Annual update on the NIH-funded ClinGen Cerebral Creatine Deficiency Syndromes (CCDS) Variant Curation Expert Panel (VCEP)

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Background

The Clinical Genome Resource (ClinGen)

A National Institutes of Health (NIH)-funded consortium dedicated to creating a public resource on the clinical impact of genes and variants[1].

ClinGen Variant Curation Expert Panels (VCEPs)

Groups of researchers, clinicians, laboratory specialists and variant scientists that generate gene-specific variant classification guidelines ("specifications"), share data, and classify variants, to create a **public resource** for the medical and scientific community[2].

Fig 1. ClinGen VCEP workflow

VCEP gene-specific variant classification guidance*

→ **Variant list**
- Publications
- ClinVar
- Registries

→ **Collect data**
- Population
- Computational
- Functional
- Case-level

→ **Variant classification**
- Pathogenic
- Likely Pathogenic
- VUS
- Likely Benign
- Benign

→ **Public databases**
- ClinGen ERepo
- ClinVar ★★★ (FDA-Recognized Database)

*Reviewed and approved by the ClinGen Variant Classification Review and Oversight Committees

The goals and progress of the ClinGen CCDS VCEP

Overall goal

To provide publicly-available and expert-reviewed classification of variants in the 3 CCDS genes - *GATM, GAMT,* and *SLC6A8*.

Goal 1: Generation of gene-specific guidance for variant classification

- We have generated gene-specific guidance for the classification of variants in all 3 CCDS genes[3].
- The *SLC6A8* specifications were recently updated and approved by the ClinGen Variant Classification Review Committee (Table 1). The Version 2 (SLC6A8v2) gene specification guidelines provide increased granularity for weighting of pathogenic or benign evidence for specific criteria as well as overall variant interpretation. The updated guidelines have enabled more sensitivity and power to correctly classify *SLC6A8* variants identified in females and include updates to current variant classification guidance.

Goal 2: Classify variants in the 3 CCDS genes

- We have collected available data (from published literature, databases, registries, and internal laboratory data), have used our gene-specific guidance to classify variants in a 3 genes, and have submitted those classifications to public databases (Fig 2)
- Classifications are revisited routinely following ClinGen's recuration policy (every 2 years for LP and VUS; within 3 months if another ClinVar submitter has a clinically-relevant conflicting classification).

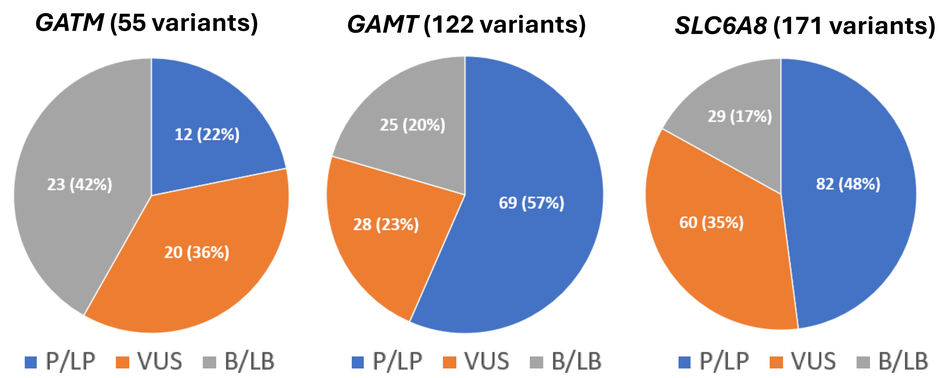
Goal 3: Collaborate with the ACD's CreatineINFO registry

- At a previous meeting, we reported how the use of case-level data, kindly shared by participants in the CreatineINFO registry, improved variant classification (ACD Scientific Symposium, 2024).
- We have reviewed the current list of variants in the CreatineINFO registry to prioritize those variants for which additional case-level data could be helpful (Fig 3).

Table 1. Approved CCDS VCEP specification updates for *SLC6A8* (v2) - overview of major changes

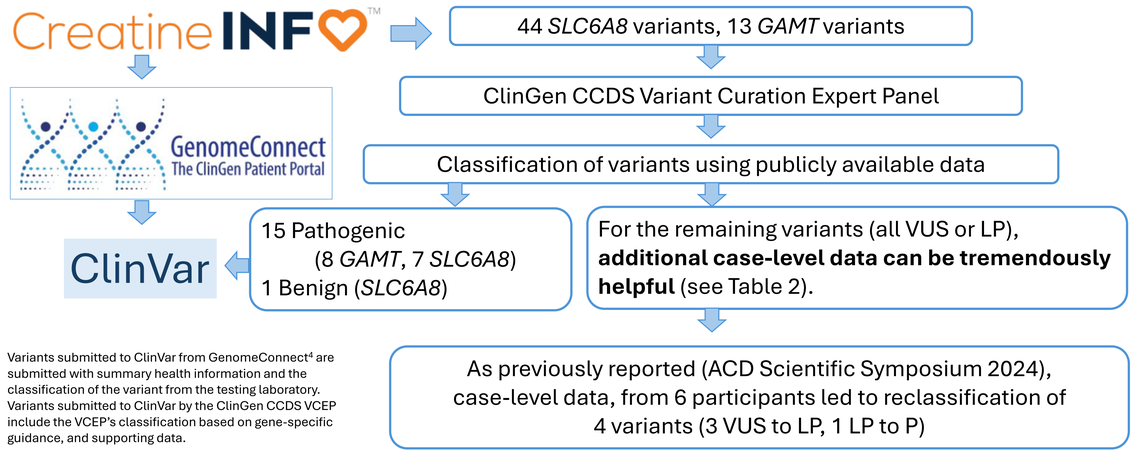
Update	SLC6A8v1	SLC6A8v2	Reason
General Scoring	Richards, et.al. 2015 combining criteria	Bayesian point scoring framework	Allows more sensitive variant curations on a points-based framework. Especially important for variants with conflicting evidence
PVS1 (nonsense, frameshift, canonical splice variants)	General guidelines, minimal granularity	Flowchart for all potentially protein truncating variants	Significant increase in granularity for all potentially truncating variants. Allows for modification of strength from supporting (+1) to very strong (+8)
Splice variants in same region	n/a	Allows scoring a novel variant in the same splice region as a reported variant	Allows adding of points for pathogenicity or benignity if a new variant is detected in the same region as a previously reported variant
Phenotype specificity	Applied for males only	Applied for both males and females on a points- based system	Enables scoring phenotype specificity in females based on biochemical findings, creatine uptake studies, MRS creatine peak, and breadth of testing methodology used to detect variant
Segregation evidence	Females not applicable	Affected females are applicable for segregation evidence, asymptomatic females are not counted against segregation evidence	Acknowledges that phenotypes in females with *SLC6A8* variants have highly variable phenotypes ranging from asymptomatic to severely affected; allows to use families for which females may be asymptomatic or mildly affected

Figure 2. Summary of variant classifications submitted to ClinVar



P=Pathogenic; LP=Likely Pathogenic; VUS=Variant of Uncertain Significance; LB = Likely Benign; Benign = Benign

Figure 3. Collaboration with CreatineINFO, the ACD's patient registry



Variants submitted to ClinVar from GenomeConnect[4] are submitted with summary health information and the classification of the variant from the testing laboratory. Variants submitted to ClinVar by the ClinGen CCDS VCEP include the VCEP's classification based on gene-specific guidance, and supporting data.

Table 2. Additional data that may be requested from CreatineINFO participants

Data requested*	Criteria that require this data
Pre-treatment creatine and guanidinoacetate levels; brain magnetic resonance spectroscopy (MRS) results; enzyme/transporter activity	PP4 (all), PS4 (*SLC6A8*)
Parental (mother, father) genetic testing results	PM3 (*GATM*, *GAMT*); PS2/PM6 (*SLC6A8*)
Affected family member biochemical, MRS, and genetic testing data	PP1 (*SLC6A8*)

Future work

- Continue to classify variants in all three CCDS genes as they are published in the scientific and medical literature, and to recurate variants based on ClinGen's recuration policy.
- Gene-specific variant classification guidance for all three genes (*GATM*, *GAMT*, and *SLC6A8*) will undergo a major update upon the publication of the next iteration of the ACMG/AMP/ClinGen Variant Classification Guidance, SVCv4. Publication of the updated general guidance is expected within the next year.
- Classify all variants in the CreatineINFO registry and work with the registry coordinator to request additional data from participants. **If you or a family member is a participant in the CreatineINFO registry, providing this additional data, when requested, is optional; however, we greatly appreciate your consideration of this request**.

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