The growing research toolbox for SLC13A5 Citrate Transporter Disorder: a rare disease with animal models, cell lines, and an ongoing Natural History Study.

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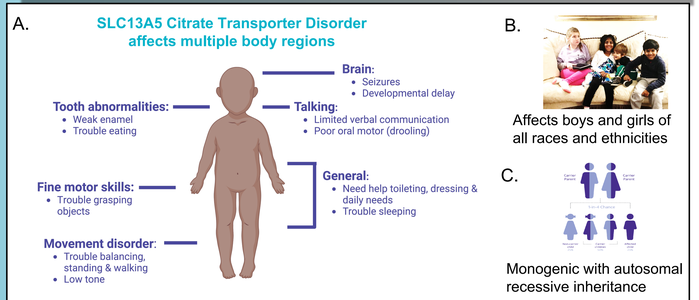
TESS Research Foundation: the only organization dedicated to SLC13A5 Citrate Transporter Disorder

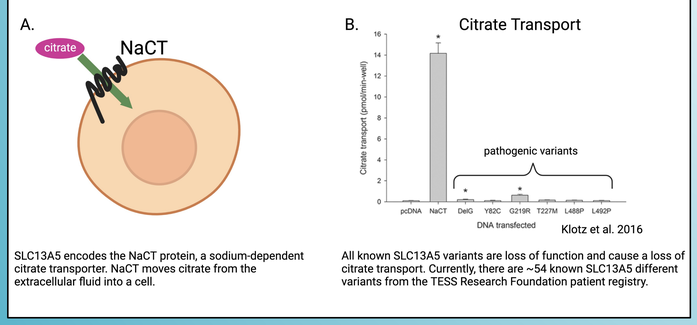
- Our mission is to improve the lives of those impacted by SLC13A5 Epilepsy, a citrate transporter disorder, through research and community

What does SLC13A5 Citrate Transporter Disorder look like?



- An ultra-rare disorder that affects many aspects of daily life
- Patients need 24-hour care
- Patients have trouble eating, walking, talking, and sleeping
- Current standards of care are anti-seizure medications; *there are no treatments that address the underlying cause*

SLC13A5 codes for the protein NaCT: a protein that transports citrate into the cell



SLC13A5 encodes the NaCT protein, a sodium-dependent citrate transporter. NaCT moves citrate from the extracellular fluid into a cell.

All known SLC13A5 variants are loss of function and cause a loss of citrate transport. Currently, there are ~54 known SLC13A5 different variants from the TESS Research Foundation patient registry.

Engaging the SLC13A5 patient and family community: Supporting families and staying patient-centered

Staying patient-centered

Providing support and community

- Monthly support groups
- Family-only Facebook groups
- Letters of support for insurance, school, resources

Empowering with scientific literacy and resources

- A blog that breaks down scientific topics
- Family newsletters
- Resource sharing on social media
- Sharing patient/family stories

Prioritizing the patient voice

- Inviting families to participate at conferences
- Asking for feedback: surveys of needs and requests

Multiple SLC13A5 research tools exist

Growing the SLC13A5 research toolkit

Model	General Description	Summary
Mouse	Global KO; C57Bl/6J	Global loss of SLC13A5 leads to protection from metabolic phenotypes, similar to animals undergoing calorie restriction. KO mice exhibit seizure activity starting at 7 weeks of age, no obvious behavioral phenotype, and elevated citrate levels in the CSF[1,2]
Mouse	cKO; slc13a5$^{fl/fl}$	Ongoing studies are investigating the conditional loss of SLC13A5 in various tissues[3]
Mouse	Humanized G219R mouse	Human SLC13A5 with most common mutation inserted into endogenous mouse locus, uncharacterized
Mouse	SLC13A5 overexpression	Autistic-like behaviors, poor white matter integrity[4]
Zebrafish	slc13a5a/slc13a5b crispants (LOF) 4 zebrafish lines available from ZIRC	Ongoing characterization, unpublished 4 alleles available, uncharacterized
Flies	Indy (I'm not dead yet)	Mutations in Indy improve metabolism in a similar manner to calorie restriction and increase life span[5]

Model	Description
iPSC lines	TESS funded the development of patient- and carrier-derived iPSC lines. The iPSC line with the most common mutation (G219R) also has an isogenic control line.
NPCs	Neural Precursor Cell lines were derived from patient-derived iPSC lines.
Plasmids	Gateway entry clones with codon-optimized ORF sequence for SLC13A5.

Building a collaborative research community

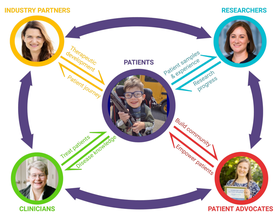
Building a patient-centered SLC13A5 research community

A. 7 Research Roundtables with researchers, clinicians, patients, and industry

Monthly SLC13A5 Research Community Updates

Resource sharing is included in our research contracts

B. **Our patient-centered research network**

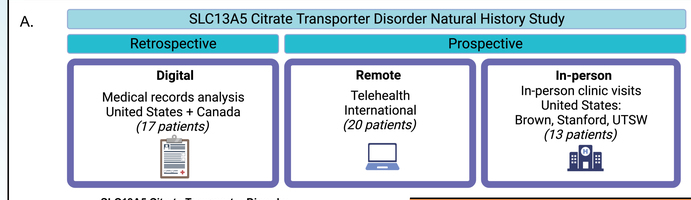


C.

- We fund early-career, mid-career, and well-established researchers through invitation and open research funding announcements
- TESS provides seed funding; we offer letters of support for NIH grants, openly share resources, and make introductions to key researchers
- TESS actively participates in research and publishes peer-reviewed publications

Understanding the Natural History Study of SLC13A5 Citrate Transporter Disorder

A.



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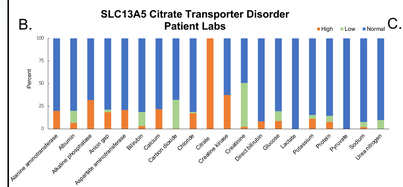

C.

ASM Medication (Top 5)	# of patients taking the medication	# of seizure free patients
Valproic acid	10	4
Topiramate	5	3
Phenobarbital	5	1
Levetiracetam	4	2
Acetazolamide	4	0

Citrate may be a potential biomarker for SLC13A5 Citrate Transporter Disorder. Citrate is elevated in patients, as well as rodent models[1,3,6,7].

Daily anti-seizure medication usage/patient	
Range: 0-5	Average: 3

Revisiting and updating our strategic plan: staying mission-focused

Developing a strategic plan

1. Accelerate and drive research and professional education to find a cure, improve symptom management, and ensure quality of care for those affected by SLC13A5 Epilepsy

2. Empower constituents through information, education, and support to improve quality of life of individuals and families and to engage them in research

3. Expand and strengthen development initiatives to sustain organization programs and services

Future Directions

We need to develop more treatments and further our understanding of this disorder. Our future plans include:

- Continue to drive basic, translation, and clinical research
- Funding high priority science and applying for grants as an organization
- Partnering to drive patient-centered research
  - Partnering in NHS
  - Developing an updated SLC13A5 research agenda
  - Publishing SLC13A5 research
- Developing treatments: seeking academic and industry partners for developing assays and drug repurposing
- Preparing clinical and family community for clinical trials
- SLC13A5 Research Roundtable at Brown University in summer 2024

Acknowledgements + References

We are grateful to CZI Rare As One, our donors, Scientific Advisory Board, Board of Directors, research and clinical community, and our amazing TESS families.
Figures were made using BioRender.com.

[1]Henke, C. *et al.* Disruption of the sodium-dependent citrate transporter SLC13A5 in mice causes alterations in brain citrate levels and neuronal network excitability in the hippocampus. *Neurobiology of Disease* **143**, 105018 (2020). [2]Willmes, D. M. *et al.* The longevity gene mIndy (I'm Not Dead, Yet) affects blood pressure through sympathoadrenal mechanisms. *JCI Insight* **6**, (2021).[3]Dirckx, N. *et al.* A specialized metabolic pathway partitions citrate in hydroxyapatite to impact mineralization of bones and teeth. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2212178119 (2022). [4]Rigby, M. J. *et al.* SLC13A5/sodium-citrate co-transporter overexpression causes disrupted white matter integrity and an autistic-like phenotype. *Brain Commun* **4**, fcac002 (2022). [5]Knauf, F., Rogina, B., Jiang, Z., Aronson, P. S. & Helfand, S. L. Functional characterization and immunolocalization of the transporter encoded by the life-extending gene Indy. *PNAS* **99**, 14315–14319 (2002).[6]Bainbridge, M. N. *et al.* Analyses of SLC13A5-epilepsy patients reveal perturbations of TCA cycle. *Mol Genet Metab* **121**, 314–319 (2017).
[6]Bainbridge, M. N. *et al.* Analyses of SLC13A5-epilepsy patients reveal perturbations of TCA cycle. *Mol Genet Metab* **121**, 314–319 (2017).