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

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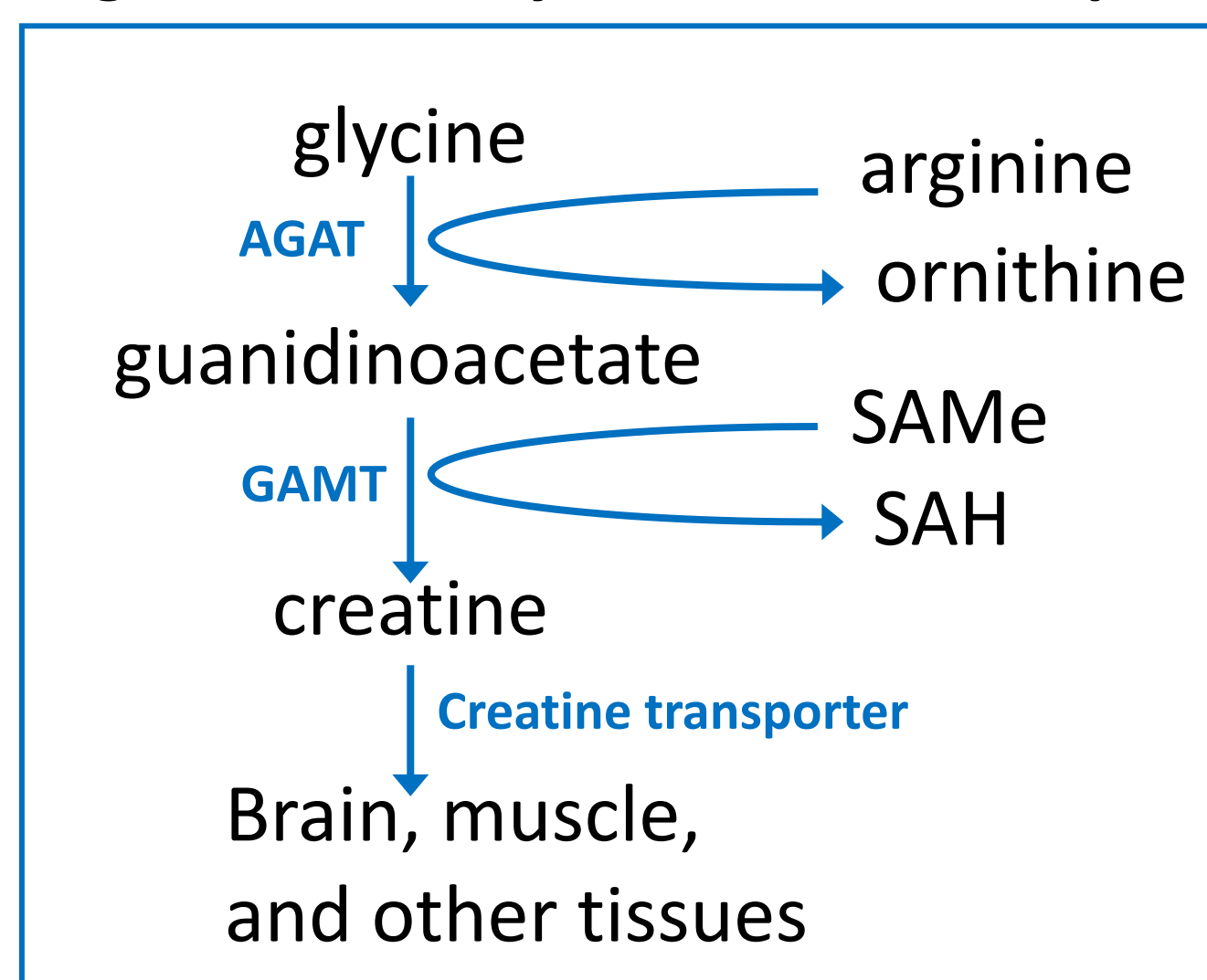
Background

- 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:glycine amidinotransferase (AGAT) deficiency	AR
GAMT	guanidinoacetate methyltransferase (GAMT) deficiency	AR
SLC6A8	creatine transporter deficiency (CTD)	Xl

Fig 1. Creatine synthesis and transport

glycine → arginine
AGAT → ornithine
guanidinoacetate → SAMe
GAMT → SAH
creatine
Creatine transporter
Brain, muscle, and other tissues

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- This effort aims to accumulate published and unpublished case level data on variants in the genes involved in the CCDS to provide informative variant classifications to be shared in public databases.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/).
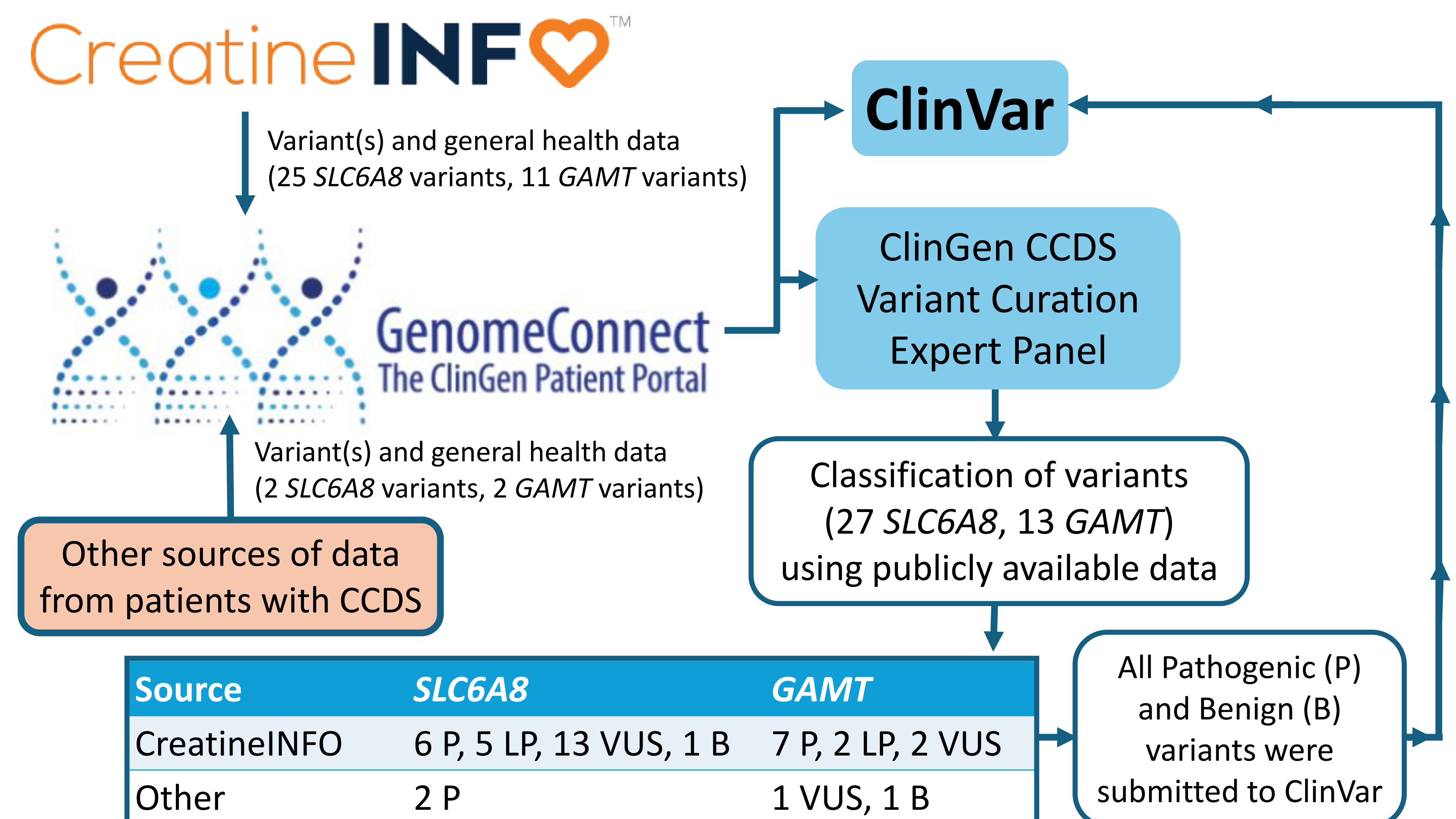
Acknowledgements

References

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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

CreatineINFO™
Variant(s) and general health data (25 SLC6A8 variants, 11 GAMT variants)
GenomeConnect The ClinGen Patient Portal
Variant(s) and general health data (2 SLC6A8 variants, 2 GAMT variants)
Other sources of data from patients with CCDS
ClinVar
ClinGen CCDS Variant Curation Expert Panel
Classification of variants (27 SLC6A8, 13 GAMT) using publicly available data
All Pathogenic (P) and Benign (B) variants were submitted to ClinVar

Source	SLC6A8	GAMT
CreatineINFO	6 P, 5 LP, 13 VUS, 1 B	7 P, 2 LP, 2 VUS
Other	2 P	1 VUS, 1 B

- 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.	Likely pathogenic PP4_Str., PM3, PP3, PM2_Supp.
GAMT	c.328G>T (p.Val110Phe)	Likely pathogenic PP4_Str., PP3, PS3_Supp., PM2_Supp., PM3_Supp.	Likely pathogenic 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.