Association for Creatine Deficiencies

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To provide patient, family, and public education, to advocate for early intervention through newborn screening, and to promote and fund medical research for treatments and cures for Cerebral Creatine Deficiency Syndromes (CCDS).

Cerebral Creatine Deficiency Syndromes (CCDS) are inherited metabolic disorders that interrupt the formation or transportation of creatine, resulting in language and motor delays, intellectual disability, behavioral problems, hypotonia and seizures. It is estimated that 1–3% of patients with intellectual disabilities of unknown origin may have Creatine Transporter Deficiency, though there are only a few hundred currently diagnosed cases worldwide. Most CCDS patients cannot lead an independent life.

Eight-year-old Louis, who has a GAMT deficiency — one of three cerebral creatine deficiency syndromes — takes medications four times per day. These treatments will allow him to live independently and avoid seizures and intellectual disabilities

During the Grant Period

Impact Spotlight

Since the discovery of Cerebral Creatine Deficiency Syndrome, Guanidinoacetate Methyltransferase (GAMT) deficiency in 1994, nutritional supplements have been the standard of care. Creatine supplements can be highly effective in improving symptoms like developmental delay, seizures, and behavioral issues, when started early in life. However, the supplements are not a cure for the disease, and significant damage can occur for patients who are not diagnosed and placed on supplements early in life.

Recognizing the critical importance of early diagnosis, Heidi Wallis and other leaders of the Association for Creatine Deficiencies (ACD) sprung into action. In May 2022, ACD's advocacy efforts, underway since 2016, were successful, when GAMT was endorsed by a review committee for addition to the Recommended Uniform Screening Panel (RUSP), a list of disorders that the Secretary of the Department of Health and Human Services (HHS) recommends states screen for as part of their state newborn screening programs. GAMT was officially added to the RUSP in January 2023.

ACD isn't stopping there. In February 2020, the organization launched a gene therapy consortium to facilitate the sharing of information and tools in order to shorten the timeline and effort required to develop gene therapy solutions for creatine deficiencies.

ACD also awarded four grants to researchers working to advance gene therapy over the following year. One grant was awarded to a researcher at UCLA to support efforts in gene therapy for GAMT deficiency. In June

2022, applying their gene therapy approach, the UCLA researcher demonstrated that they could increase creatine levels in mice that had been genetically modified to have GAMT deficiency to normal levels and restore their cognitive function.

Key research and research infrastructure achievements

- Launched the ACD-owned and -operated CreatineInfo Patient Registry and Natural History Study (120+ participants in first 7 months).
- In January 2023, held the CCDS Externally-Led Patient Focused Drug Development meeting, attended by more than 300 individuals worldwide.

Key publications

- *Molecular Therapy: Methods & Clinical Development* (2022): demonstrates via mouse model that a gene therapy for GAMT restored cerebral and myocardial creatine and resolved behavioral abnormalities (funded by the Association for Creatine Deficiencies; authors thank Executive Director Heidi Wallis for 'helpful discussions').
- *Molecular Genetics and Metabolism* (2021): a report on the first two cases of GAMT deficiency identified at birth by newborn screening in Utah (where newborn screening for GAMT began in 2015) and New York (where newborn screening for GAMT began in 2018); the publication preceded the addition of GAMT to the national RUSP in May 2022 (co-authored by Executive Director Heidi Wallis).

Key operational achievements

- Hired one full-time Executive Director and two part-time staff focused on patient registry development, social media and fundraising.
- Increased fundraising by 558% over grant period.

Key community achievements

Established a fellowship program to develop future generations of CCDS experts.

After the Grant

- In March 2023, ACD formed the Creatine Deficiency Research Center (CDRC) at the University of Utah and ARUP Laboratories, a collaboration of young researchers and seasoned experts. The first project is exploring whether delivery of AGAT and GAMT to neurons would allow for creatine synthesis within the brain, overcoming the creatine transporter deficiency (CTD) issues of crossing the blood brain barrier.
- In May 2024, ACD announced the first clinical drug trial available to its Creatine Transporter Deficiency community. The trial's priorities and outcomes were informed by ACD's Core Outcome Set (COS), a resource developed under the association's PCORI-funded project ,"**P**arents **A**dvancing **R**esearch **N**e**T**work**S**: **PAR**e**Nts**", to inform future GAMT and CTD clinical trials based on input and consensus from key stakeholders, including patients and parents. ACD began a second PCORI-funded project in September 2024, PAReNts 2.0: ExCiTE, to identify considerations needed for implementing the COS from the first grant.
- In March 2024, ACD announced funding of a research project to validate repurposable drug screening hits in human cells after a fellow's positive results in engineered cells during the RAO grant period.
- As of June 2024, The CCDS ClinGen Variant Curation Expert Panel, of which ACD is a part, has curated 181 variants including 72 variants in GAMT, 45 variants in GATM, and 64 variants in SLC6A8 and submitted these to ClinVar.

Heidi Wallis, Executive Director of the Association for Creatine Deficiencies, speaks about the organization's work to advance policies and systemic approaches to scaling genetic diagnosis at the Chan Zuckerberg Initiative Science in Society 2024 Meeting.

"Since 2020, when we received the CZI Rare As One grant, research into Cerebral Creatine Deficiency Syndromes (CCDS) has made remarkable strides. After nine years with ACD, I can confidently say this progress has been transformational for our rare disease group. Our community now has so much more hope and opportunity, with truly positive developments on the horizon. Not only is ACD at the forefront, regularly involved in pivotal collaborations with researchers, but we are helping lead the charge for change. The RAO grant was a game-changer for us, having an enduring and profound impact on CCDS families — an impact that cannot be overstated."

Heidi Wallis
Executive Director, Association for Creatine Deficiencies