CreatineINFO™

Patient Registry Annual Report 2025

ACD
ASSOCIATION FOR CREATINE DEFICIENCIES

Data Source

The data in this report were collected from the CreatineINFO Patient Registry & Natural History Study. It consists of patient- and caregiver-reported data from participants with cerebral creatine deficiency syndromes (CCDS).

The CreatineINFO Patient Registry is sponsored and managed by the Association for Creatine Deficiencies (ACD), hosted on the National Organization for Rare Disorders (NORD®) IAMRARE® registry platform. It has Institutional Review Board (IRB) approval from North Star Review Board.

Data in this report are current as of December 31, 2025. There are currently 207 participants consented in the registry.

Data Reporting

Each graph, table, and/or statistic includes the number of participants ("*n*") who provided information to analyze. Reported percentages (%) are based on the number of participants included in each data element, unless otherwise specified.

In certain situations, identified on a case-by-case basis, we adhered to a small cell size suppression policy to reduce potential identification of individual participants. In other words, we have not shown data that greatly increases the chances of a particular individual being identified.

As a rare disease community, a common challenge we face is small sample sizes. Data collected from a small group of participants may not represent the experiences of the entire population. This is particularly true when we look at sub-populations (e.g., females with CTD, participants with a specific genetic mutation). For this reason, we advise caution when interpreting data in this report.

Acknowledgments

We thank the CCDS patients and their caregivers who participate in the CreatineINFO Registry and generously share their information and experiences with the registry. Their voices drive CCDS research towards curing creatine deficiencies.

We also thank members of ACD's Registry Oversight, Registry Advisory, and Family Advisory boards who contribute their time and expertise to the development and maintenance of the CreatineINFO Patient Registry.

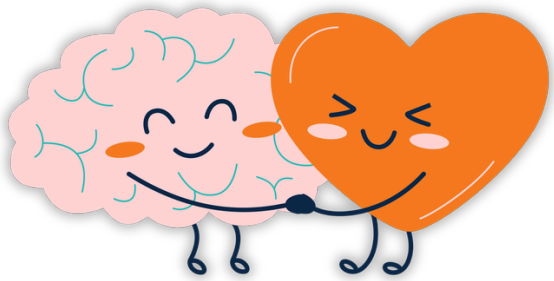
Thank you to Jennifer Goldstein, PhD, CGC, Juliann Savatt, MS, CGC, and Caitlin Cooney, MS, CGC, for their guidance on the genetic analyses in this report. Additionally, thank you to Andrew Marshall, PhD, for his assistance with general data analysis and visualization.

Additional Resources

This report can be downloaded at https://creatineinfo.org/creatineinfo-registry.

To enroll in the CreatineINFO Registry, visit https://creatineinfo.iamrare.org.

For more information about the patient registry, email registry@creatineinfo.org.



The Association for Creatine Deficiencies

History

The Association for Creatine Deficiencies (ACD) was established in 2012, by parents of children diagnosed with a cerebral creatine deficiency syndrome (CCDS) that decided a rare disease needs a unified community to effect change for the future. The ACD Board consists of unpaid CCDS parents.

Mission

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 CCDS.

Vision of the Future

Our vision is to have effective treatments and newborn screening for all three CCDS while providing community support. In this future, the rare disease diagnostic odyssey changes from seven years to seven days to treatment, and all CCDS patients achieve their potential.

CCDS community, friends, and supporters

We are pleased to present the 2025 CreatineINFO Patient Registry Annual Report. Since its launch in 2021, the CreatineINFO Patient Registry & Natural History Study has enrolled more than 200 individuals affected by Cerebral Creatine Deficiency Syndromes (CCDS) and remains the only CCDS registry based on patient- and caregiver-reported data. The registry's mission is to collect comprehensive information on the health, lived experiences, and disease progression of individuals with CCDS in order to deepen understanding of these conditions and support the identification of effective treatments.

This Annual Report highlights the valuable data generously contributed by CCDS patients and families. It showcases the progress achieved since the registry's inception and summarizes select insights currently available. We hope this report will inform our community, encourage research partnerships, and contribute to the advancement of therapeutic development.

We trust that this report will be both informative and thought-provoking, underscoring the critical role of patient- and caregiver-reported data within the CCDS community. We believe that this is a pivotal moment for CCDS research, with significant progress underway in gene therapies, small-molecule development, drug repurposing, and newborn screening initiatives.

This work would not be possible without the dedication of the CCDS community. We extend our sincere thanks to the patients and caregivers who generously share their experiences and information. Their participation is the foundation of this effort, and this report reflects their commitment to advancing CCDS research.

Emily Reinhardt, MS
Patient Registry Coordinator

Heidi Wallis
Executive Director

Sangeetha Iyer, PhD
Director of Research

Table of Contents

ACD
ASSOCIATION FOR CREATINE DEFICIENCIES

CREATINEINFO BASICS

Our History & Objectives

ACD launched the CreatineINFO Patient Registry & Natural History Study in 2021 to advance research for cerebral creatine deficiency syndromes (CCDS). This patient- and caregiver-reported registry is the only known patient registry for CCDS.

CreatineINFO Patient Registry Objectives

Improve understanding of the natural history and impact of CCDS in patients' lives

Share community-reported recommendations and standards of care

Assist ACD with representing the CCDS community accurately

Provide valuable information to doctors, scientists, and industry leaders to help develop treatments and improve patient outcomes for the CCDS community

CREATINEINFO BASICS

Registry Surveys & Oversight

The CreatineINFO Registry collects information about socio-demographics, medical history, disease progression, management of care, quality of life, and genetic and laboratory reports for patients diagnosed with a CCDS.

There are currently **seven participant/caregiver surveys** to collect information about the participant's experience with CCDS.

1. *Getting Started (Which CCDS does the participant have?)*
2. *Participant Demographics*
3. *Diagnosis*
4. *Cardiovascular Health*
5. *Oral Medication Preferences*
6. *Medical Notes*
7. *Clinical Research ID (CRID)* - ***New for 2025!***

Registry Oversight

The registry is approved and overseen by an independent **Institutional Review Board (IRB)**, whose responsibility is to assure the protection of the rights and welfare of participants in the the registry. North Star Review Board serves as the independent IRB for the CreatineINFO Patient Registry.

ACD's **Registry Oversight Board** oversees the conduct of the registry study and includes scientists, doctors, and patient advocates. They advise on the development of surveys and review combined registry data. They ensure proper evaluation of all research requests for use of the registry data.

CREATINEINFO BASICS

2025 Highlights

CreatineINFO successfully migrated to the National Organization for Rare Disorders (NORD) **updated IAMRARE registry platform**.

ACD curated **19 unique CCDS genetic reports** within CreatineINFO. The de-identified data were shared with the ClinVar Genetic Database.

ACD launched the **Clinical Research Identification (CRID) survey**. This survey collects a participant's personal unique identification code to link available clinical and registry data to their biological samples in the future.

CreatineINFO **data were published** in three peer-reviewed scientific publications.

> Orphanet J Rare Dis. 2025 Aug 7;20(1):408. doi: 10.1186/s13023-025-03900-3.

Establishing a core outcome set for creatine transporter deficiency and guanidinoacetate methyltransferase deficiency

Zahra Nasseri Moghaddam [# 1], Emily K Reinhardt [# 2], Audrey Thurm [3], Beth K Potter [4], Maureen Smith [5], Celeste Graham [6 7], Beth H Tiller [7], Steven A Baker [8], Deborah A Bilder [9], Regina Bogar [7], Jacobus Britz [7], Rachel Cafferty [7], Daniel P Coller [6 7], Ton J DeGrauw [10], Vicky Hall [7], Gerald S Lipshutz [11], Nicola Longo [10 11], Saadet Mercimek-Andrews [10 12], Judith S Miller [13], Marzia Pasquali [10 14], Gajja S Salomons [10 15], Andreas Schulze [10 16], Celine P Wheaton [7], Kayla F Williams [7], Sarah P Young [10 17], Jasmine Li [1], Sofia Balog [6 18], Theresa Selucky [19], Sylvia Stöckler-Ipsiroglu [# 1 10 20], Heidi Wallis [# 6 7]

Affiliations + expand

PMID: 40775643 PMCID: PMC12333098 DOI: 10.1186/s13023-025-03900-3

> Front Neurosci. 2025 Feb 25:19:1548182. doi: 10.3389/fnins.2025.1548182. eCollection 2025.

How a patient-led advocacy organization supports the road to diagnosis and treatment of creatine transporter deficiency

Heidi Wallis [# 1], Sangeetha Iyer [# 1], Emily K Reinhardt [1]

Affiliations + expand

PMID: 40078706 PMCID: PMC11897708 DOI: 10.3389/fnins.2025.1548182

> HGG Adv. 2025 Oct 9;6(4):100489. doi: 10.1016/j.xhgg.2025.100489. Epub 2025 Aug 7.

Evaluation of SLC6A8 species conservation and the effect of pathogenic variants on creatine transport

Taryn Diep [1], Gerald S Lipshutz [2]

Affiliations + expand

PMID: 40781773 PMCID: PMC12398244 DOI: 10.1016/j.xhgg.2025.100489

Meet our CreatineINFO Community

We asked caregivers to share a little bit about their child(ren)'s personality and favorite things to do.

> **"Full of life and mischief. He loves playing in water and being outside."**
> - Mother of son with GAMT

> **"Le gusta bailar, nadar. Es un niño amable, sociable, y muy sentimental."**
> - Mother of son with CTD

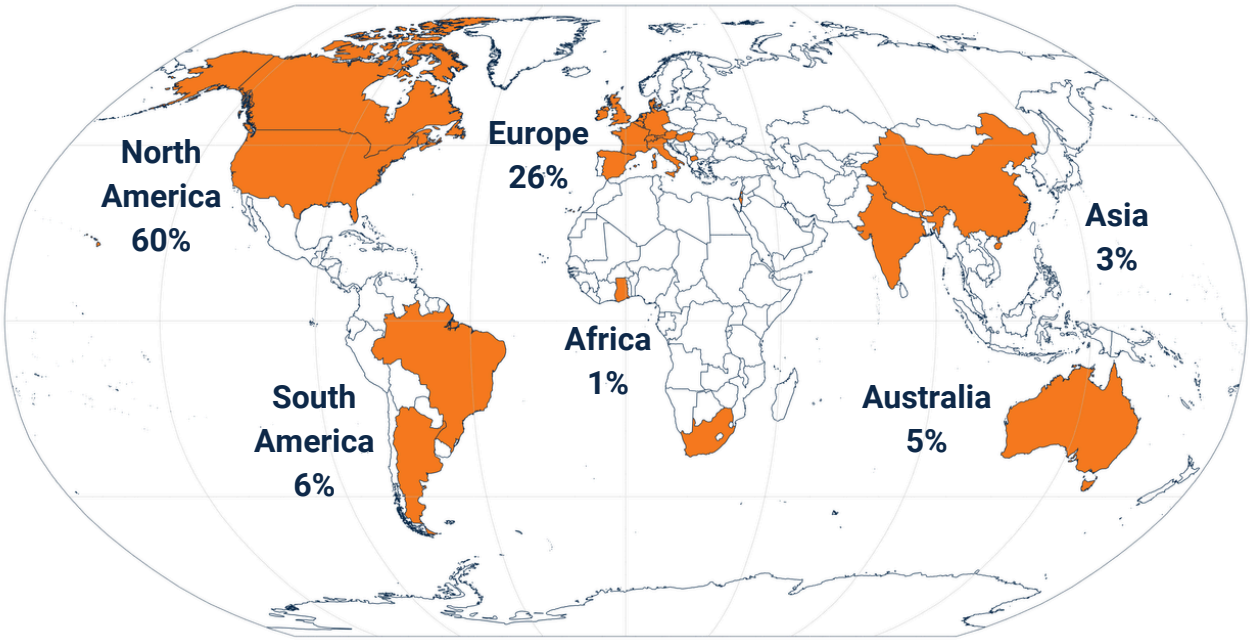
> **"She is happy, funny, hard working. She is emotional and tender. She is very proud of how hard she works."** - Mother of daughter with CTD

> **"Loving cheeky boy with great sense of humour."** - Mother of son with CTD

> **"Ela gosta muito de dançar."**
> - Father of daughter with GAMT

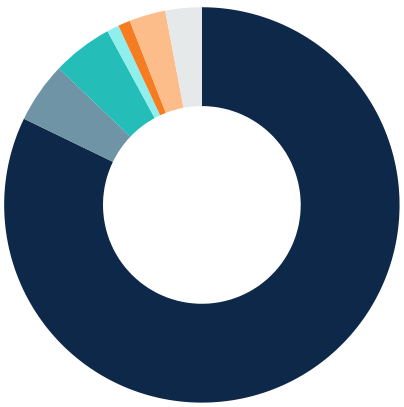
CCDS Around the World

CCDS occurs worldwide, with current estimations likely underscoring the global prevalance of these disorders. CreatineINFO registry participants represent **25 different countries** and every inhabited continent (*n*=172).



Our goal is to improve global CCDS representation in the registry to accurately reflect patient experiences. We will accomplish this by:

1) Translating the registry into **multiple languages**;
2) Partnering with our Global Ambassadors to increase **local community engagement**;
3) Advocating for **newborn screening globally.**



Race of the CreatineINFO Registry Participants (*n*=155)

- White (83%)
- Asian (5%)
- Multiracial (5%)
- Hispanic/Latino (1%)
- Middle Eastern/North African (1%)
- Other (3%)
- Not specified (2%)

AGAT DEFICIENCY

Overview & Demographics

L-Arginine:glycine amidinotransferase (AGAT) deficiency is an inherited autosomal recessive disorder. Mutations found in the *GATM* gene result in AGAT deficiency. Patients with AGAT do not make the AGAT enzyme, which is the first step in producing creatine. Therefore, patients are unable to make the creatine their brains and bodies need for energy.[1]

AGAT patients typically have less severe symptoms in comparison to GAMT and CTD patients because they have **functioning creatine transporters** to utilize creatine found naturally in the diet, and they do **not have a buildup of guanidinoacetate (GAA)**.[2]

Treatment with **oral supplementation of creatine monohydrate** is effective in replenishing the body's needed creatine supply and greatly improves outcomes if initiated early for AGAT patients. Diet restrictions are not typically recommended for AGAT patients.[2]

AGAT deficiency is the rarest of all three CCDS, with only a few dozen known cases worldwide. **Only 1% of registry participants have AGAT deficiency.**

Do you or someone you know have AGAT? Please join the registry and complete the surveys so we can learn more about AGAT to support treatment for this ultra rare disorder!

GAMT DEFICIENCY

Overview

Guanidinoacetate methyltransferase (GAMT) deficiency is an autosomal recessive disorder caused by a mutation in the *GAMT* gene. Due to a lack of the GAMT enzyme, patients with GAMT are unable to break down guanidinoacetate (GAA) formed in the first step of creating creatine, which means they are **unable to make creatine**.[3] This also results in a **buildup of GAA**, which is believed to be toxic to the brain at high levels.[4-5]

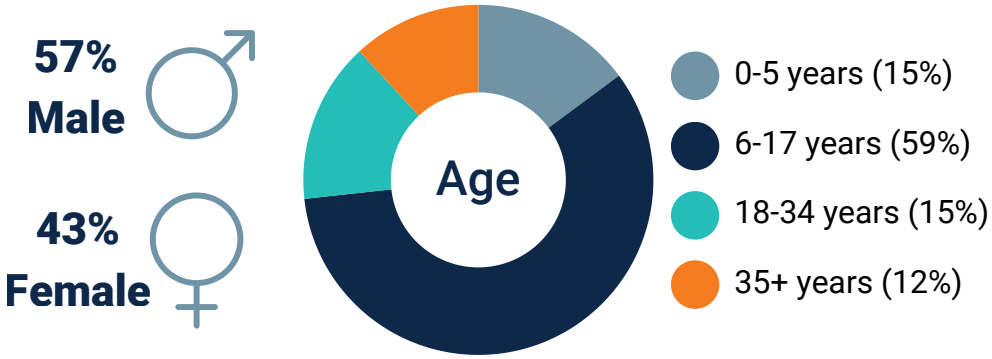
GAMT severity differs among patients, with **global developmental delays** being an early and common sign. Most individuals experience **intellectual disabilities, seizures, muscle weakness, behavioral issues, and movement disorders**. Delayed motor skill development, such as sitting or walking, is common, and severely affected patients may lose previously learned abilities like head control or sitting independently.[6-7]

Treatment is aimed at reducing GAA production and supplying the creatine that is not produced by the body. Patients are typically prescribed **oral supplements of creatine monohydrate and l-ornithine**. Some physicians also recommend **diet restrictions** and **sodium benzoate supplementation** to further minimize GAA accumulation.[8-9]

GAMT DEFICIENCY

Demographics

Current prevalence estimates suggest that 1:500,000 people have GAMT deficiency.[10] In the CreatineINFO Registry, **GAMT participants account for approximately 22% (*n*=36) of registry participants**.

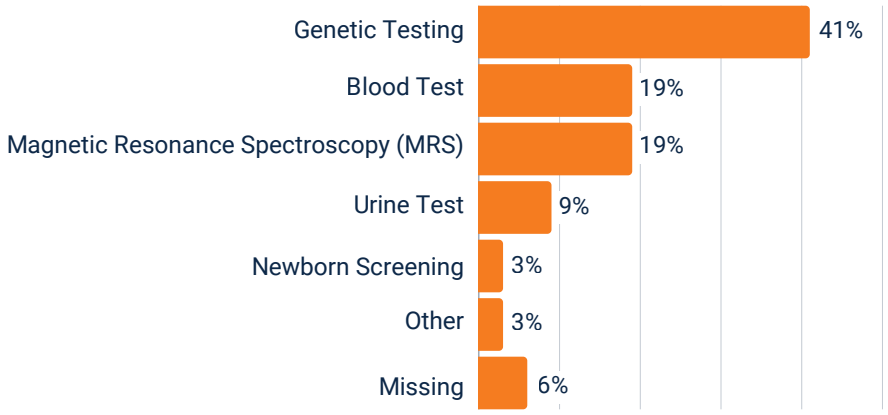


34 GAMT participants contributed to these analyses.

The majority of GAMT participants are between 6-17 years old.

Early detection of GAMT is paramount, as timely intervention can significantly enhance treatment efficacy and patient outcomes. **Genetic testing was the most commonly reported diagnostic test that first indicated a creatine diagnosis (41%).** However, we are hopeful that the addition of GAMT to the U.S. Recommended Uniform Screening Panel (RUSP) will result in more GAMT patients being diagnosed at birth via newborn screening.[11]

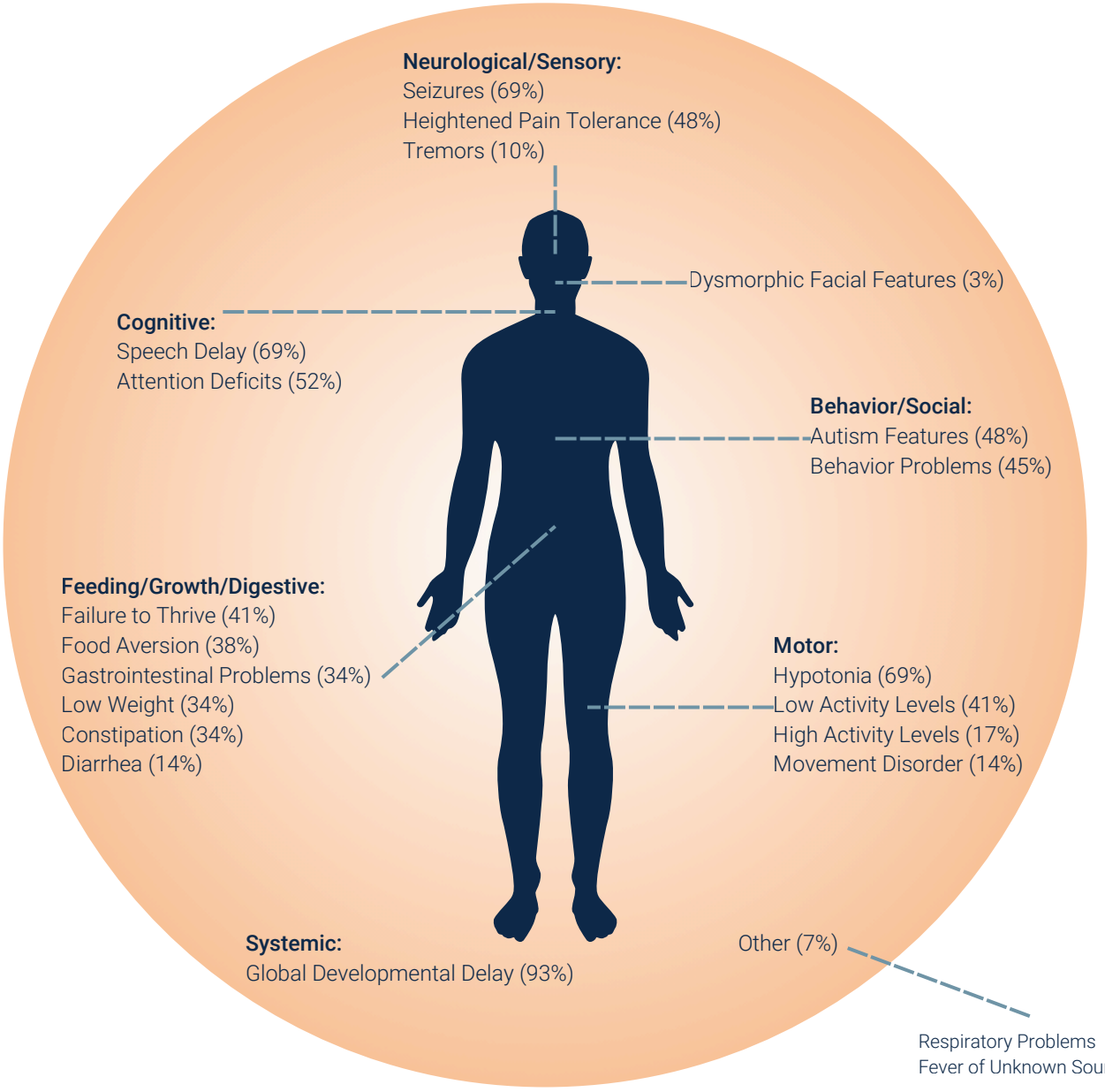
Which test first indicated a creatine deficiency? (*n*=32)



GAMT DEFICIENCY

Symptoms

Patients with GAMT deficiency may develop a range of symptoms. We asked caregivers to identify which symptoms participants exhibited prior to their GAMT diagnosis. The most commonly reported symptoms among GAMT participants (*n*=29) who were diagnosed anytime after the first month of life were: **global developmental delay (93% of participants), hypotonia (69%), seizures (69%),** and **speech delay (69%).**

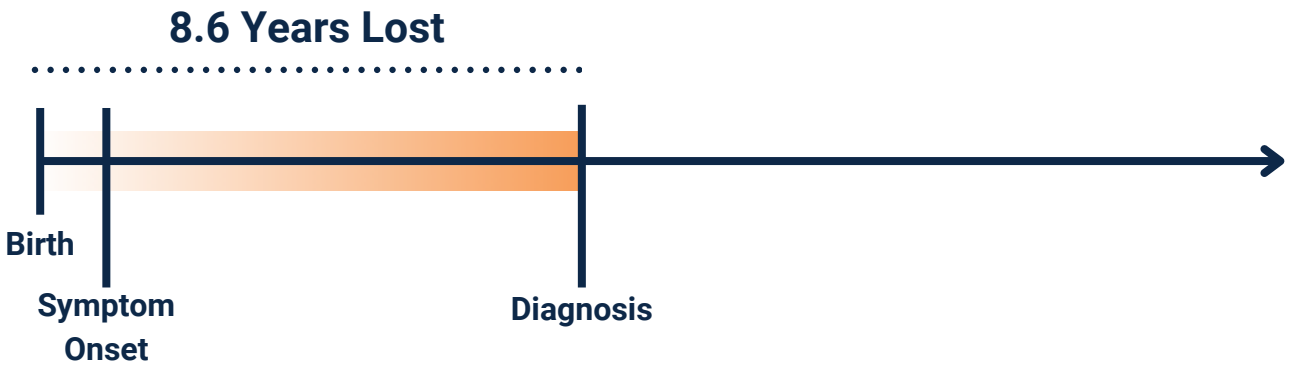


GAMT participants who were diagnosed within the first month of life do not report the majority of these symptoms and were therefore excluded from these analyses (n=3).

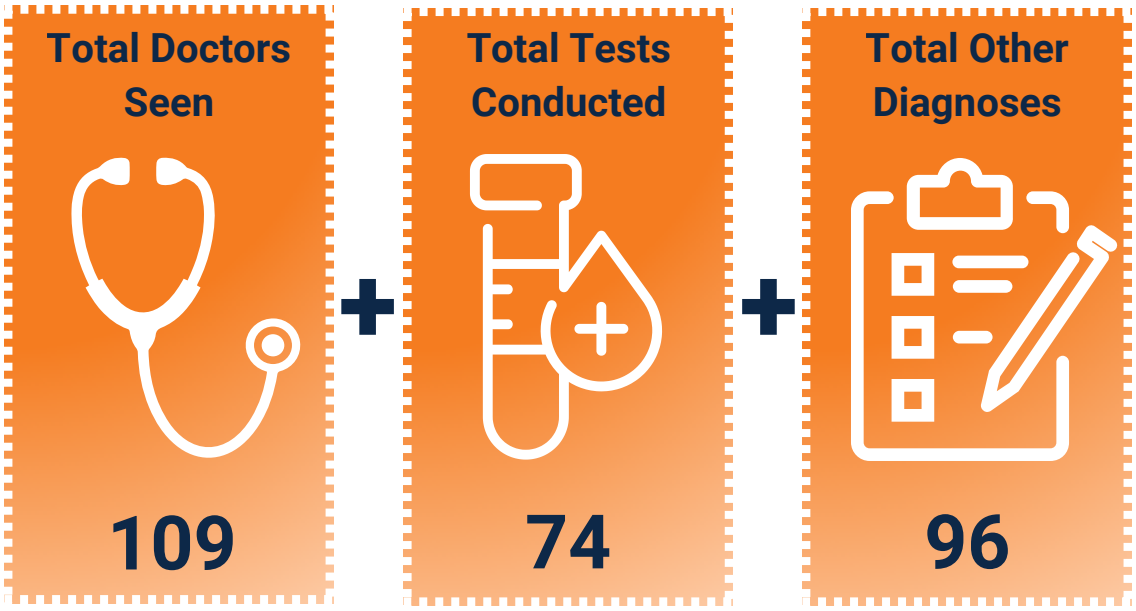
GAMT DEFICIENCY

Time Lost Searching for a Diagnosis

Because GAMT is so rare, most doctors are not aware of the disorder and do not know what symptoms to look for. Despite first showing **symptoms at an average of 10.7 months**, it took GAMT participants (*n*=28), on average, an **additional 7.8 years to receive a diagnosis**.



Time is not the only resource that is lost when families are searching for a GAMT diagnosis. We asked caregivers to identify the various **doctors** the participant saw, the **tests** that were conducted, and any other **diagnoses** the participant received prior to finally being diagnosed with GAMT. The values below reflect the cumulative totals among GAMT participants (*n*=29).



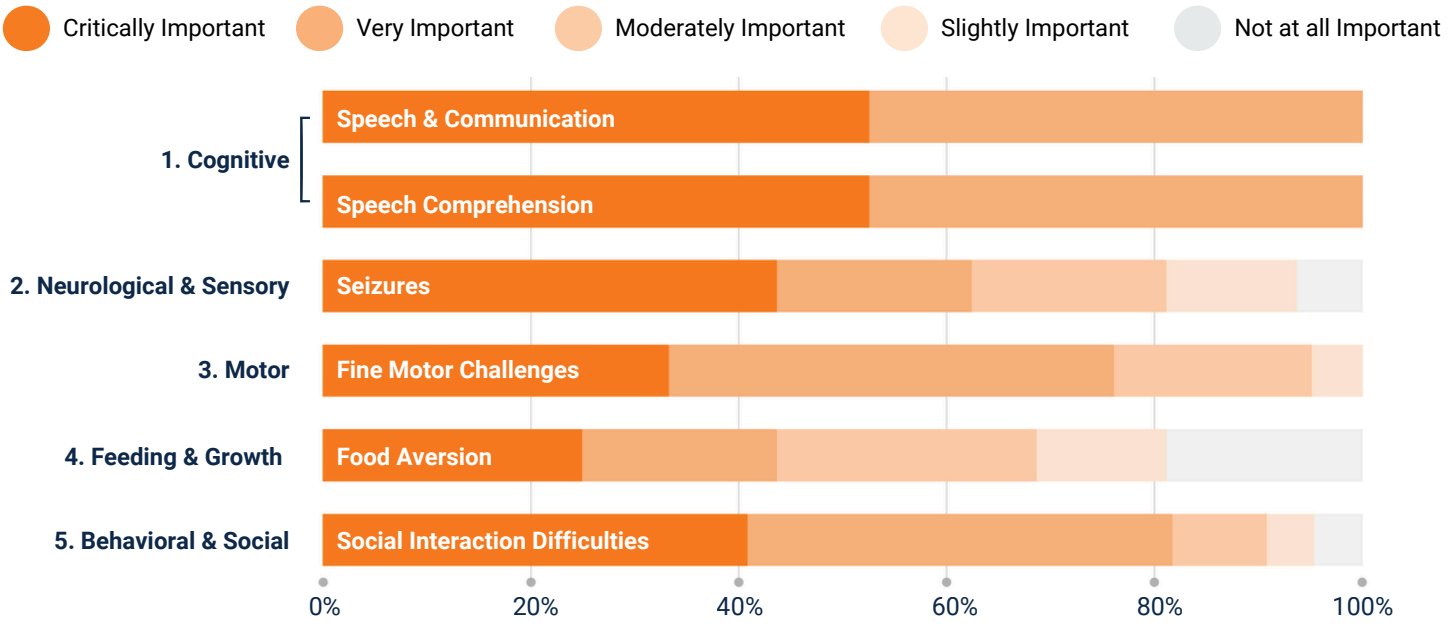
GAMT participants who were diagnosed within the first month of life were excluded from these analyses (n=3).

GAMT DEFICIENCY

Patient Meaningful Outcomes

Treatments are developed and tested by researchers to make sure they work and are safe. To do this, researchers examine the effects those treatments have on patients by looking at outcomes. It is important that the outcomes researchers choose to study in clinical trials are meaningful to patients and caregivers.[12-13]

GAMT participants were shown a list of 24 outcomes and asked to **rate how important each outcome was to them, such that an improvement in an outcome would have a meaningful impact on the participant and their family**. Outcomes were organized into **five groups** in the survey. The outcome rated the most important in each group is shown below (*n*'s=16-22).



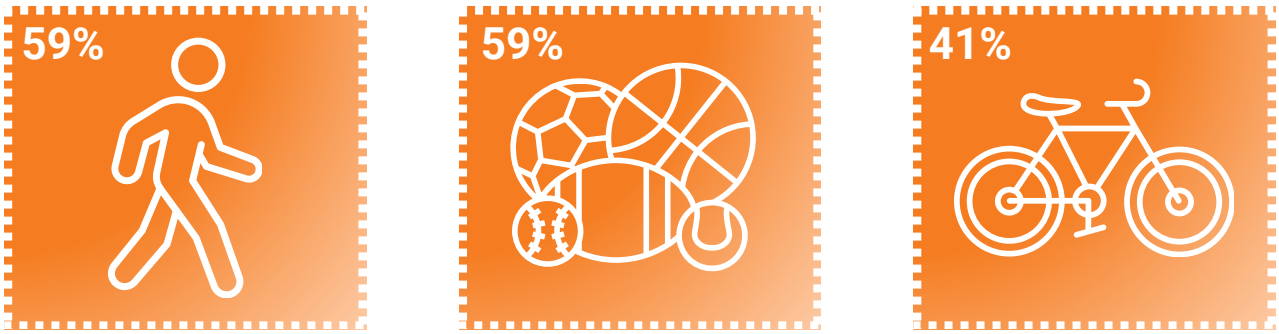
We also asked participants (*n*=23) to **rank their top 5 most important outcomes** that they would like to see improved. The following outcomes were the highest ranked outcomes:

GAMT participants who were diagnosed within the first month of life were excluded from these analyses (n=3).

GAMT DEFICIENCY

Cardiovascular Health

We asked GAMT participants (*n*=14) what physical activities they do to stay active. The top 3 reported activities were **walking, playing a sport,** and **bike/scooter riding**!



While researchers have found that CTD patients may have an increased risk of developing a heart condition called prolonged QTc,[14] it is unclear if GAMT patients are at a similar risk. Therefore, we asked GAMT participants (*n*=14) which heart conditions (if any) they have ever experienced. **The majority (86%) of GAMT participants reported no heart conditions.** Interestingly, **half (50%) of GAMT participants have been seen by a cardiologist**.

- No heart conditions (86%)
- Do not know (14%)

50% of GAMT participants have seen a cardiologist

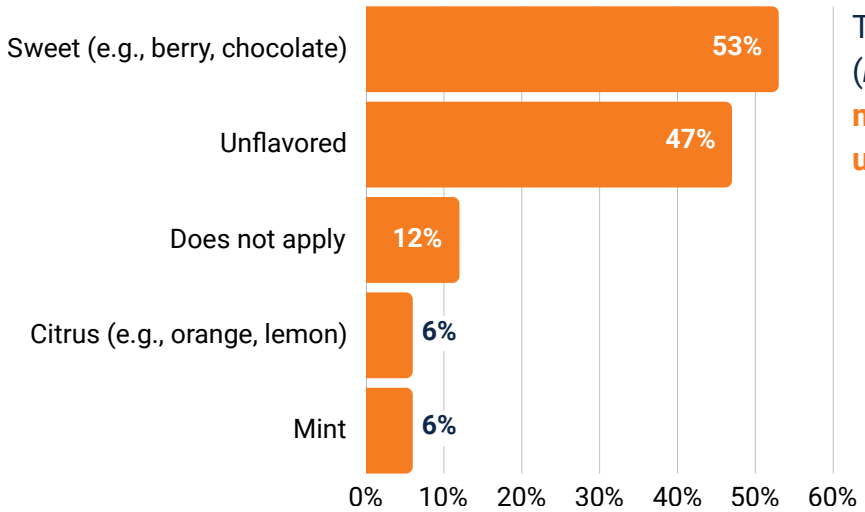
GAMT participants who were diagnosed within the first month of life were excluded from these analyses (n=3).

GAMT DEFICIENCY

Oral Medication Preferences

Taking supplements and medications can be challenging for many GAMT patients. Some GAMT supplements are especially difficult because they have an unpleasant flavor. So, we asked caregivers **what foods and liquids they use to help GAMT participants (*n*=17) successfully take their medicines and supplements**. While water, applesauce, and yogurt were the most popular choices, there were a variety of responses.

We also asked caregivers what attributes of an oral medication are the most important for GAMT participants (*n*=17) to consistently take their medications. Overwhelmingly, the top two most important attributes of a medication were **having a neutral or desirable taste (88%)** and having a **manageable volume or quantity of dose (71%)**.



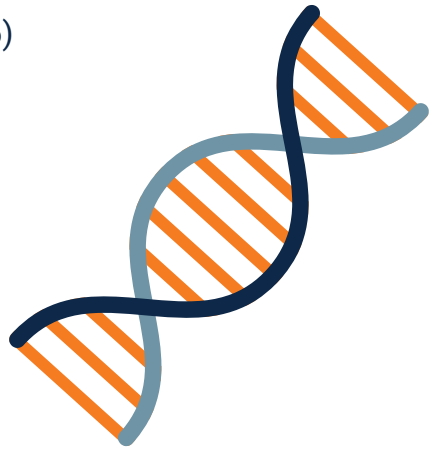
The majority of GAMT participants (*n*=17) prefer **sweet-flavored medication (53%)**, followed by **unflavored medication (47%)**.

GAMT DEFICIENCY

GAMT Variants in CreatineINFO

18 GAMT participants have generously shared their genetic information with the registry. Among these participants, there are currently **13 unique *GAMT* genetic variants** which are classified as pathogenic, likely pathogenic, or a variant of uncertain significance (VUS).

1. NM_000156.4:c.1A>G (p.Met1?)
2. NM_000156.6:c.59G>C (p.Trp20Ser)
3. NM_000156.6:c.145del (p.Tyr49IlefsTer?)
4. NM_000156.6:c.233T>A (p.Val78Glu)
5. NM_000156.6:c.299_311dup (p.Arg105GlyfsTer26)
6. NM_000156.6:c.316C>T (p.Gln106Ter)
7. NM_000156.6:c.327G>A (p.Lys109=)
8. NM_000156.4:c.328G>T (p.Val110Phe)
9. NM_000156.6:c.407C>T (p.Thr136Met)
10. NM_000156.6:c.491dup (p.Val165ArgfsTer26)
11. NM_000156.6:c.505T>C (p.Cys169Arg)
12. NM_000156.6:c.522G>A (p.Trp174Ter)
13. NM_000156.6(GAMT):c.570+1G>A



Some variants in this list are classified as a variant of uncertain significance (VUS), meaning that additional clinical data are required in order to confirm disease pathogenicity. Genetic information is collected from patient reports. Some reports provide more information than others. While information is cross-referenced with the ClinGen Allele Registry, some information may be missing.[15] *Please contact ACD at registry@creatineinfo.org if you are interested in learning more about these variants.*

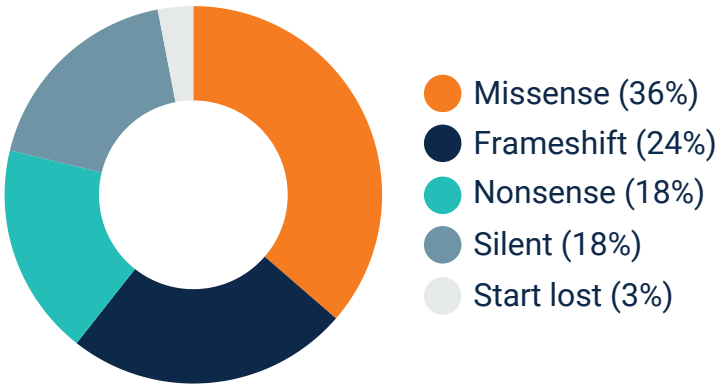
GAMT DEFICIENCY

Genetics at a Glance

GAMT deficiency is an autosomal recessive disorder, meaning that patients inherit two mutated variants of the *GAMT* gene (one from each parent). Patients can receive two different variants (compound heterozygous) or the same variant from each parent (homozygous). **The majority of reported *GAMT* variants were compound heterozygous (91%) instead of homozygous (9%).**

Among the compound heterozygous *GAMT* variants, only **47% were confirmed as trans** (located on different chromosomes).

The type of *GAMT* variant a patient has determines the effect on the GAMT enzyme. Knowing these variant types may help researchers develop treatments that target different types of mutated GAMT enzymes. **The two most reported *GAMT* variants were missense (36%) and frameshift (24%)**.



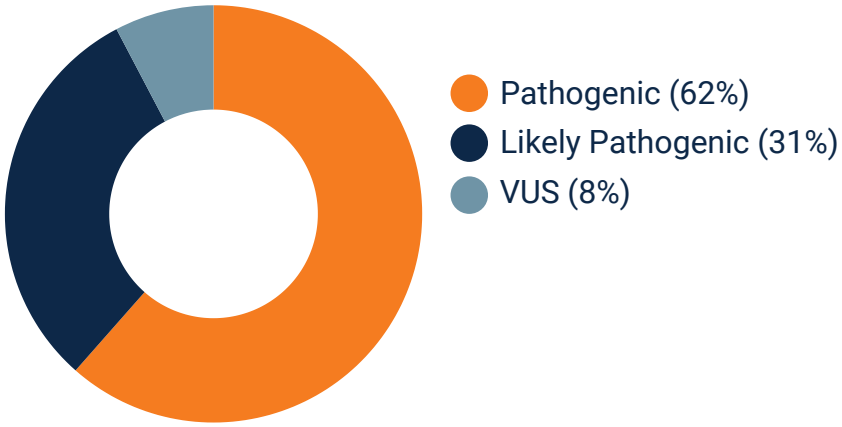
18 GAMT participants were included in these analyses. Genetic information is collected from patient reports. Some reports provide more information than others. Please contact ACD at registry@creatineinfo.org if you are interested in learning more.

GAMT DEFICIENCY

Genetics at a Glance

Genetic variants are classified into categories which identify whether that variant is disease-causing or harmless. These categories help doctors provide accurate diagnoses, guide patient treatment, and assess risks for family members.

1. **Benign & Likely Benign** = Variant is not known to cause any significant health or developmental differences
2. **Variant of Uncertain Significance (VUS)** = The variant's effect is unknown; additional information is required
3. **Pathogenic & Likely Pathogenic** = The variant is known to be disease-causing



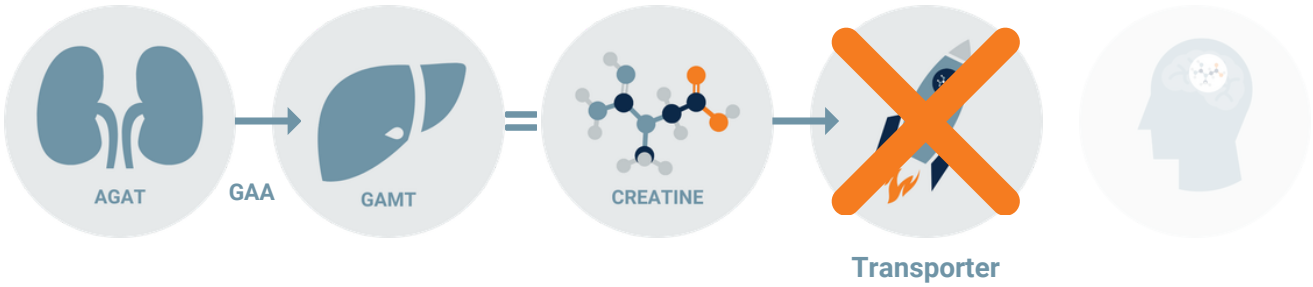
The majority (93%) of unique *GAMT* variants reported were classified as Pathogenic or Likely Pathogenic.

18 GAMT participants were included in these analyses. Genetic information is collected from patient reports. Some reports provide more information than others. Please contact ACD at registry@creatineinfo.org if you are interested in learning more.

CREATINE TRANSPORTER DEFICIENCY

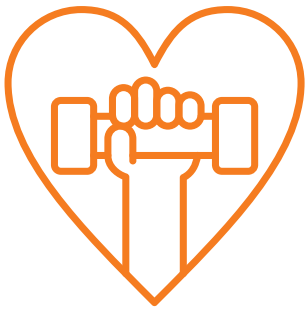
Overview

Creatine transporter deficiency (CTD) is an X-linked inborn error of metabolism, caused by a mutation in the SLC6A8 gene. The mutation impairs the creatine transporter. While patients with CTD are able to make creatine, they cannot move it from the bloodstream into the brain and muscles where it is needed.[16]



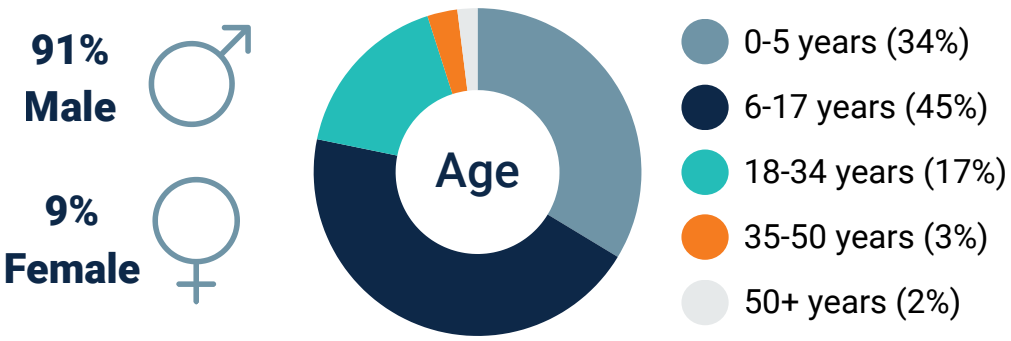
CTD severity varies by patient, with **global developmental delays** often appearing first. Common features include **intellectual disability, speech and language delays, autistic behavior,** and **seizures**. Additional symptoms may include muscle weakness, hyperactivity, behavior issues, gastrointestinal problems, slow growth, delayed motor skills, and fatigue.[6-7]

There are no currently approved treatments for CTD. However, **early therapeutic intervention** (e.g., speech, physical, occupational) and prescribed supplementation of **creatine monohydrate, l-arginine, and glycine** may be beneficial for some patients.[17]



Demographics

CTD is the most common of the three CCDS, with current prevalence estimates indicating that 1:200,000 people have CTD.[18] In the CreatineINFO Registry, **CTD participants account for approximately 77% (*n*=129) of registry participants**.



120 CTD participants contributed to these analyses.

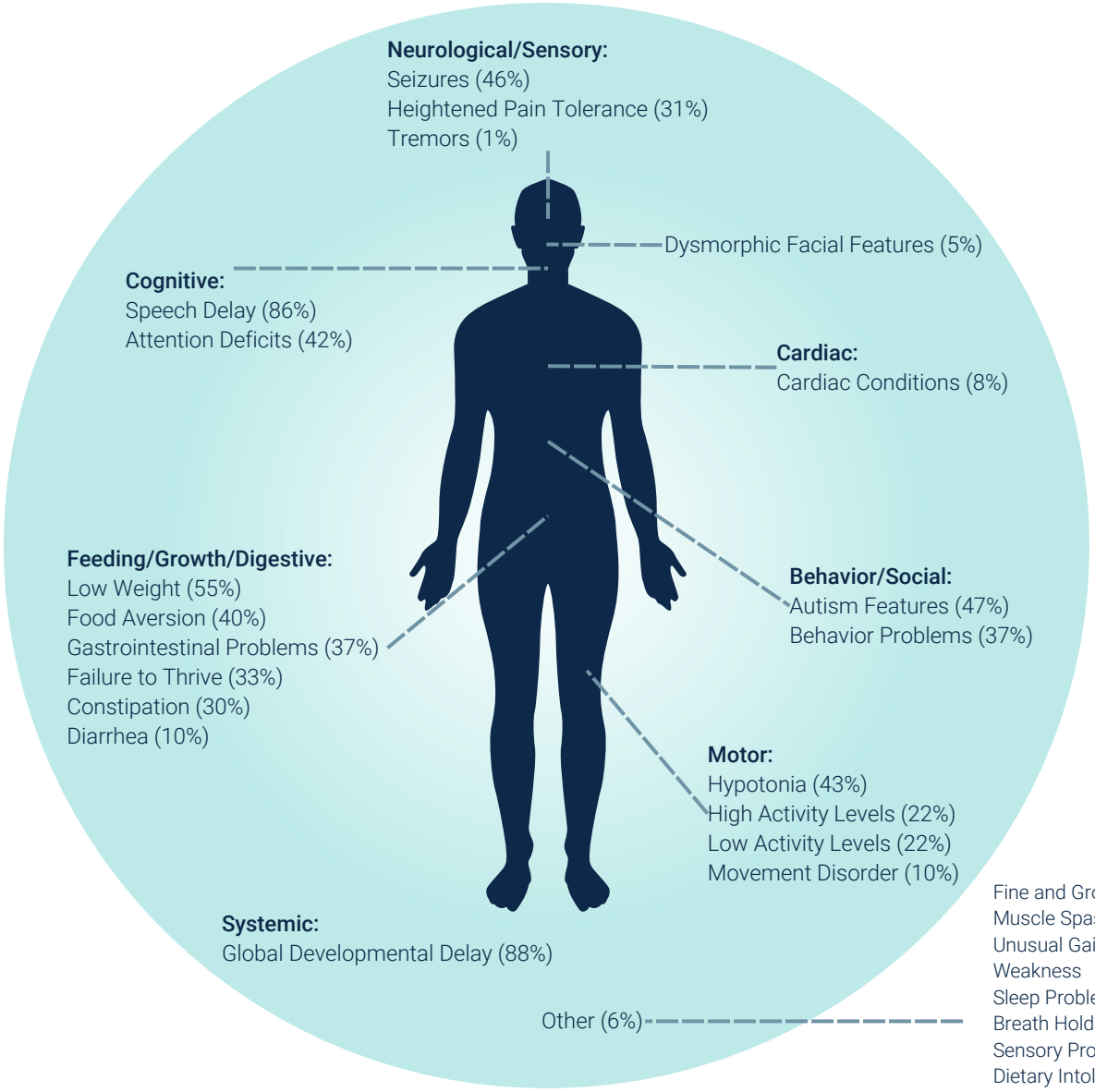
Women and girls with CTD are underdiagnosed and underrepresented.

Since CTD is an X-linked disorder, most of what we know from the literature is based on males with CTD.[19] **Females with CTD have been reported to show less severe symptoms, however this is not always the case.**[20]

To best capture the experiences of females and males with CTD in the registry, some analyses in this report analyzed these two groups separately. **Data exclusively from males with CTD can be found on pages 25-28 and data exclusively from females with CTD can be found on pages 30-31.**

Symptoms

Male patients with CTD deficiency develop a broad range of symptoms. We asked caregivers to identify which symptoms participants exhibited prior to their CTD diagnosis. The most commonly reported symptoms among male CTD participants (*n*=97) were: **global developmental delay (88% of participants), speech delay (86%), low weight (55%), and autism features (47%).**

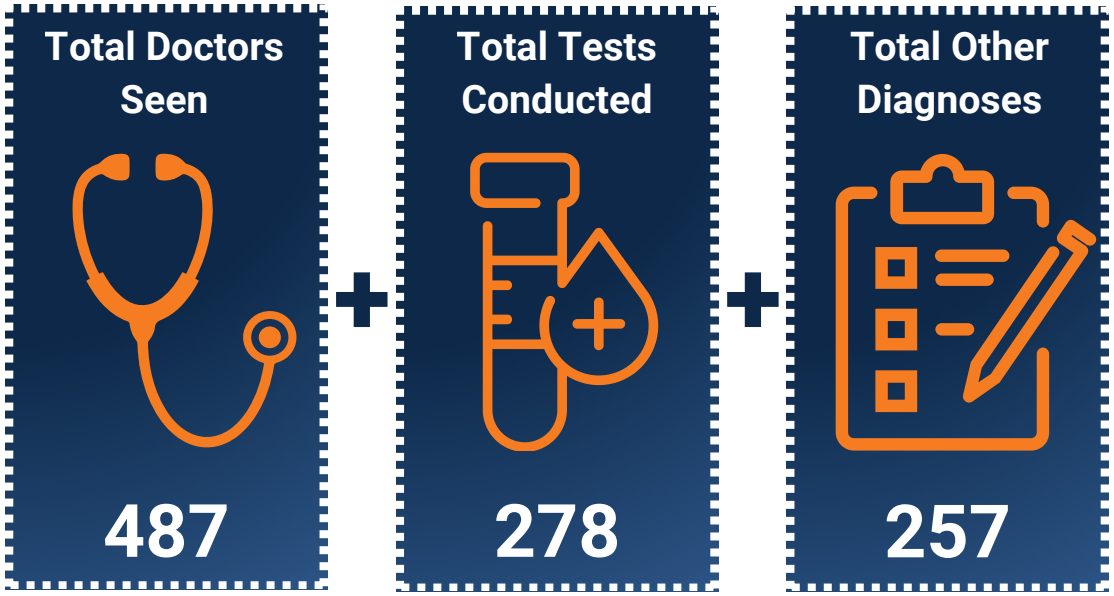


Only males with CTD were included in these analyses. For more information about females with CTD, refer to pages 30-31.

Time Lost Searching for a Diagnosis

Most doctors are not familiar with CTD and are not aware of what symptoms to look for. Despite first showing **symptoms at an average of 11.7 months**, it took male CTD participants (*n*=92), on average, an **additional 3.7 years to receive a diagnosis**.

Time is not the only resource that is lost when families are searching for a CTD diagnosis. We asked caregivers to identify the various doctors the participant saw, the tests that were conducted, and any other diagnoses the participant received prior to finally being diagnosed with CTD. The numbers below reflect the cumulative totals among male CTD participants (*n*=97).

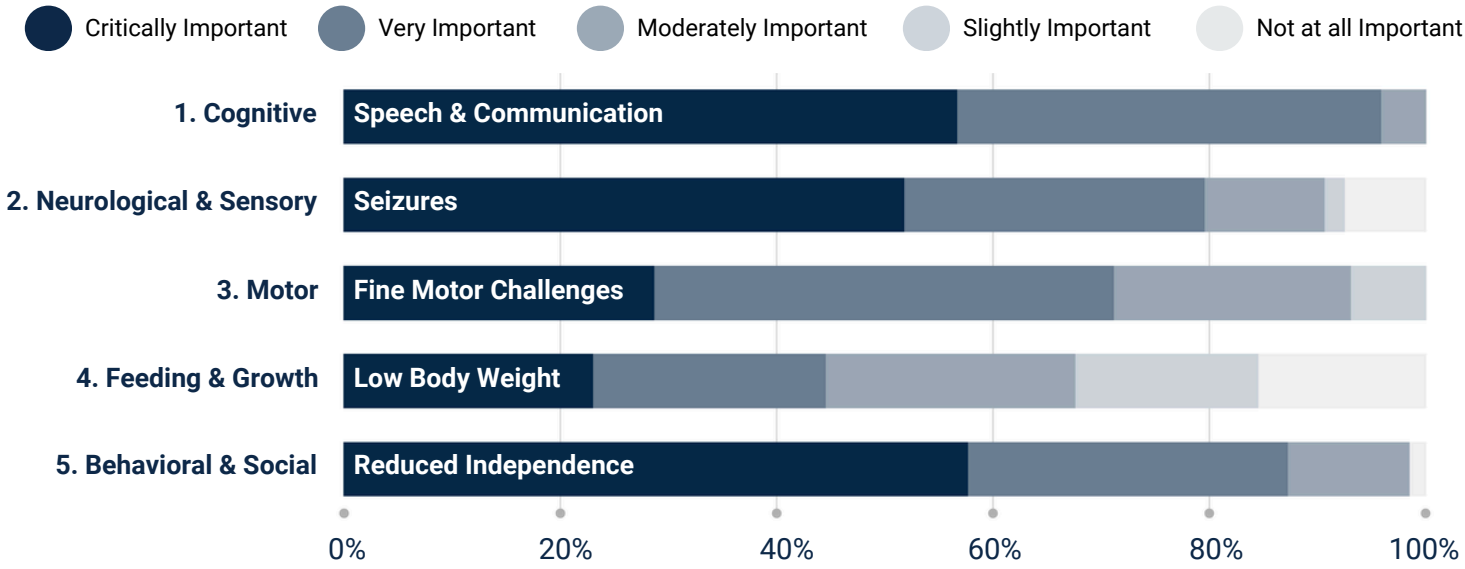


Only males with CTD were included in these analyses. For more information about females with CTD, refer to pages 30-31.

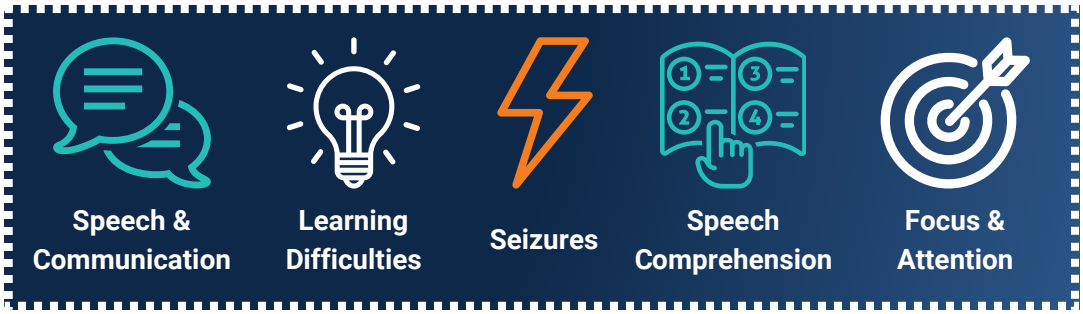
Patient Meaningful Outcomes

Treatments are developed and tested by researchers to make sure they work and are safe. To do this, researchers examine the effects those treatments have on patients by looking at outcomes. It is vital that the outcomes researchers choose to study in clinical trials are meaningful to patients and caregivers.[12-13]

Male CTD participants were shown a list of 24 outcomes and asked to **rate how important each outcome was to them, such that an improvement in an outcome would have a meaningful impact on the participant and their family**. Outcomes were organized into **five groups** in the survey. The outcome rated the most important in each group is shown below (*n*'s=54-74).



We also asked male participants (*n*=76) to **rank their top 5 most important outcomes** that they would like to see improved. The following outcomes were the highest ranked outcomes:



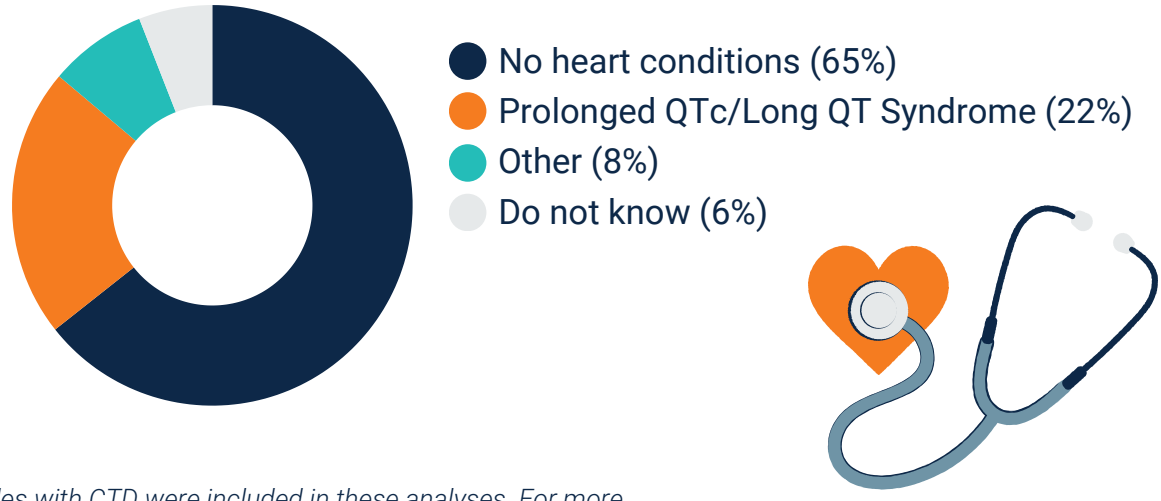
Only males with CTD were included in these analyses. For more information about females with CTD, refer to pages 30-31.

CREATINE TRANSPORTER DEFICIENCY

Cardiovascular Health

We asked CTD participants (*n*=51) what physical activities they do to stay active. The top 3 reported activities were **walking, playing on playground equipment,** and **swimming**!

Researchers have found that CTD patients may have an increased risk of developing a heart condition called prolonged QTc.[14] Therefore, we asked CTD participants (*n*=51) which heart conditions (if any) they have ever experienced. While the majority of male CTD participants indicated no heart conditions, **22% reported experiencing prolonged QTc or Long QT Syndrome**. It is therefore promising that **75% of male CTD participants (*n*=51) have seen a cardiologist**.



Only males with CTD were included in these analyses. For more information about females with CTD, refer to pages 30-31.

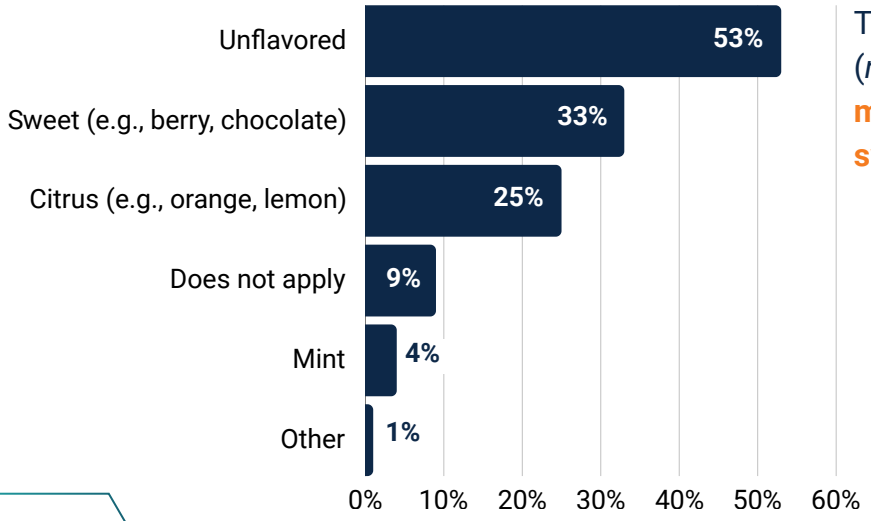
75% of male CTD participants have seen a cardiologist

CREATINE TRANSPORTER DEFICIENCY

Oral Medication Preferences

Taking medications and supplements can be challenging for many CTD patients. Some CTD supplements are especially difficult because they have an unpleasant flavor. So, we asked caregivers **what foods and liquids they use to help CTD participants (*n*=74) successfully take their medicines and supplements**. While water, applesauce, and yogurt were the most popular choices, there were a variety of responses.

We also asked caregivers what attributes of an oral medication are the most important for CTD participants (*n*=74) to consistently take their medications. Overwhelmingly, the top two most important attributes of a medication were **having a neutral or desirable taste (70%)** and having a **manageable volume or quantity of dose (69%)**.



The majority of CTD participants (*n*=74) prefer **unflavored medication (53%)**, followed by **sweet-flavored medication (34%)**.

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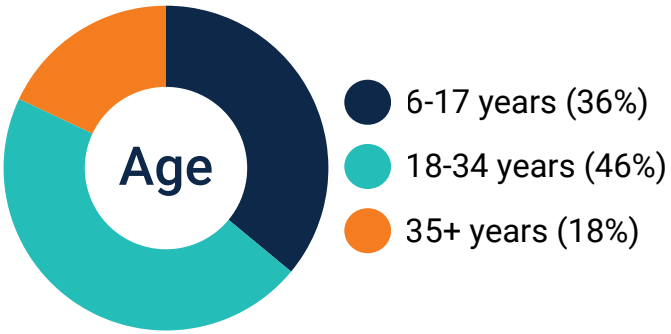
CREATINE TRANSPORTER DEFICIENCY

Women and Girls with CTD

As an X-linked disorder, most of what we know about CTD is based on research in males with CTD.[19] **We believe that as more women and girls who have CTD are diagnosed, we can learn from them to find the best ways to support them.**

Currently, there are 11 females (*n*=11) with CTD enrolled in the registry.

64% of female registry participants with CTD are adults (aged 18+ years).

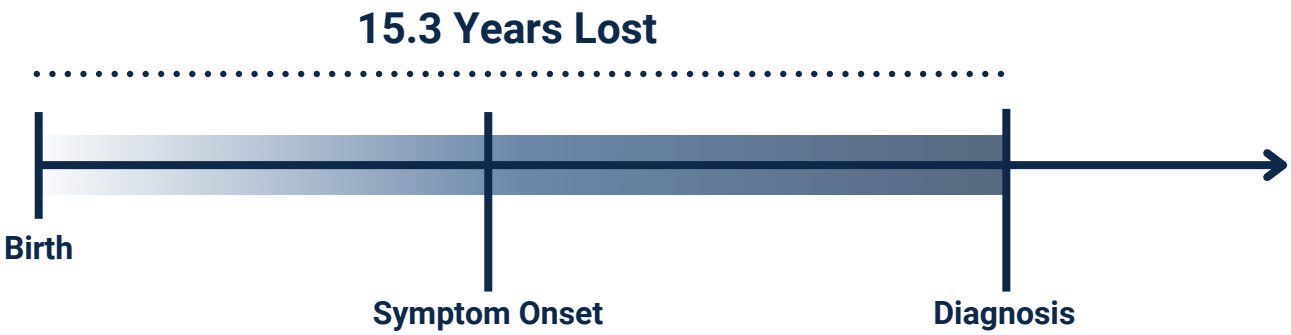


We asked female CTD participants and caregivers to identify the **symptoms that they experienced prior to receiving their CTD diagnosis**. The most commonly reported symptoms were:

- **Autism features** (73%)
- **Global developmental delay** (64%)
- **Speech delay** (64%)
- **Behavior problems** (64%)

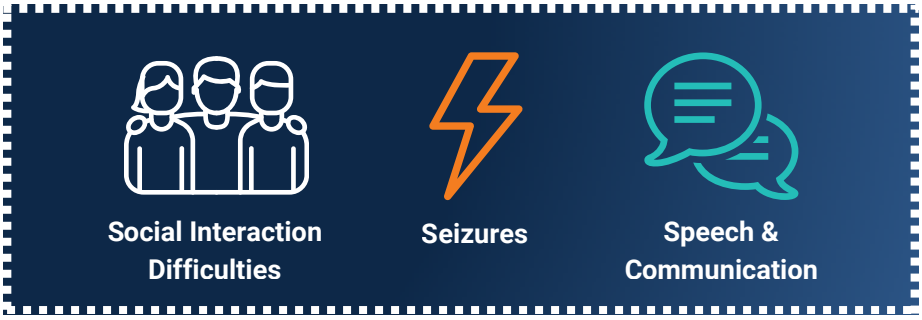
Women and Girls with CTD

Females with CTD have been reported to show less severe symptoms compared to their male CTD peers, however this is not always the case.[20] This can make it more challenging for them to receive an early diagnosis, if they ever receive a diagnosis at all. Females with CTD who are enrolled in the registry (*n*=11) first showed **symptoms at an average age of 7 years**, yet it took, on average, an **additional 8.3 years to receive a diagnosis**. On average, females with CTD were **3 times older when they were diagnosed**, compared to males with CTD.



While CTD is linked to an increased risk of a heart condition called prolonged QTc, most of this research has been done in males with CTD.[14] **It is not clear what the cardiac risk (if any) is for females with CTD.**

We also showed female CTD participants (*n*=10) a list of 24 outcomes and asked them to rank their top most important outcomes that they would like to see improved. The **highest ranked outcomes** they would like to see improved were:



CREATINE TRANSPORTER DEFICIENCY

SLC6A8 Variants in CreatineINFO

55 CTD participants have generously shared their genetic information with the registry. Among these participants, there are currently **44 unique *SLC6A8* variants** which are classified as pathogenic, likely pathogenic, or a variant of uncertain significance (VUS).

1. NM_005629.4:c.-6G>T, NC_000023.10:g.152954024G>T
2. NM_005629.4:c.200G>A (p.Gly67Asp)
3. NM_005629.4:c.230G>T (p.Arg77Leu)
4. NM_005629.3:c.257G>A (p.Gly86Asp)
5. NM_005629.4:c.262+18C>A, NC_000023.10:g.152954309C>A
6. NM_005629.4:c.321_323del (p.Phe107del)
7. NM_005629.4:c.340C>A (p.Gln114Lys)
8. NM_005629.3:c.342G>C (p.Gln114His)
9. NM_005629.3:c.373A>T (p.Asn125Tyr)
10. NM_005629.4:c.420dup (p.Val141ArgfsTer48)
11. NM_005629.3:c.507G>A (p.Trp169Ter)
12. NM_005629.4:c.570_571del (p.Ala191GlnfsTer10)
13. NM_005629.3:c.760G>A (p.Val254Ile)
14. NM_005629.3:c.777+1G>A, NC_000023.10:g.152957563G>A
15. NM_005629.4:c.829_843dup (p.Val277_Leu281dup)
16. NM_005629.3:c.912G>C (p.Gln304His)
17. c.913-1G>A
18. NM_005629.3:c.928G>A (p.Gly310Arg)
19. NM_005629.3:c.930del (p.Thr311ProfsTer85)
20. NM_005629.4:c.942_944del (p.Phe315del)
21. NM_005629.3:c.1006_1008del (p.Asn336del)
22. NM_005629.4:c.1081_1083del (p.Ser361del)
23. NM_005629.4:c.1142-2A>G, NC_000023.11:g.153693903A>G
24. NM_005629.3:c.1145C>T (p.Pro382Leu)
25. NM_005629.3:c.1161C>G (p.Ile387Met)
26. NM_005629.4:c.1168C>T (p.Pro390Ser)
27. NM_005629.4:c.1222_1224del (p.Phe408del)
28. NM_005629.3:c.1232T>C (p.Leu411Ser)
29. NM_005629.4:c.1249A>C (p.Ser417Arg)
30. NM_005629.3:c.1250G>A (p.Ser417Asn)
31. c.1255-3_1255-2delCA
32. NM_005629.4:c.1255-2A>G, NC_000023.10:g.152959583A>G
33. NM_005629.4:c.1260_1281del (p.Gly421AlafsTer35)
34. NM_005629.3:c.1283del (p.Gly428AlafsTer35)
35. NM_005629.3:c.1290_1309del (p.Asp431LeufsTer27)
36. NM_005629.4:c.1318C>A (p.Arg440Ser)
37. NM_005629.3:c.1370T>A (p.Ile457Asn)
38. NM_005629.3:c.1403_1406del (p.Tyr468SerfsTer42)
39. NM_005629.3:c.1487G>A (p.Trp496Ter)
40. NM_005629.4:c.1536del (p.Tyr513ThrfsTer7)
41. NM_005629.3:c.1540C>T (p.Arg514Ter)
42. NM_005629.4:c.1684dup (p.Trp562LeufsTer28)
43. [GRCh37]Xq28(152858835_152960127)x0
44. [GRCh37]Xq28(152951692_152969636)x0-1

Some variants in this list are classified as a variant of uncertain significance (VUS), meaning that additional clinical data are required in order to confirm disease pathogenicity. Two benign variants were removed from this list, as they are not disease-causing. Genetic information is collected from patient reports. Some reports provide more information than others. While information is cross-referenced with the ClinGen Allele Registry, some information may be missing.[15] *Please contact ACD at registry@creatineinfo.org if you are interested in learning more about these variants.*

CREATINE TRANSPORTER DEFICIENCY

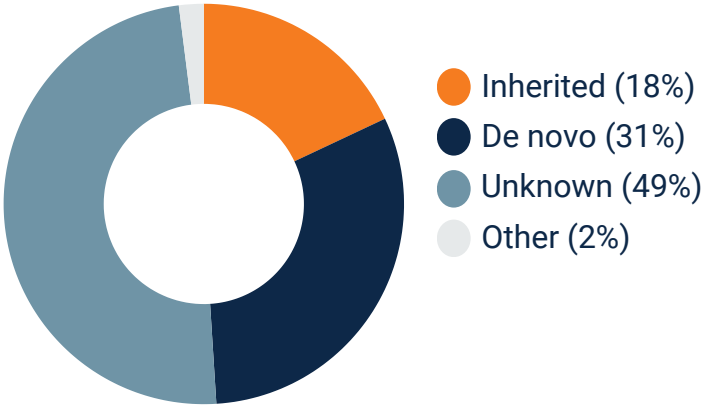
Genetics at a Glance

The *SLC6A8* gene is located on the X chromosome, which makes CTD an X-linked disorder. CTD patients can have either 1) an **inherited** variant (the genetic change is passed from mom to child) or 2) a ***de novo*** variant (the genetic change is unique to the child).

Testing biological parents can help us identify the inheritance pattern for CTD patients, which may be helpful for several reasons:

1. Parents may want to know their chances of **having another child with CTD**;
2. **Mothers who have mild symptoms** may learn that they also have an *SLC6A8* mutation;
3. It supports **variant classification efforts** which may help future CTD families;
4. The more genetic information available, the **more support families can receive** from their genetic counselors.

31% of CTD participants (*n*=55) report a *de novo* *SLC6A8* mutation. However, we do not know the inheritance pattern for approximately half of the CTD participants.



A total of 55 CTD participants were included in these analyses, including 5 female participants. Genetic information is collected from patient reports. Some reports provide more information than others. Please contact ACD at registry@creatineinfo.org if you are interested in learning more.

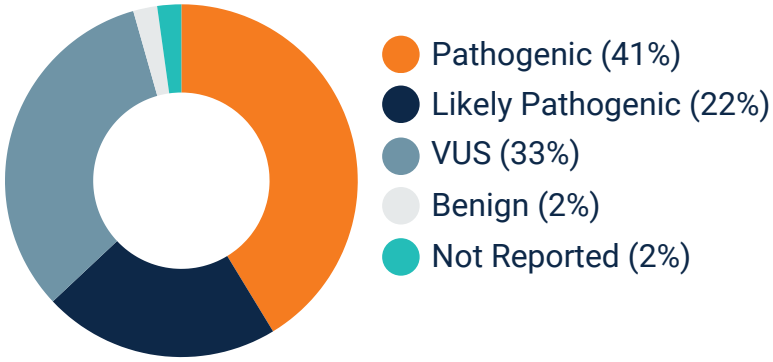
CREATINE TRANSPORTER DEFICIENCY

Genetics at a Glance

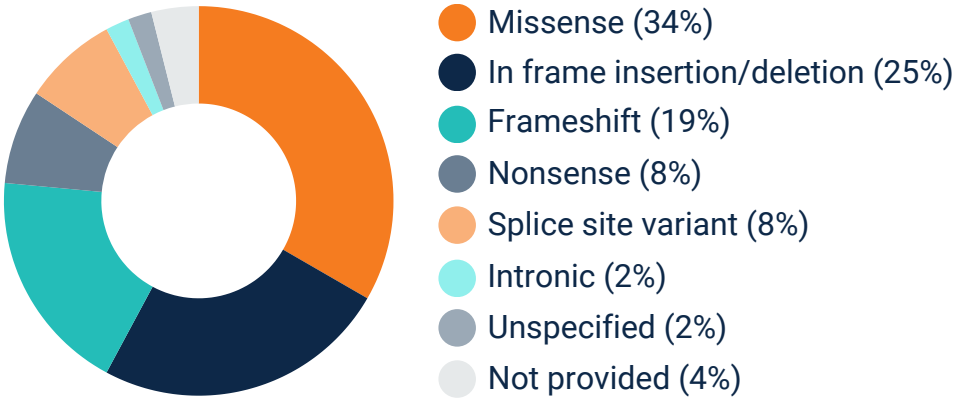
Genetic variants are classified into categories which identify whether that variant is disease-causing or harmless. These categories help doctors provide accurate diagnoses, guide patient treatment, and assess risks for family members.

1. **Benign & Likely Benign** = Variant is not known to cause any significant health or developmental differences
2. **Variant of Uncertain Significance (VUS)** = The variant's effect is unknown; additional information is required
3. **Pathogenic & Likely Pathogenic** = The variant is known to be disease-causing

63% of unique *SLC6A8* variants reported were classified as Pathogenic or Likely Pathogenic.
Approximately ⅓ of *SLC6A8* variants need additional information to determine pathogenicity.



The type of *SLC6A8* variant a patient has determines the effect on the creatine transporter protein. Knowing these variant types may help researchers develop treatments that target different types of mutated creatine transporters. **The most common *SLC6A8* variants reported were missense (34%), in frame insertion/deletion (25%), and frameshift (19%).**



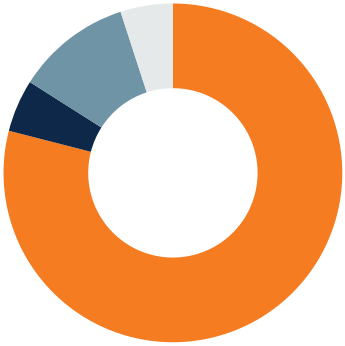
The total number of CTD participants included in these analyses ranged between 53-55, including 5 female participants. Genetic information is collected from patient reports. Some reports provide more information than others. Please contact ACD at registry@creatineinfo.org if you are interested in learning more.

CCDS DIAGNOSTIC LANDSCAPE

Current State of Diagnosis

CCDS patients and their families each have their own diagnostic stories, many of whom have shared them with the registry. Each experience is different and has changed since the first CCDS was first discovered more than 30 years ago. It is important to understand how CCDS patients are getting diagnosed so we can better support future families and their physicians. **To assess what the current CCDS diagnosis process looks like, we examined data from CCDS participants who were diagnosed within the last 5 years.**

79% of CCDS participants (*n*=19) diagnosed within the last 5 years were diagnosed via genetic testing.

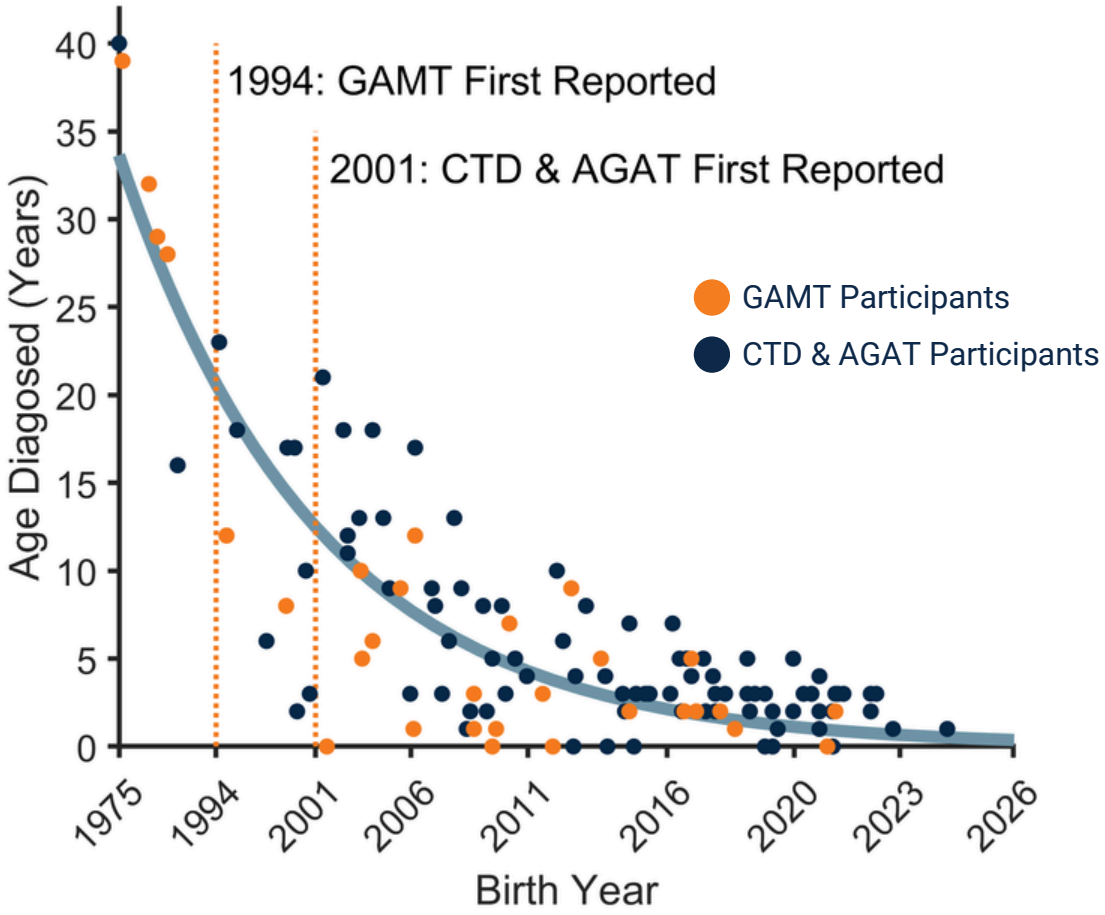


Of 10 reports from CCDS participants, the most commonly reported CCDS diagnosing physicians (*n*=10) within the last 5 years were Pediatricians (30%), Pediatric Neurologists (20%), and Neurologists (20%).

Improvements in CCDS Diagnosis

With increased awareness of CCDS and its increasing addition to newborn screening panels globally, **the time to diagnosis is decreasing**. This reduced time to diagnosis reflects significant progress made since CCDS was first discovered and provides hope for future CCDS patients and their families.

CCDS participants are being diagnosed earlier in life, permitting greater opportunity for earlier intervention.



The graph shows the relationship between the participant's birth year and the age they were diagnosed with CCDS. Individual dots represent individual participants. Due to the small number of AGAT participants, they were grouped with CTD to prevent identification. The curved line in the graph highlights the increasing likelihood of detecting CCDS in younger children. A total of 129 CCDS participants were included in these analyses.

GET INVOLVED

Join the CreatineINFO Patient Registry!

CCDS Patients and Families - Your input helps researchers and clinicians gain deeper insight into CCDS – from symptoms and treatments to quality of life. Together, our community is improving understanding, care, and future therapies.

Visit creatineinfo.iamrare.org to participate!

📱 **You can also download the IAMRARE Mobile App from the App Store and Google Play.**

Questions? Email registry@creatineinfo.org for support.

RESEARCHERS >>> **Interested in furthering your CCDS research with data from this registry? Email registry@creatineinfo.org to learn how we may collaborate.**

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