEATURES: DEVELOPMENT

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



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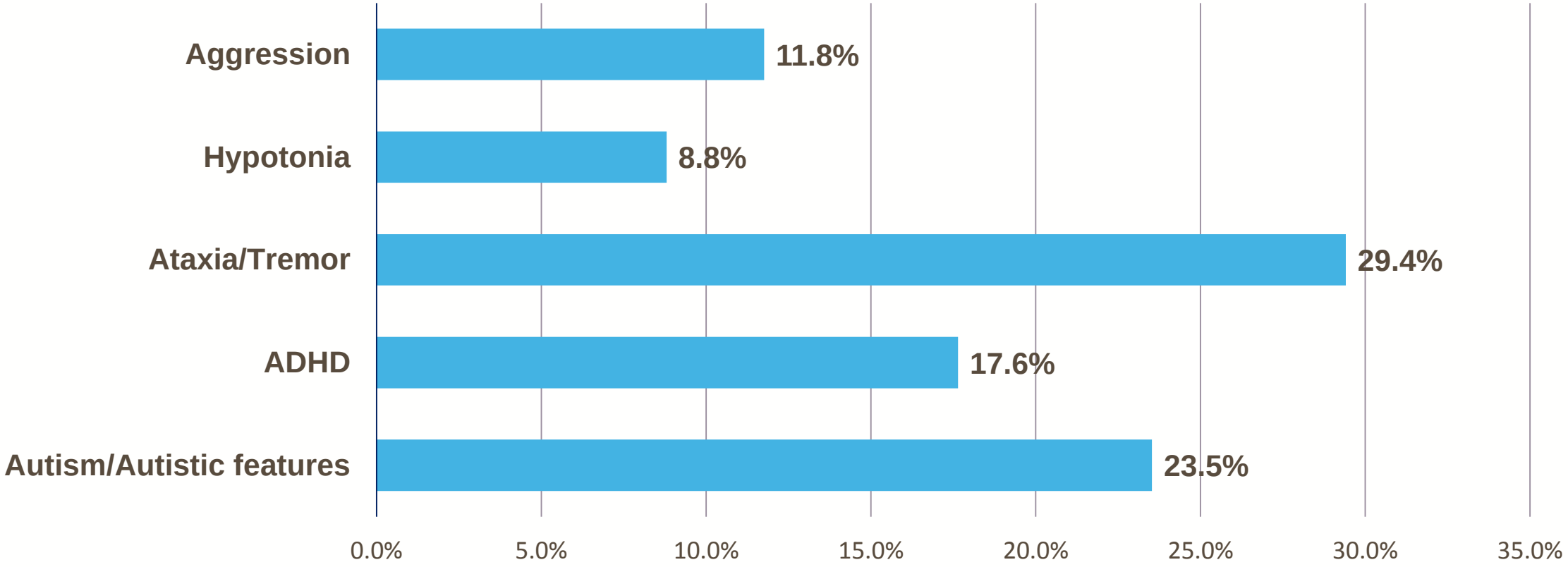
OTHER NEUROLOGICAL FEATURES



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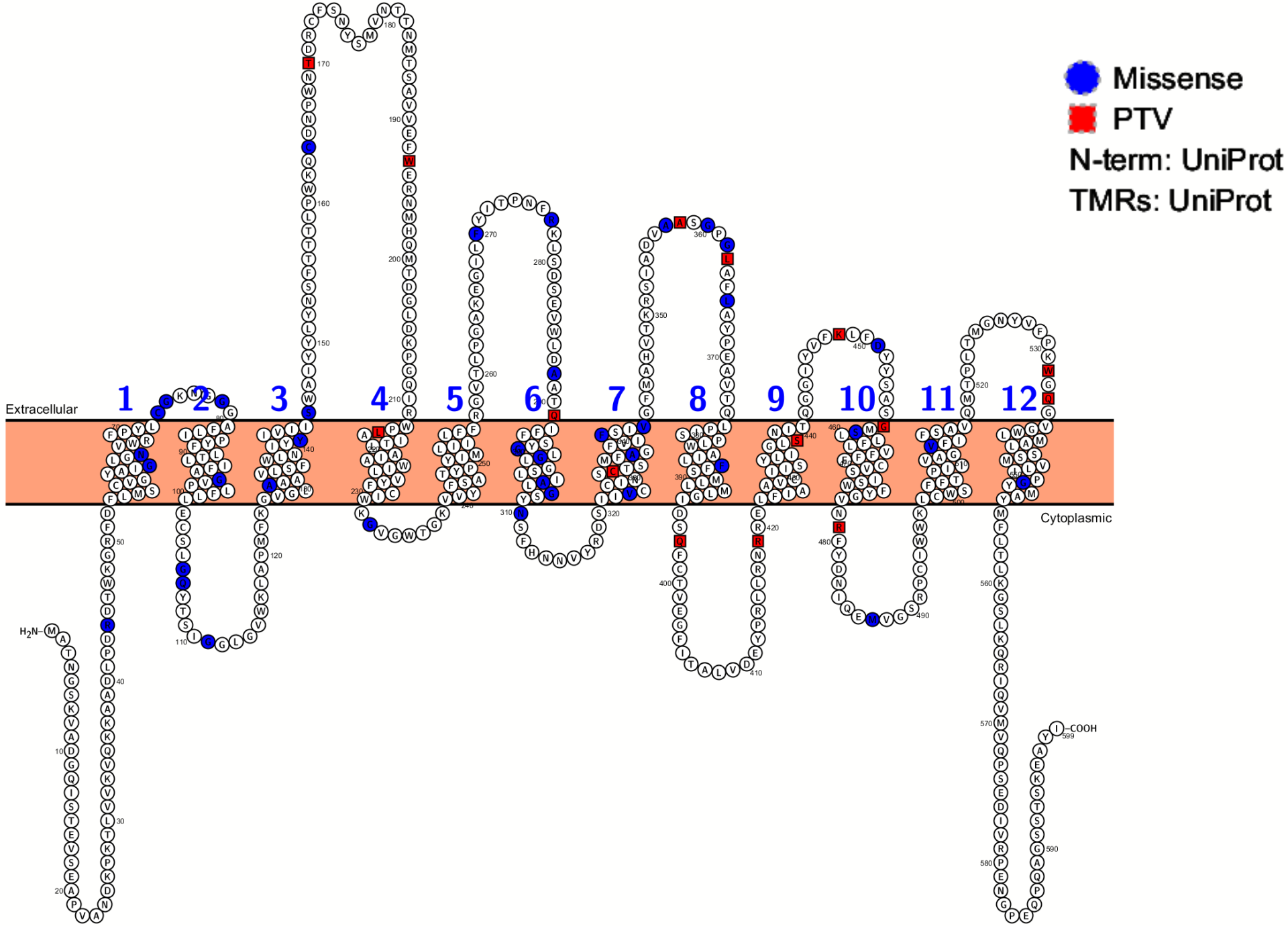
SLC6A1 GENETIC SPECTRUM

- 60 (likely) pathogenic variants reported in ClinVar
- 70 variants reported in HGMD
- Most commonly reported variant c.863C>T; p.(Ala288Val)


Missense
PTV
N-term: UniProt
TMRs: UniProt
Extracellular
Cytoplasmic
1
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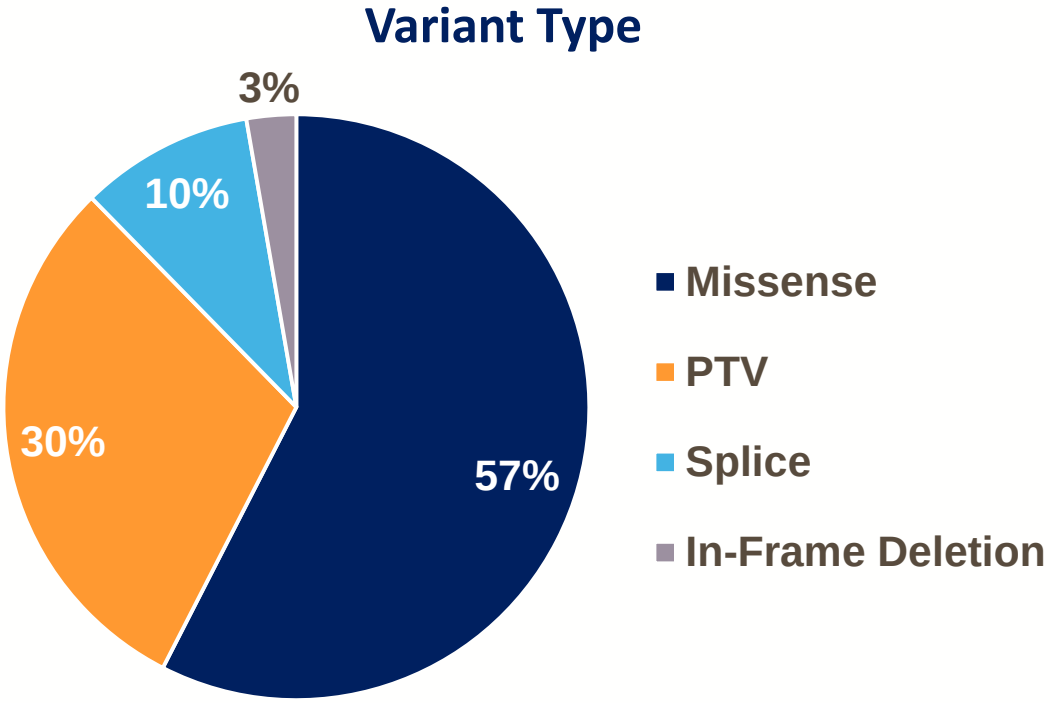
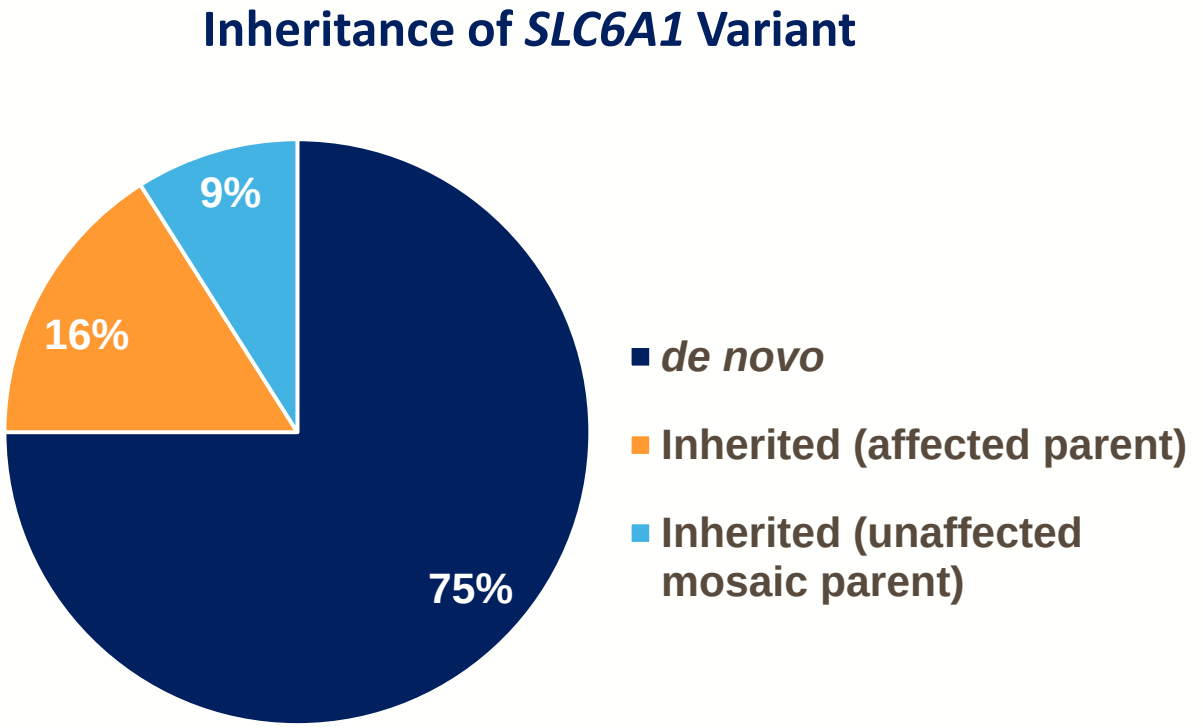
H2N–
–COOH

SLC6A1 GENETIC SPECTRUM





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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

Back Row

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Ingo Helbig, MD

Xilma Ortiz-Gonzalez, MD, PhD

Holly Dubbs, MS, LCGC

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Mark Fitzgerald, MD, PhD

Shavonne Massey, MD

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