Poster #17

An ongoing collaboration: The Association for Creatine Deficiencies and the Clinical Genome resource work together to facilitate variant classification.

Jennifer L. Goldstein*[1], Heidi Wallis[2], Emily Reinhardt[2], Juliann M. Savatt[3], Erin Rooney Riggs[3], Amanda Thomas-Wilson[4], Emily Groopman[5], Vimla Aggarwal[6], Simona Bianconi[7], Raquel Fernandez[8], Kim Hart[9], Emily Kyle[8], Nicole Liang[10], Nicola Longo[11], Christine Preston[12], Daniel Reich[13], Meredith Weaver[8], Sarah Young[14], Saadet Mercimek-Andrews[14]

[1] Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2] Association for Creatine Deficiencies, Carlsbad, CA, USA, [3] Geisinger, Danville, PA, USA, [4] New York Genome Center, New York, NY, USA, [5] Children's National Hospital, Washington, DC, USA, [6] Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, NY, USA, [7] Kaiser Permanente, Southern California Permanente Group, CA, USA, [8] American College of Medical Genetics and Genomics, Bethesda, MD, USA, [9] Newborn Screening Program, Utah Public Health Laboratory, Department of Health and Human Services, Salt Lake City, UT, USA, [10] Clinical and Metabolic Genetics, The Hospital for Sick Children (SickKids), Toronto, Canada, [11] Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, UT, USA, [12] School of Medicine, Stanford University, Palo Alto, CA, USA, [13] ARUP Laboratories, Salt Lake City, UT, USA, [14] Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA, [15] Department of Medical Genetics, University of Alberta, Edmonton, Alberta, Canada

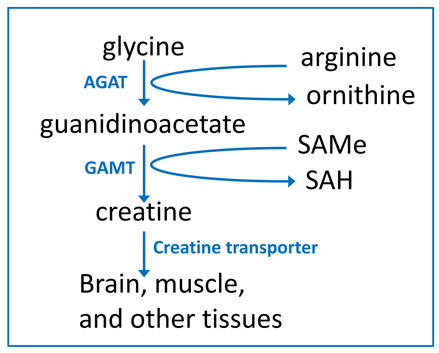
Background

- Cerebral creatine deficiency syndromes (CCDS) are inborn errors of metabolism characterized by developmental delay / intellectual disability, lack of speech / few words, seizures, movement disorder, behavioral problems, and diminished creatine level in the brain (ref. 1).
- These disorders are caused by problems with creatine synthesis and transport (Table 1, Figure 1).
- The creatine synthesis disorders (AGAT deficiency and GAMT deficiency) can be treated with creatine supplementation and other dietary modifications. Currently, there is no effective treatment for creatine transporter deficiency.
- Newborn screening for GAMT deficiency was added to the recommended Uniform Screening Panel for newborns in the USA in January 2023.

Table 1. Cerebral Creatine Deficiency Syndromes

Gene	Disease entity	Inheritance
GATM	arginine:glycyine amidinotransferase (AGAT) deficiency	AR
GAMT	guanidinoacetate methyltransferase (GAMT) deficiency	AR
SLC6A8	creatine transporter deficiency (CTD)	Xl

Fig 1. Creatine synthesis and transport



Goals

- Accurate classification of the pathogenicity of genetic variants is critical for the timely diagnosis of patients and testing for family members.
- This effort aims to accumulate published and unpublished case level data on variants in the genes involved in the CCDS to provide informative variant classifications to be shared in public databases.
- To do this, the ClinGen CCDS VCEP (ref 2) obtained a list of variants in the CCDS genes, classified them using publicly available data, submitted variants with pathogenic or benign classifications to ClinVar, and requested case-level data from the participating registries for variants classified as variants of uncertain significance (VUS) or likely pathogenic (LP).

Methods: Description of the groups involved

The ClinGen CCDS Variant Curation Expert Panel (VCEP)

- Has specified the general ACMG/AMP variant interpretation guidelines for classification of variants in the three genes involved in CCDS (*GATM*, *GAMT*, and *SLC6A8*) (ref 2).
- Has submitted 248 variant classifications to ClinGen's public Evidence Repository and to ClinVar as part of an FDA-approved genomic database to date.

The Association for Creatine Deficiencies (ACD)

- A patient advocacy organization that supports families with CCDS (https://creatineinfo.org/).
- The ACD partners with the National Organization for Rare Disorders (NORD) to provide an IRB-approved, patient- and caregiver-reported registry, **CreatineINFO**.
- Patients with any of the three CCDS diagnoses, worldwide, can participate in the CreatineINFO registry.

GenomeConnect

- A registry that is part of ClinGen, allows patients and patient registries to share their genetic and health information with ClinVar. GenomeConnect does not re-classify variants. The variant classification provided by the testing lab is the classification submitted to ClinVar (https://www.clinicalgenome.org/genomeconnect/).

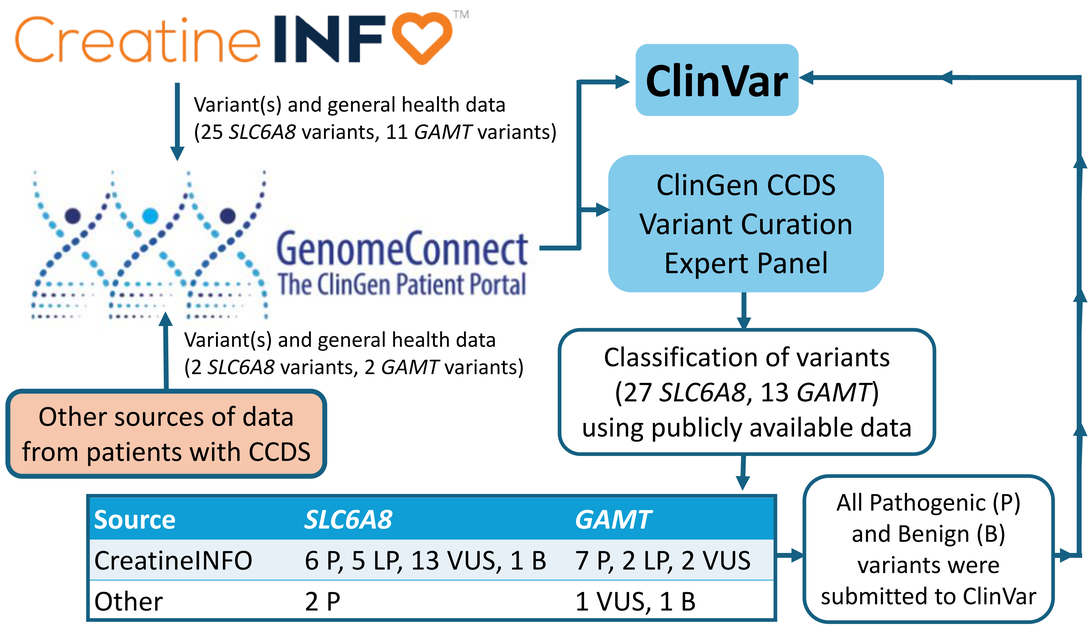
Acknowledgements

We are very grateful to the participants of the CreatineINFO registry and GenomeConnect, and their families, for sharing their data. We thank the NHGRI for funding this project (Grant # U24HG009650, U24HG006834). Thank you also to the ClinGen community, including the ClinGen Sequence Variant Interpretation Working Group and ClinGen Stanford Informatics team for their support.

References

1) Mercimek-Andrews S, Salomons GS, Creatine Deficiency Disorders. 2009 Jan 15 [updated 2022 Feb 10]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2024. PMID: 20301745
2) Goldstein JL, Thomas-Wilson A, et al, ClinGen variant curation expert panel recommendations for classification of variants in GAMT, GATM and SLC6A8 for cerebral creatine deficiency syndromes. Mol Genet Metab. 2024 Mar 2;142(1):108362. doi: 10.1016/j.ymgme.2024.108362. Online ahead of print. PMID: 38452609

Methods: Data sharing workflow



- As classification of variants other than pathogenic or benign could be further informed by additional case level data, a list of these variants was sent to the CreatineINFO registry coordinator.
- Participants were contacted, under an IRB-approved protocol, to request additional information (Table 2) that could further inform the variant classification.

Table 2. Additional data requested from CreatineINFO participants

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

*To avoid double counting evidence, participants were also asked if they knew if their data had been published and, if so, to provide the reference.

Results – Registry data facilitates variant classification

Table 3. Impact on variant classification of CreatineINFO data received to date (n=6 probands)

Gene	Variant	Initial classification	Updated classification
SLC6A8	c.342G>C (p.Gln114His)	VUS PM2_Supp., PP3	**Likely pathogenic** **PP4_Str., PM6**, PM2_Supp., PP3
SLC6A8	c.1370T>A (p.Ile457Asn)	VUS PM2_Supp.	**Likely pathogenic** **PP4_Str., PM6**, PM2_Supp.
GAMT	c.1A>G (p.Met1?)	VUS PVS1_Mod., PM2_Supp.	VUS PVS1_Mod., **PP4**, PM2_Supp.
GAMT	c.233T>A (p.Val78Glu)[1]	Likely pathogenic PP4_Str., PM3, PP3, PM2_Supp.	LP PP4_Str., PM3, PP3, PM2_Supp.
GAMT	c.328G>T (p.Val110Phe)	Likely pathogenic PP4_Str., PP3, PS3_Supp., PM2_Supp., PM3_Supp.	LP PP4_Str., PP3, PS3_Supp., PM2_Supp., PM3_Supp.
GAMT	c.505T>C (p.Cys169Arg)[2]	Likely pathogenic PM3, PP4, PM2_Supp., PM5_Supp.	**Pathogenic** **PM3_Str., PP4_Mod.**, PM2_Supp., PM5_Supp.

[1] Data already published; [2] Data from two probands from CreatineINFO; Bold = Changed classification or code

Summary / Future plans

- By partnering with the ACD's patient registry (CreatineINFO) and ClinGen's GenomeConnect, to accumulate unpublished case-level data, the ClinGen CCDS VCEP hopes to be able to further inform the classification of variants in the three genes involved with CCDS *(GATM*, *GAMT*, SLC6A8).
- Only recently did we begin to request additional data from CreatineINFO participants. **We have already received data from 6 probands that led to reclassification of 3 out of 6 variants.**
- We will continue to collect case-level data with the goal of reclassifying additional variants.