De novo GLUL missense variant in individual with neurodevelopmental disorder prompts ClinGen gene curation, ClinVar submission, and new GeneMatcher cohort

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Introduction

- In the brain, the *GLUL* gene produces glutamine synthetase that converts neurotoxic glutamate to harmless glutamine, detoxifying ammonia and recycling neurotransmitter function
- Biallelic pathogenic missense variants had been associated with autosomal recessive congenital brain dysgenesis
- A 2024 publication reported clustered heterozygous start-loss variants in the *GLUL* gene as a cause of developmental and epileptic encephalopathy (Jones et al, 2024)
- Variants clustered in the Met1 codon, requiring the use of a downstream methionine that results in loss of sensitivity to negative feedback from high glutamine levels

Jones AG, Aquilino M, Tinker RJ, et al. Clustered de novo start-loss variants in GLUL result in a developmental and epileptic encephalopathy via stabilization of glutamine synthetase. *Am J Hum Genet*. 2024;111(4):729-741.

GENYSIS, ClinGen, ClinVar, and GeneMatcher Reciprocity

- The **GENYSIS** research recharge core provides genetic analysis for the Genetic Determinants of Neurological and Developmental Disorders (GDNDD) study
- Suspicion of the *GLUL* variant p.Cys163Thr (p.C163T) was raised in a proband exome based on phenotypic overlap and *de novo* status
- p.C163T was submitted to **GeneMatcher** and **ClinVar** as a variant of uncertain significance (VUS) based on phenotypic suspicion
- Before ACMG/AMP/ClinGen variant classification guidelines can be applied, a Moderate disease-gene relationship is recommended to be established
- **ClinGen's** Epilepsy Gene Curation Expert Panel (GCEP) was contacted to discuss curation of *GLUL*
- *GLUL* received a **Moderate** classification for its relationship to **genetic developmental and epileptic encephalopathy** from the Epilepsy GCEP

A Pathway for Future Collaborations

- The *GLUL* Moderate gene-disease relationship allowed the p.C163T variant to be classified as a VUS in relation to developmental and epileptic encephalopathy and submitted to the individual's medical record
- The GDNDD individual has now been recruited to a growing research cohort to study the functional effects of non-Met1 *GLUL* missense variants
- Following the **GENYSIS** submission to **ClinVar**, additional *de novo* heterozygous missense variants in *GLUL* have been added, as well as inquiries from additional *GLUL* researchers

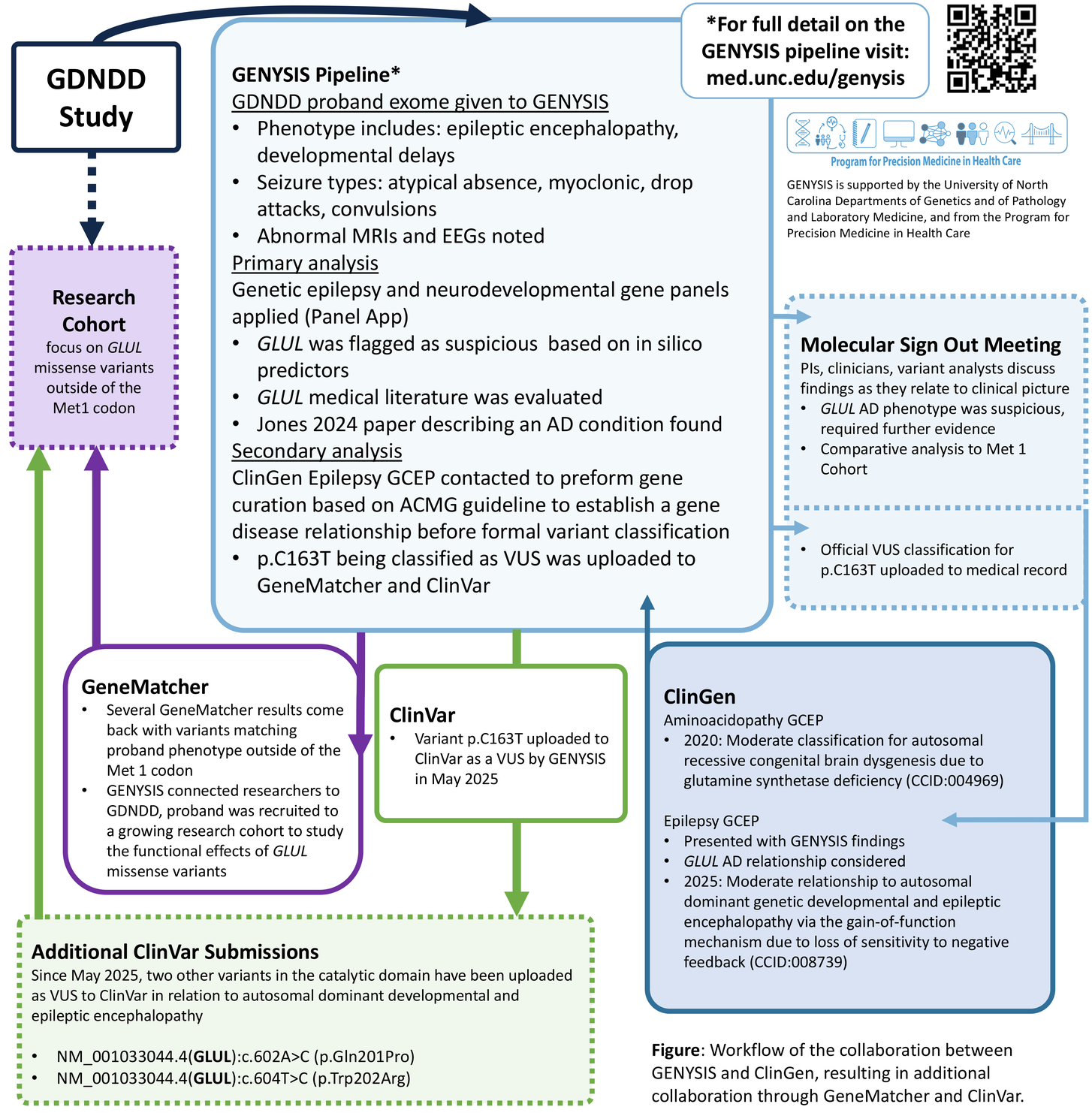

Figure: Workflow of the collaboration between GENYSIS and ClinGen, resulting in additional collaboration through GeneMatcher and ClinVar.