Functional Genomics of Rare Coding Region Variants in the GABA Transporter, GAT-1 (SLC6A1)

PRESENTER:

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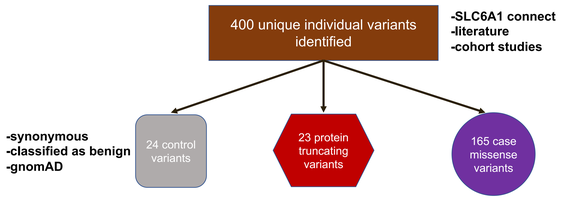
SLC6A1/GAT-1 mutations lead to clinical symptoms by a loss-of-function mechanism. Mutations are dispersed across the protein.

BACKGROUND: The goal of this study was to characterize a large subset of *SLC6A1*/GAT-1 variants to clarify the genotype-phenotype relationship and learn how these mutations affect GAT-1 protein function and localization.

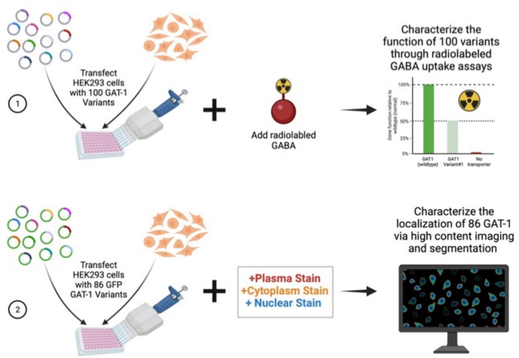
- Genetic variants in SLC6A1 are strongly associated with **myoclonic atonic epilepsy**, **generalized epilepsy, intellectual disability, and autism spectrum disorder.**
- Currently, the mechanisms by which these variants contribute to CNS disorders and their effects on GAT-1 function are poorly understood.

METHODS

1. Variant Selection Process



2. Experimental overview to study the function of *SLC6A1* variants *in-vitro*



RESULTS

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Figure 1

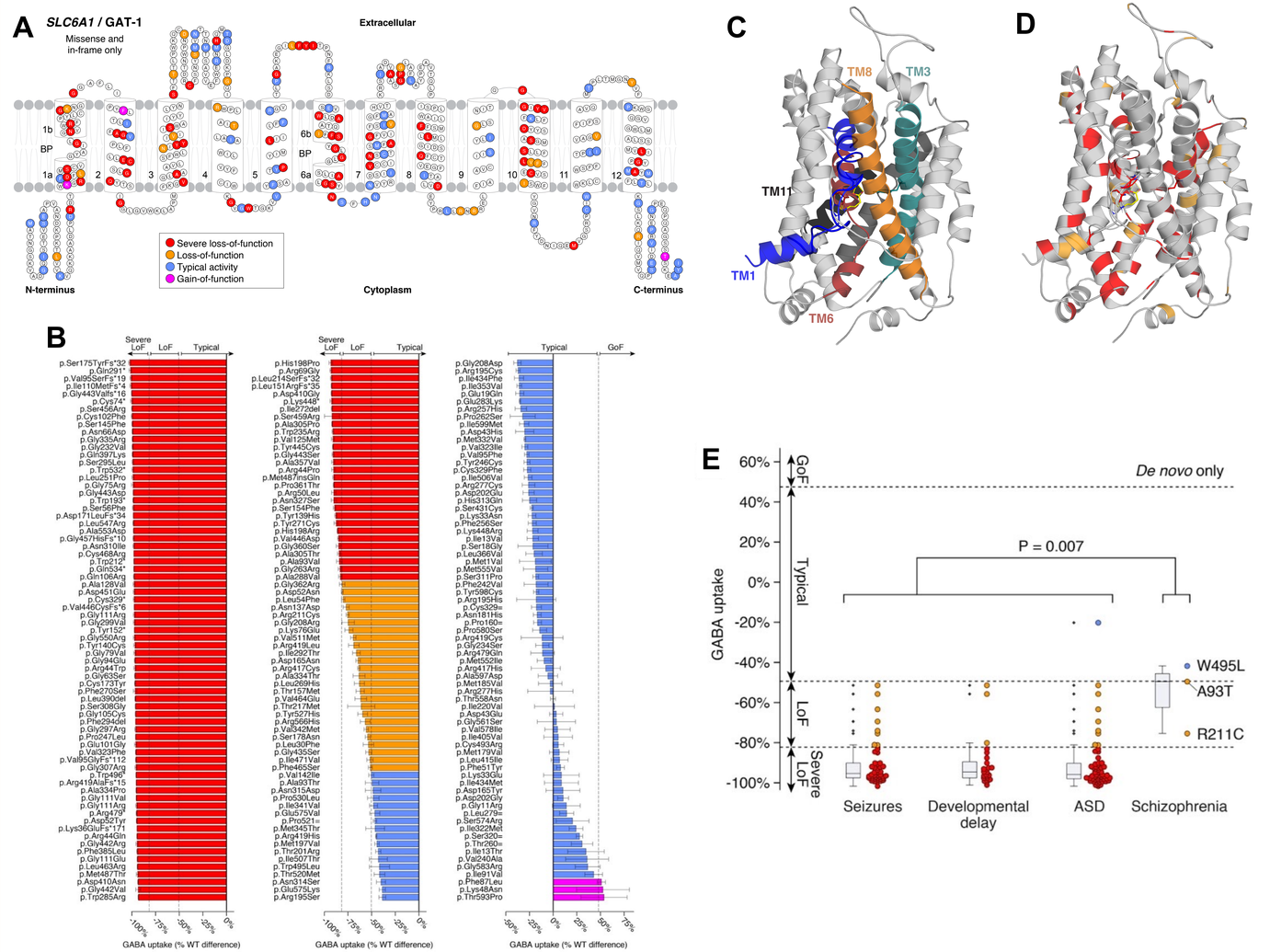

Figure 1. Topology of the GAT-1 protein and GABA uptake values by functional type and phenotype. (**A**) The 2D representation of the GAT-1 protein is shown and organized by 12 transmembrane domains and linking or terminal chains. Only missense and in-frame variants are highlighted. (**B**) GABA uptake functional data is shown as a percentage of wildtype difference and highlighted by activity type for 213 variants tested across the 599 amino acids of the GAT-1 protein. Individual data bars represent mean ±SEM of three biological replicates performed in triplicates. (**C**) GAT-1 structure with transmembrane domains labeled (**D**) GAT-1 structure highlighted with LoF or severe LoF variants (**E**) GABA uptake values are shown for de novo variants by the presence of seizures, developmental delay, autism spectrum disorder, or schizophrenia. If phenotypes are comorbid (e.g., seizures and developmental delay) the variant is shown for all phenotypes for which it is reported.

Figure 2

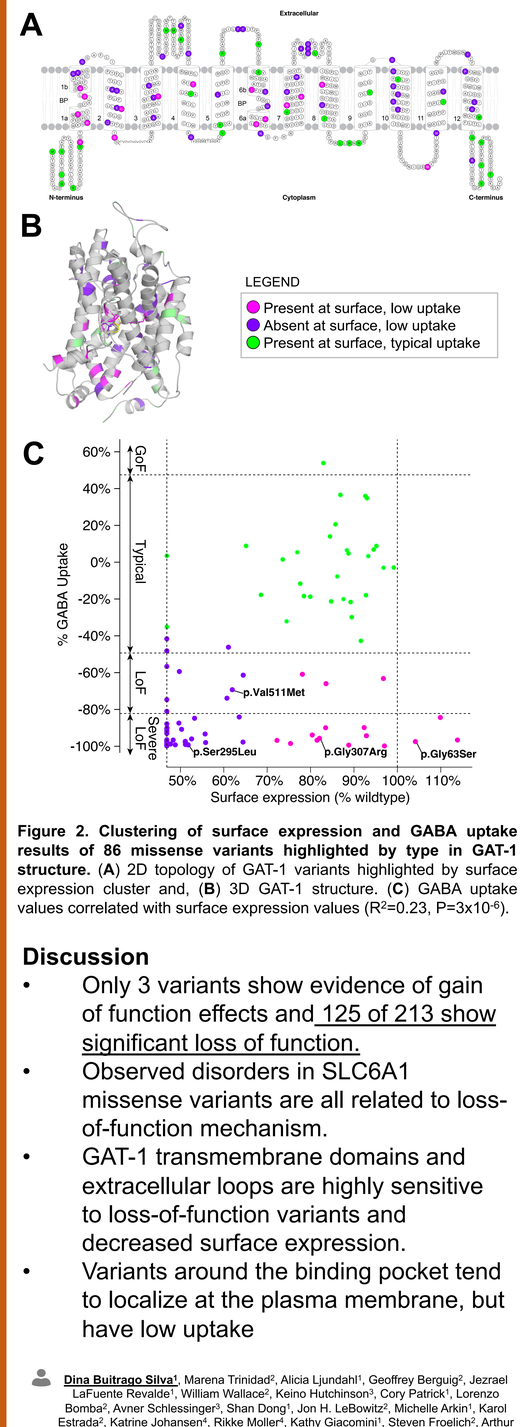

Figure 2. Clustering of surface expression and GABA uptake results of 86 missense variants highlighted by type in GAT-1 structure. (**A**) 2D topology of GAT-1 variants highlighted by surface expression cluster and, (**B**) 3D GAT-1 structure. (**C**) GABA uptake values correlated with surface expression values (R^2=0.23, P=3x10^{-6}).

Discussion

- Only 3 variants show evidence of gain of function effects and 125 of 213 show significant loss of function.
- Observed disorders in SLC6A1 missense variants are all related to loss-of-function mechanism.
- GAT-1 transmembrane domains and extracellular loops are highly sensitive to loss-of-function variants and decreased surface expression.
- Variants around the binding pocket tend to localize at the plasma membrane, but have low uptake

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