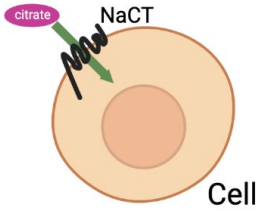
SLC13A5 Citrate Transporter Disorder

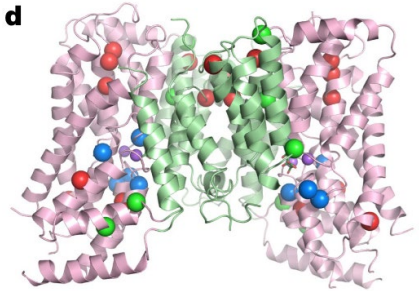
Brenda Porter, MD, PhD
Professor of Neurology and Pediatrics
Stanford University
Stanford Medicine Children's Health

SLC13A5 Natural History Study Principal Investigator

What is SLC13A5?

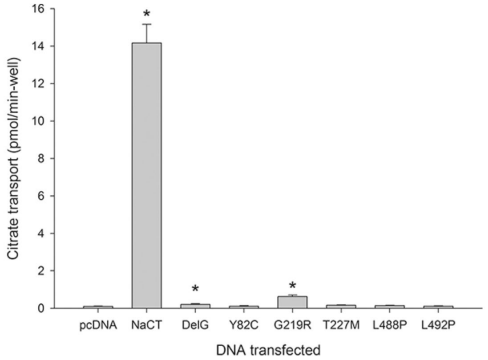
- The **SLC13A5** gene encodes the **NaCT** protein
- NaCT: a sodium-dependent citrate transporter
  - Transports citrate into the cell
  - Expressed highest in liver, brain, and reproductive organs
- The cryoEM structure of NaCT shows the regions with pathogenic variants
  - All SLC13A5 variants lead to a loss of citrate transport





Sauer et al. 2021

Citrate transport



Klotz et al. 2016

What is SLC13A5 Citrate Transporter Disorder?

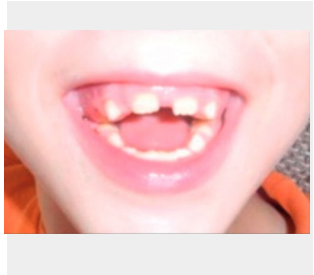
Common clinical characteristics

Intractable epilepsy beginning in infancy

Minimally verbal with good receptive language

Movement disorder, hypotonia

Developmental delay, Intellectual disability



Tooth issues: hypodontia, amelogenesis imperfecta

Challenging to track patients without an ICD10 code to track incidence and prevalence:
Estimate: 1900 patients in US and Europe; may be higher than known due to a lack of prior testing

Thevanon et al. 2014, Hardies et al. 2015, Matricardi et al. 2020, Yang et al. 2020, Taysha April 2021 Press Release
Photos shared with permission

SLC13A5 Citrate Transporter Disorder affects daily life

- Patients need 24/7, protective supervision
- Patients need help with daily tasks:
  - Toileting
  - Dressing
  - Eating
  - Communicating
  - Ambulation

The severity and requirements of this disorder impact entire families and require lifelong clinical care

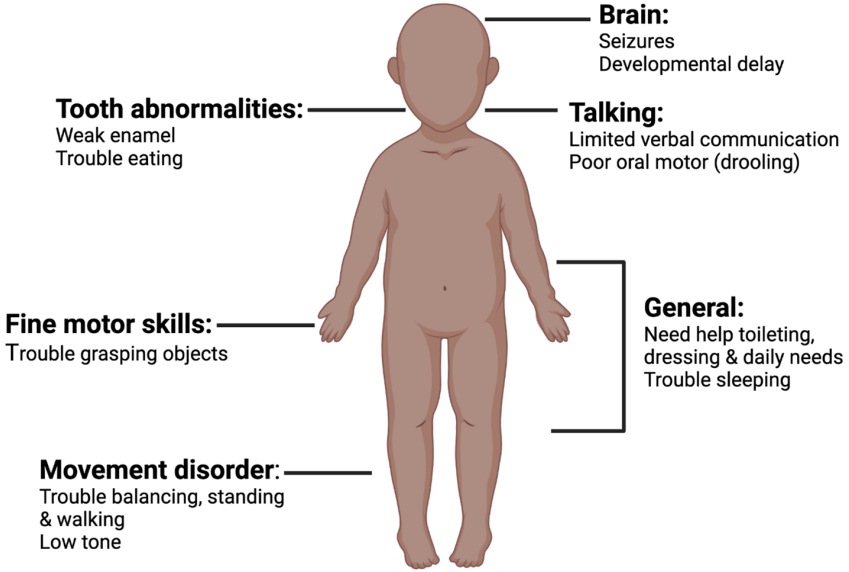
Why is SLC13A5 Citrate Transporter unique?

- SLC13A5 Citrate Transporter Disorder is **clearly defined**
  - Neonatal epilepsy present in *all* patients
  - Severe developmental delay
  - Intellectual disability
  - Movement disorder
  - Minimally verbal
  - Increased citrate levels in blood
  - Monogenic, autosomal recessive inheritance
  - Affects boys and girls of all races and ethnicities
  - Oldest known patients are in their 50s
  - Incidence and prevalence are expected to be higher than yet known due to a lack of prior testing
  - Database classifications: clearly defined in OMIM #615905, NORD

Thevanon et al. 2014, Hardies et al. 2015, Bainbridge et al. 2017, Matricardi et al. 2020, Yang et al. 2020, Arvio and Lehdetie 2021, Brown et al. 2021, Goodspeed et al. 2022

A unique and specific SLC13A5 Citrate Transporter Disorder ICD code would improve patient care

- Antiseizure medications
  - Rescue meds provided early in life
  - Remove contraindications
- Physical and Occupational Therapy
  - Early, intensive and consistent for both fine and gross motor skills
- Dental support
  - Appropriate dental care team
- Speech Therapy
  - Assistive communication and multi-modal communication



SLC13A5 Citrate Transporter Disorder research progress

Clinical trials

- Triheptanoin (UX007)
- Natural History Study (non-intervention)

Pre-clinical development

- Gene therapy (TSHA-105)
- Small molecule (Ravicti)

Death in patient population

- 15.6% of known patients have died (Matricardi et al. 2021)

A unique ICD code will identify patients who will benefit from these treatments, some are only applicable for patients with variants in the SLC13A5 gene

Rare diseases are the second most commonly targeted therapeutic area for gene therapies (American Society for Gene and Cell Therapy Q4 2022 Quarterly Data Report)

At least one treatment specifically for SLC13A5 Citrate Transporter Disorder is currently in development and has received rare pediatric disease and orphan drug designations from the U.S. FDA. This treatment also received orphan drug designation from the European Commission in August of 2021.

These designations indicate that the FDA and EMA consider SLC13A5 Citrate Transporter Disorder a separate indication that cannot be grouped with others in ICD coding.

A specific ICD code will improve SLC13A5 Citrate Transporter Disorder care

A unique code will:

- Specify the specific disorder
- Specify the relevant gene (SLC13A5)
- Capture the multisystem effects of SLC13A5 Citrate Transporter Disorder
- Allow the medical records system to easily identify patients
    - Improve communication among healthcare providers
    - Identify clinical trials and research to understand this disorder
- Quickly identify appropriate and inappropriate medications
- Improve provider identification
    - Occupational therapist, physical therapists, speech therapists, dentists, etc.
- Enable patients and caregivers to better understand the diagnosis

These benefits will improve patient care

Summary

- There is no current ICD-10 code with the specificity and meaning of “SLC13A5 Transporter Disorder”
- SLC13A5 Citrate Transporter Disorder is a unique, specific, and severe disorder
  - Severe epilepsy starting shortly after birth
  - Developmental delay
  - Movement disorder
  - Tooth issues
  - Need for 24/7 care
  - *Requires lifelong clinical care*
- Incidence and prevalence may be higher than known due to a lack of prior testing

A unique code will enable:

- Ability to automatically flag inappropriate prescriptions and treatments
- Ability to determine qualification for novel treatments (e.g. precision therapy in development with Orphan Drug Designation)
- Alert families about the risk of aspiration due to hypotonia
- Alert or authorize language, physical and occupational therapies
- Alert families about implications for family planning