SynGAP Research Fund

cureSYNGAP1.org

Mike Graglia - Tony's Dad & SRF's Founder

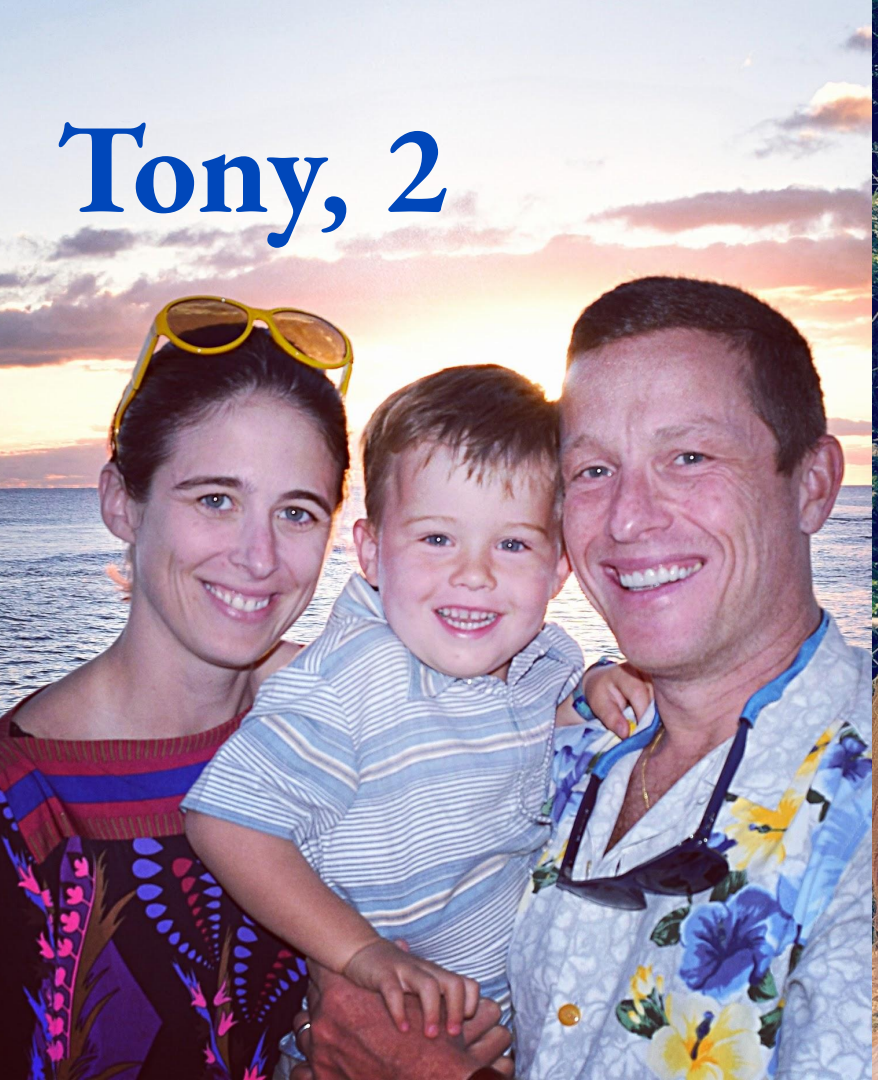
Left my career a few years ago to lead SRF. In addition to working with the team of SynGAP families and partners, I serve on Executive Board of COMBINEDBrain, AES Epilepsy Research Benchmarks Stewards Committee and a member of the Milken FasterCures LeadersLink program & as well as the Personalized Medicine Coalition.

Professional background in global development, healthcare strategy, finance and planning at top-tier institutions.

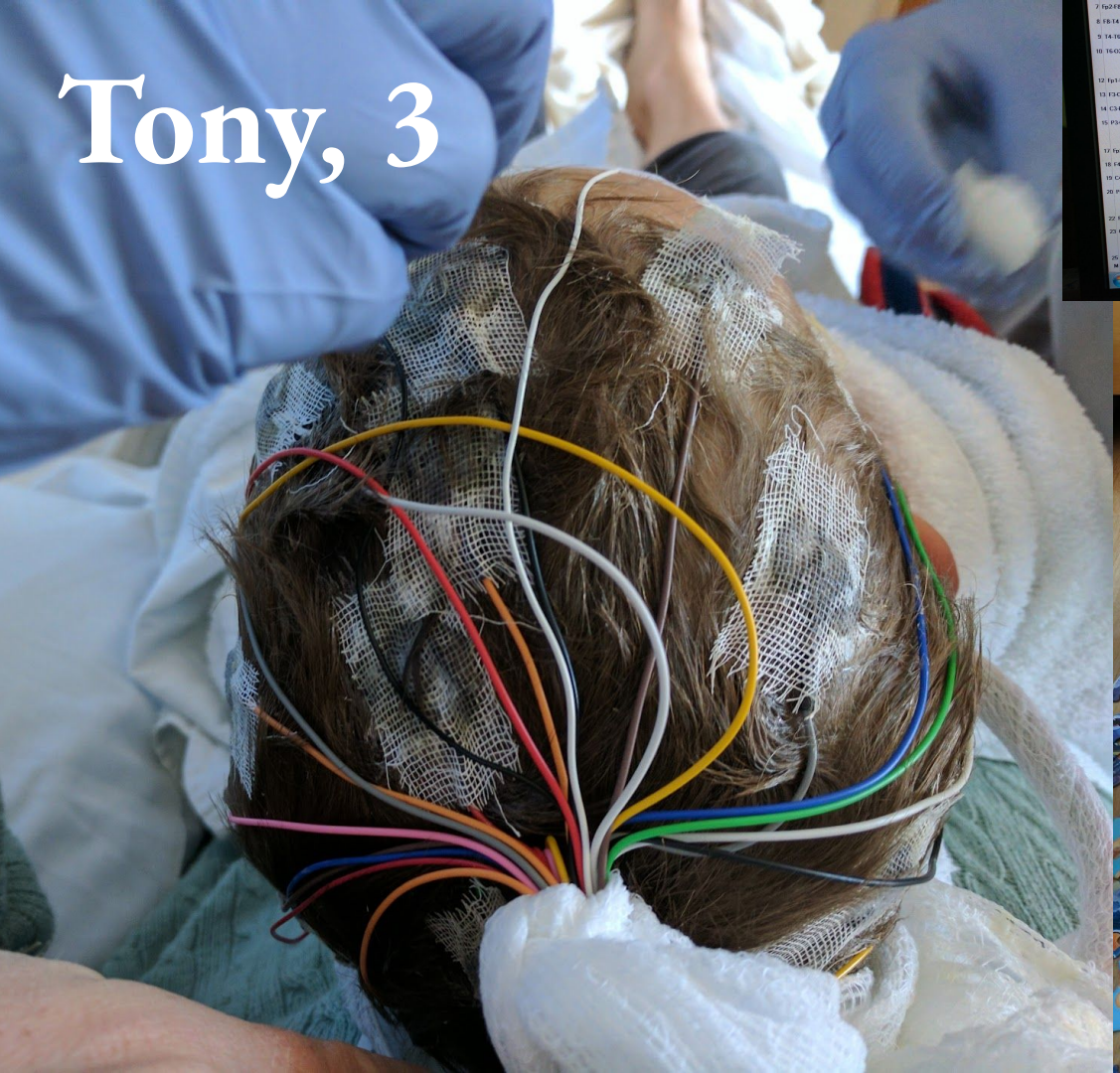
Educational background in Mathematics (BS), International Economics (MA) and Finance (MBA).

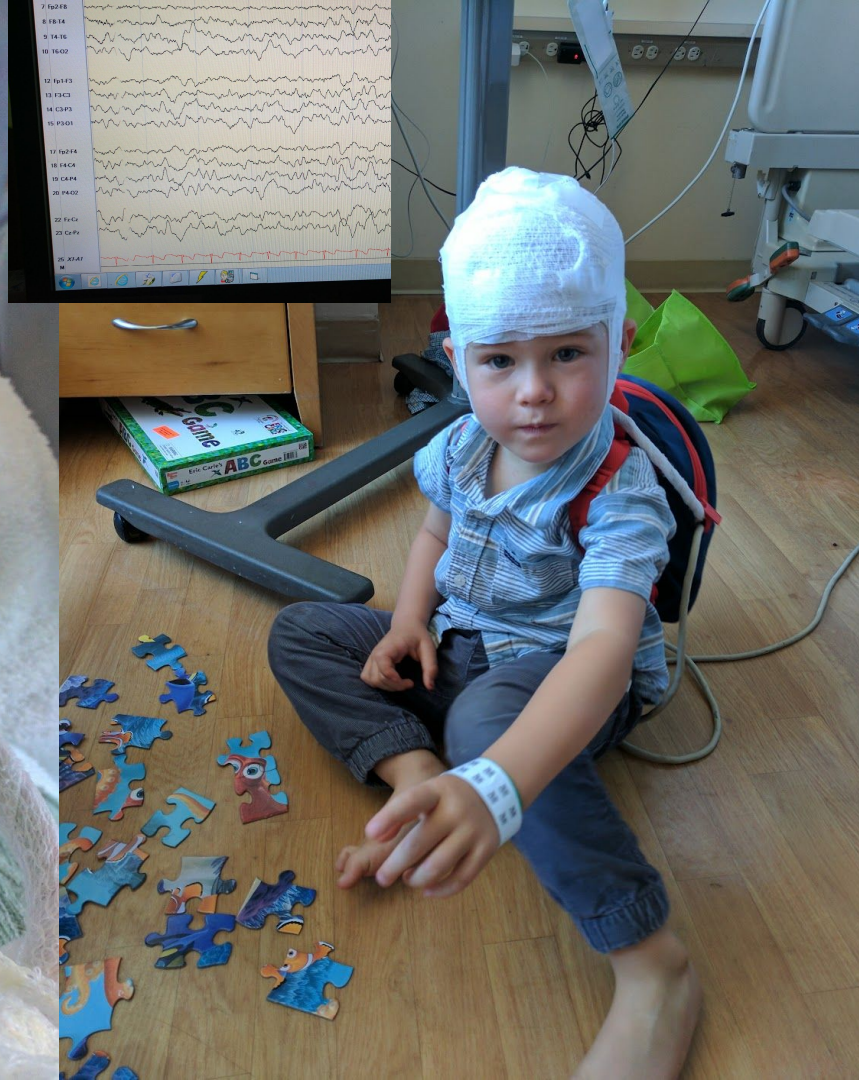

Google+
Tony, 1

Tony, 2



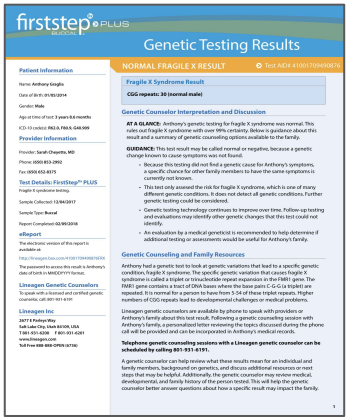
Tony, 3

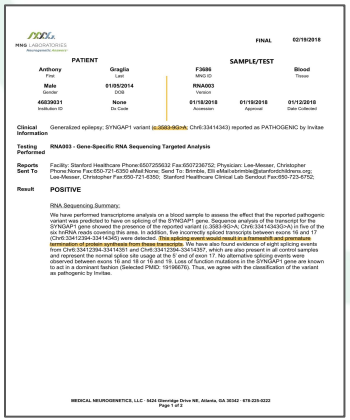




Tony's Dx Journey - How many fall through the cracks?

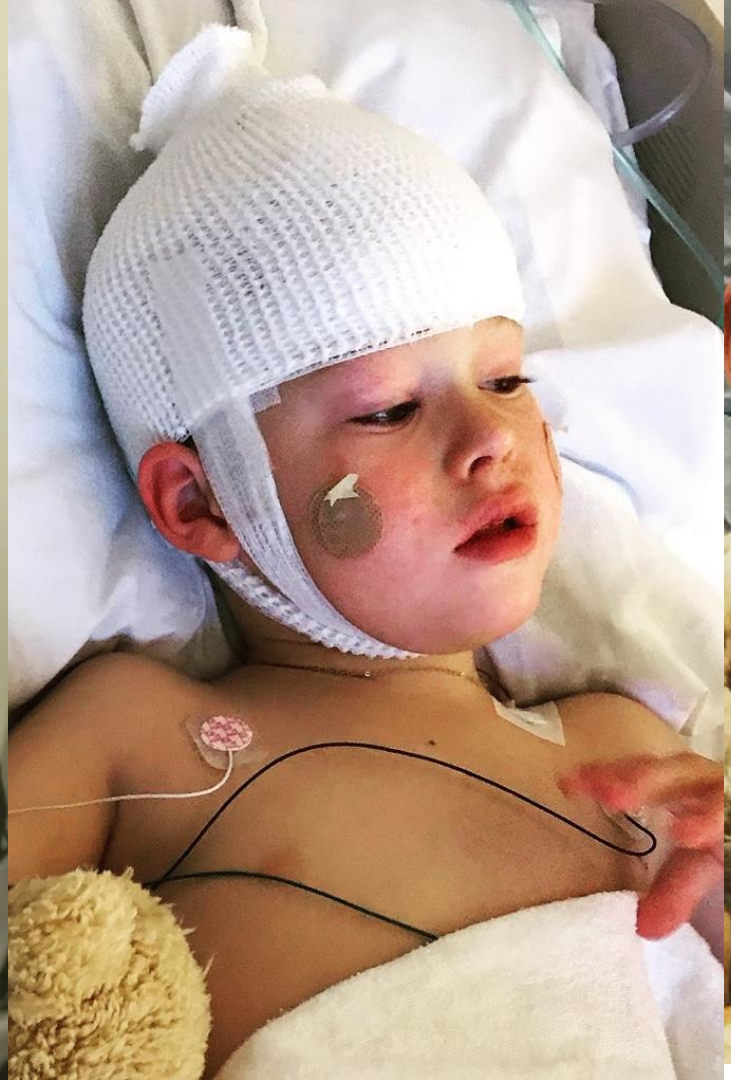
- Delays evident at 2, one clear seizure at 3, EEG confirming Epilepsy
- First, a negative CMA, then Invitae Panel leading to VUS confirmed by RNA Seq. Pathogenic diagnosis just after 4th birthday.
- **Two places where most people stop: CMA negative & VUS.**



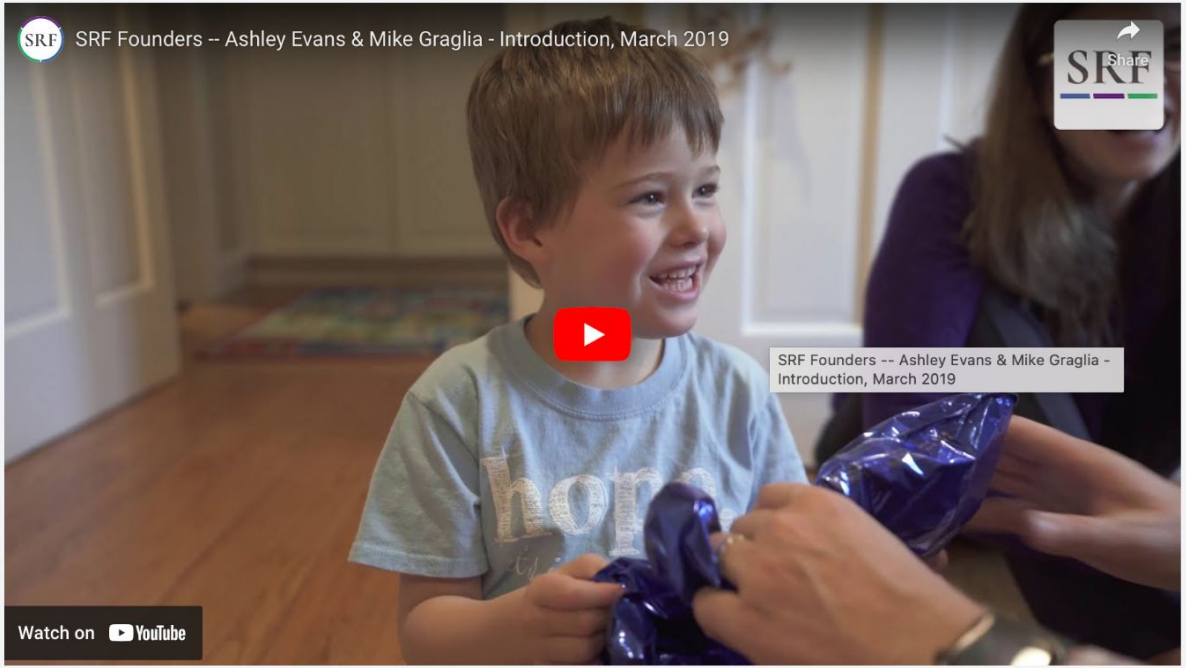


Syngap.Fund/TDx & Brimble et al. Mol Syndromol 2018

Tony, 4



Intro w/ Tony



Read more about Tony on **his Warrior Story**.

SynGAP Research Fund - a family-led, volunteer-driven 503 (c)(3) public charity

Mission	To improve the lives of patients and families suffering from SynGAP1- RD
Vision	An expeditious development of SynGAP1-RD treatments and cures accelerated by funding of high impact research, partnering with passionate industry leaders and supporting our driven and mobilized DEE community.
Mantra	Collaboration, Transparency & Urgency

Strategic Areas	Volunteer Teams
Provide Education and Support to the SynGAP1 Community	Community Activation Advocacy SRF Patient Conference
Expand Scientific Awareness & Stakeholders of SynGAP1-RD	Communications and Marketing Effective Partnerships SRF Scientific Conference
Support and Initiate Scientific Research to Advance SynGAP1-RD Treatments and Cures	Medical/Science Initiatives Resource Management Fundraising

Overview: SRF in numbers

Provide Education and Support to the SynGAP1 Community

1,497	250	209	23	4
Patients Counted	Patients in citizen health	Patients profiled	Families were/are Trustees	Geographies 

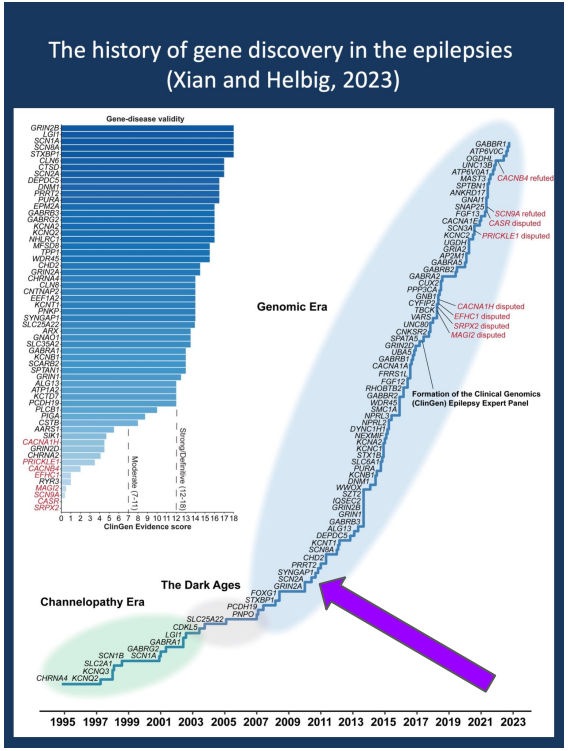
Expand Awareness of SynGAP1-RD

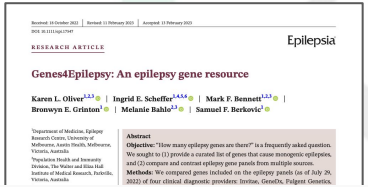
~90	3	2
Webinar available	Podcasts in 2 languages	ICD codes (10 & 11)

Support and Initiate Scientific Research

26	$5.75M
Institutions supported	Committed to grants

SYNGAP1: one of 998 epilepsy related genes, but identified early




Epilepsia

RESEARCH ARTICLE

Genes4Epilepsy: An epilepsy gene resource

Karen L. Oliver | Ingrid E. Scheffer | Mark F. Bennett | Bronwyn E. Grinton | Melanie Bahlo | Samuel F. Berkovic

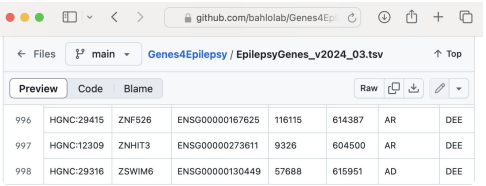
Abstract

Objective: "How many epilepsy genes are there?" is a frequently asked question. We sought to (1) provide a curated list of genes that cause monogenic epilepsies, and (2) compare and contrast epilepsy gene panels from multiple sources.

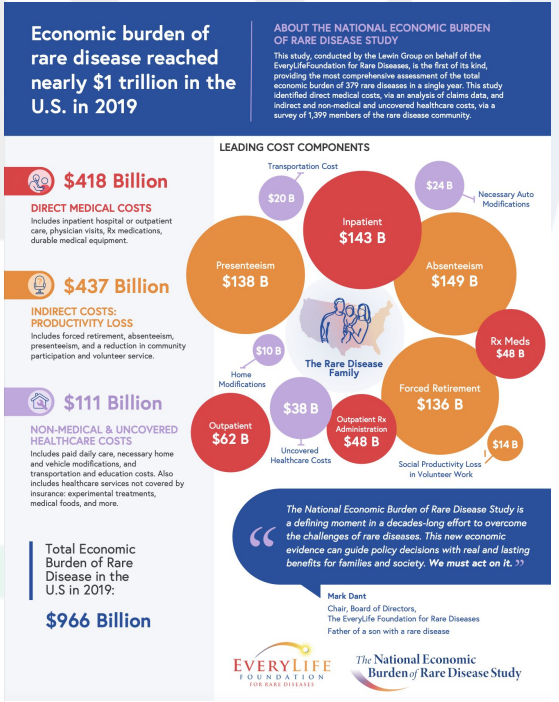
Methods: We compared genes included on the epilepsy panels (as of July 29, 2022) of four clinical diagnostic providers: Invitae, GeneDx, Fulgent Genetics,

Key points

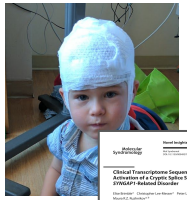
- The number of monogenic genes associated with epilepsy has risen exponentially in the last decade;
- There remains great disparity in genes included on different clinical and/or research gene panels;
- We identify >900 monogenic "epilepsy genes," with ~90% associated with developmental and epileptic encephalopathies;
- Inheritance patterns vary for different epilepsy phenotypes;
- Our curated list of monogenic epilepsy genes is publicly available from: github.com/bahlolab/genes4epilepsy and will be updated half yearly.



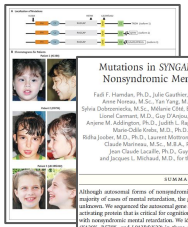
996	HGNC:29415	ZNF526	ENSG00000167625	116115	614387	AR	DEE
997	HGNC:12309	ZNHIT3	ENSG00000273611	9326	604500	AR	DEE
998	HGNC:29316	ZSWIM6	ENSG00000130449	57688	615951	AD	DEE



SYNGAP1 Timeline



Clinical Transcriptome Sequencing Confirms Activation of a Cryptic Splice Site in Suspected SYNGAP1-Related Disorder

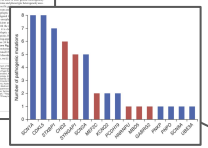


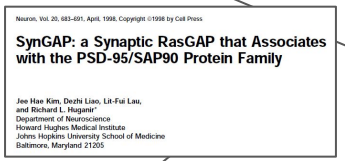
Mutations in *SYNGAP1* in Autosomal Nonsyndromic Mental Retardation

Fadi F. Hamdan, Ph.D., Julie Gauthier, Ph.D., Dan Spiegelman, M.Sc., Anne Noreau, M.Sc., Yan Yang, M.D., Stéphanie Pellerin, B.N., Sylvia Dobrzeniecka, M.Sc., Mélanie Côté, B.Sc., Elizabeth Perreau-Linck, M.Sc., Lionel Carmant, M.D., Guy D'Anjou, M.D., Eric Fombonne, M.D., Anjane M. Addington, Ph.D., Judith L. Rapoport, M.D., Lynn E. Delisi, M.D., Marie-Odile Krebs, M.D., Ph.D., Faycal Mouaffak, M.D., Ridha Joober, M.D., Ph.D., Laurent Mottron, M.D., Ph.D., Pierre Drapeau, Ph.D., Claude Martineau, M.Sc., M.B.A., Ronald G. Lafrenière, Ph.D., Jean Claude Lacaille, Ph.D., Guy A. Rouleau, M.D., Ph.D., and Jacques L. Michaud, M.D., for the Synapse to Disease Group

SUMMARY

Although autosomal forms of nonsyndromic mental retardation account for the majority of cases of mental retardation, the genes that are involved remain largely unknown. We sequenced the autosomal gene *SYNGAP1*, which encodes a ras GTPase-activating protein that is critical for cognition and synapse function, in 94 patients with nonsyndromic mental retardation. We identified de novo truncating mutations (R138X, R579X, and L813fsX22) in three of these patients. In contrast, we observed no de novo or truncating mutations in *SYNGAP1* in samples from 142 subjects with autism spectrum disorders, 545 subjects with schizophrenia, and 190 control subjects. These results indicate that *SYNGAP1* disruption is a cause of autosomal dominant nonsyndromic mental retardation.

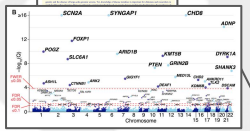


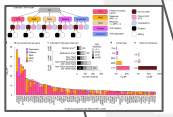


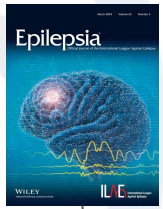
Neuron, Vol. 20, 683–691, April, 1998, Copyright ©1998 by Cell Press

SynGAP: a Synaptic RasGAP that Associates with the PSD-95/SAP90 Protein Family

Jee Hae Kim, Dezhi Liao, Lit-Fui Lau, and Richard L. Huganir*
Department of Neuroscience
Howard Hughes Medical Institute
Johns Hopkins University School of Medicine
Baltimore, Maryland 21205





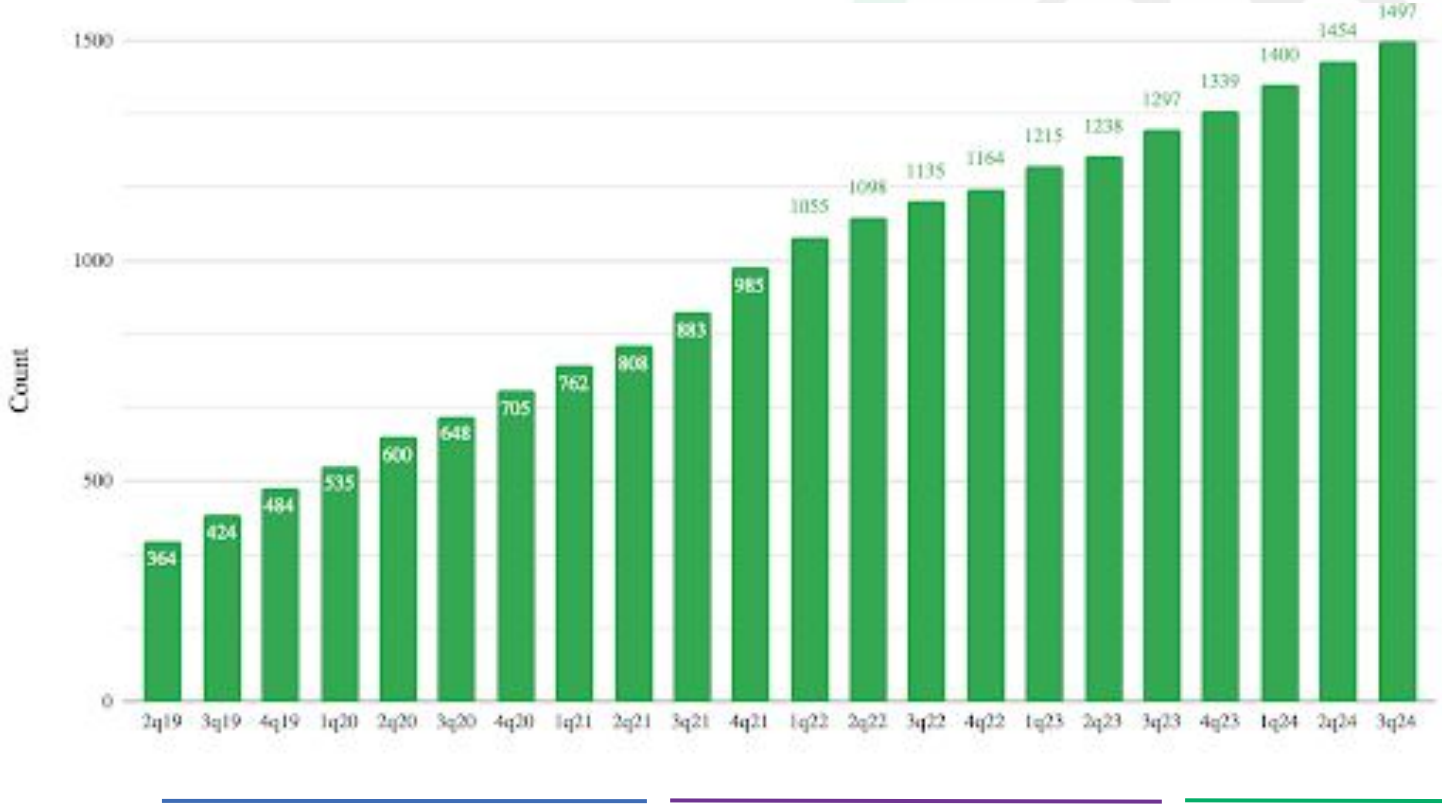


296 PubMed.gov results for SYNGAP1 from 1998 to **18 September 2024**

1998

2024: 42

#SyngapCensus - Patients known to SRF 4x in 4 years



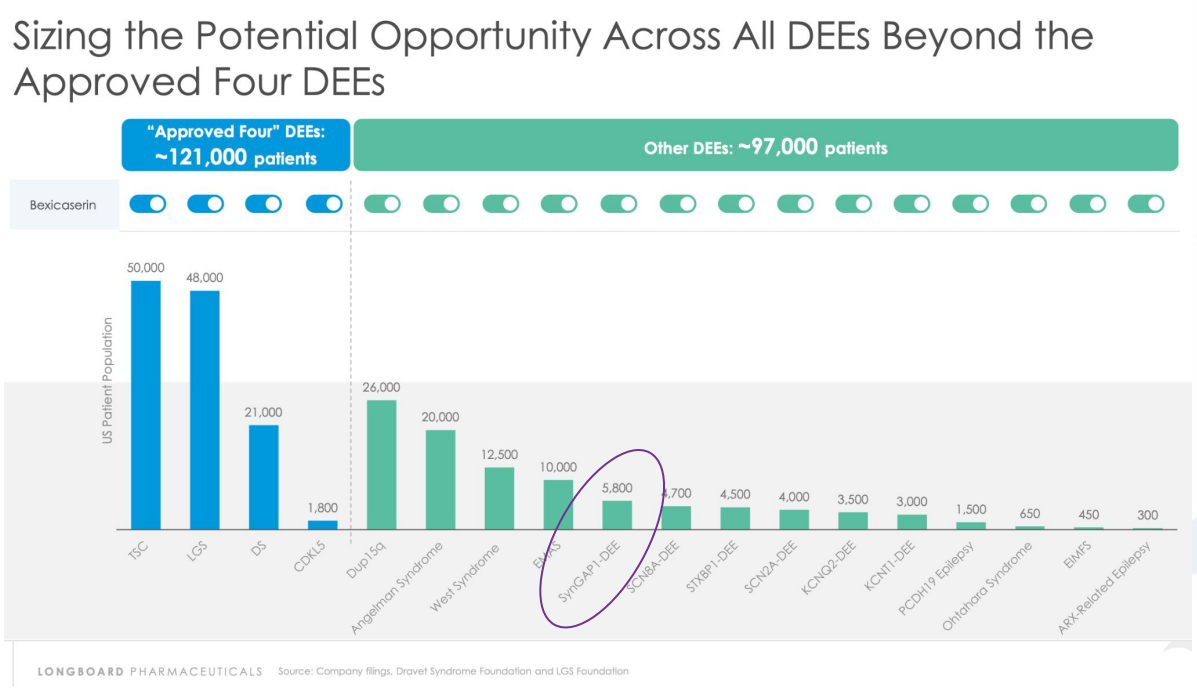
SynGAP Research Fund (SRF)
@cureSYNGAP1

How many people have SYNGAP1?
3Q24 #SYNGAPcensus = 1,497
Details: Syngap.Fund/Census

425
128
122
110
99
53
52
50
43
42
32
31
21
16
15
13
12
11
9
8
7
6
5
4
3
2

If we missed you, let us know! #SYNGAPC
#SYNGAP1

Industry estimates of SYNGAP1 US population are over 10x

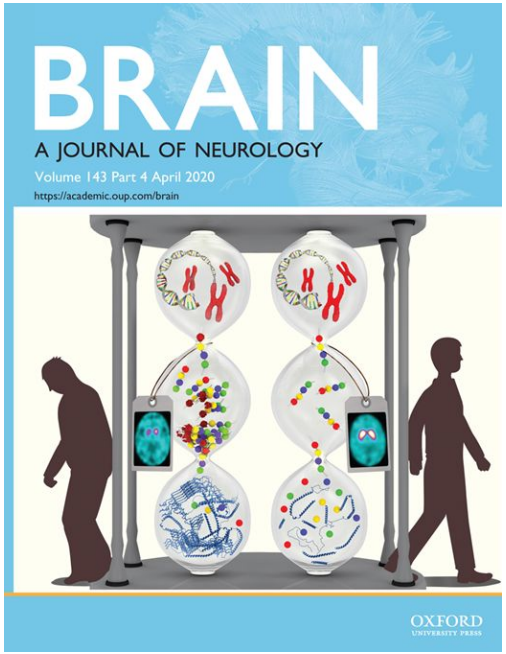


https://ir.longboardpharma.com/static-files/722f9479-7da5-41a5-b278-2c233a7067bb

ID Cohort studies suggest ½ to 1% of patients have SYNGAP

- **2009:** Hamdan noted that **3%** of patients in his study with "non-syndromic mental retardation" had SYNGAP mutations.
- **2013:** Berryer found that 9 of 186 [~**5%**] NSID (non-syndromic intellectual disability) patients had SYNGAP mutations.
- **2014:** Samocha in found that 3 of 151 [~**2%**] patients had SYNGAP mutations.
- **2015:** DDD study of 1,133 patients found 7 with SynGAP mutations [**0.6%**]; this was the fifth most identified gene in the study.
- **2017:** study called SynGAP one of the "six most significantly associated genes"
- **2018:** Wright in also found SYNGAP1 to be the **6th most diagnostic gene** after RID1B, SATB2, SCN2A, ANKRD11, MED13L.
- **2019**: Truty, reviewing 9,413 patients tested with the Invitae panel found that SYNGAP1 was the **10th highest incidence gene**, accounting for 2.5% of positive diagnoses; notably, however in addition to the 39 hits, there were another 79 VUSs ("variants of unknown significance").
- **2020:** Johannesen et al , sequenced 200 patients with Epilepsy and ID in Denmark. 46 patients [23%] had a genetic cause discovered; one 26 year-old had a SYNGAP1 mutation. 1 in 200 is **0.5%**.

Recent work refines the estimate but it is still remarkable



doi:10.1093/brain/awaa051 BRAIN 2020: 143; 1099–1105 | 1099

BRAIN
A JOURNAL OF NEUROLOGY

REPORT

A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by *de novo* variants

Javier A. López-Rivera,[1,2,3] Eduardo Pérez-Palma,[2,4] Joseph Symonds,[5,6] Amanda S. Lindy,[7] Dianalee A. McKnight,[7] Costin Leu,[2,3] Sameer Zuberi,[5,6] Andreas Brunklaus,[5,6] Rikke S. Møller[8,9] and Dennis Lal[1,2,3,4,10,11]

See Lemke (doi:10.1093/brain/awaa079) for a scientific commentary on this article.

A large fraction of rare and severe neurodevelopmental disorders are caused by sporadic *de novo* variants. Epidemiological disease estimates are not available for the vast majority of these *de novo* monogenic neurodevelopmental disorders because of phenotypic heterogeneity and the absence of large-scale genomic screens. Yet, knowledge of disease incidence is important for clinicians and researchers to guide health policy planning. Here, we adjusted a statistical method based on genetic data to predict, for the first time, the incidences of 101 known *de novo* variant-associated neurodevelopmental disorders as well as 3106 putative monogenic disorders. Two corroboration analyses supported the validity of the calculated estimates. First, greater predicted gene-disorder incidences positively correlated with larger numbers of pathogenic variants collected from patient variant databases (Kendall's $\tau = 0.093$, P-value $= 6.9 \times 10^{-6}$). Second, for six of seven (86%) *de novo* variant associated monogenic disorders for which epidemiological estimates were available (*SCN1A*, *SLC2A1*, *SALL1*, *TBX5*, *KCNQ2*, and *CDKL5*), the predicted incidence estimates matched the reported estimates. We conclude that in the absence of epidemiological data, our catalogue of 3207 incidence estimates for disorders caused by *de novo* variants can guide patient advocacy groups, clinicians, researchers, and policymakers in strategic decision-making.

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6 School of Medicine, University of Glasgow, Glasgow, UK
7 GeneDx, Gaithersburg, MD, USA
8 Department of Epilepsy Genetics and Personalized Medicine, Danish Epilepsy Centre, Dianalund, Denmark
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10 Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA
11 Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA

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Keywords: epilepsy; autism; neurodevelopmental disorder; incidence
Abbreviations: DNV = *de novo* variant; NDD = neurodevelopmental disorder; PTV = protein truncating variant

Received September 4, 2019. Revised November 27, 2019. Accepted January 13, 2020. Advance access publication March 13, 2020

Table 1

Comparison of calculated estimates to reported estimates

Gene	Disease	Incidence per 100 000 births		Significant difference [a]	Source PMID
		Predicted	Reported		
SCN1A	Dravet syndrome (OMIM: 607208)	6.69–7.62	4.78	No	26438699
			4.54	No	25778844
			5.90	No	31302675
			4.10	No	R.S. Møller[b]
SLC2A1	GLUT1 deficiency syndrome (OMIM: 606777)	1.65–2.22	1.20	No	26537434
			2.95	No	31302675
TBX5	Holt-Oram syndrome (OMIM: 142900)	0.39–0.45	0.56	No	25344219
STXBP1	STXBP1 encephalopathy (OMIM: 612164)	3.30–3.81	1.09	Yes	26865513
			0.82	Yes	R.S. Møller[b]
SALL1	Townes-Brocks syndrome (OMIM: 107480)	0.30–0.36	0.42	No	10083645
KCNQ2	KCNQ2 encephalopathy (OMIM: 613720)	2.93–3.59	1.18	No	31302675
			1.23	No	R.S. Møller[b]
CDKL5	CDKL5 deficiency disorder (OMIM: 300672)	1.81–2.49	1.77	No	31302675
			0.96	No	R.S. Møller[b]

[a]Significant difference is based on Fisher's exact test with a Bonferroni corrected cut-off of $P \leq 0.004$. See Supplementary Table 2 for specific P-values.
[b]Personal communication.

A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by de novo variants

SYNGAP1 predicted incidence is higher than most genes

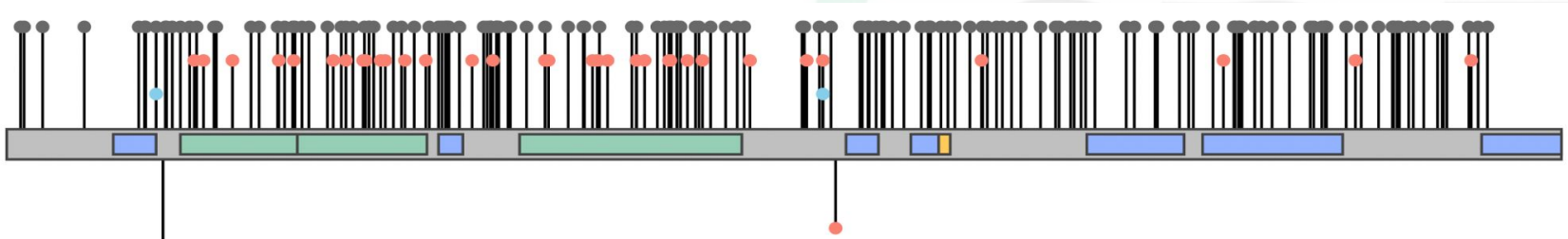
gene	chr	bp	incid_ptv	incid_mv	incidence
SCN2A	2	6018	1.941	6.049	7.991
SCN8A	12	5943	1.104	7.366	7.366
SCN1A	2	6030	2.181	5.025	7.206
SYNGAP1	6	4032	0.787	5.320	6.107
GRIN2B	12	4455	0.555	5.355	5.911
KIF1A	2	5376	3.761	5.216	5.216
STXBP1	9	1812	1.006	2.609	3.615
KCNQ2	20	2619	0.601	3.275	3.275
FOXG1	14	1470	0.091	3.113	3.204
SLC6A1	3	1800	0.300	2.350	2.650
CDKL5	X	3093	0.407	1.763	2.169
ADNP	20	3309	0.430	1.432	1.862
PTEN	10	1212	0.366	1.326	1.692

- The predicted incidence of 6.107 is about ½ of the 0.5% of all people with Intellectual Disability but it is still over 20,000 for a populations of 330M.
- When you double-click and get predicted PTV and Missense incidence, here things get more interesting
- The ratio of PTV to Missense for SYNGAP is ~1:7 which is the opposite of what we see in Clinvar, Vlaskamp & Ciitizen.

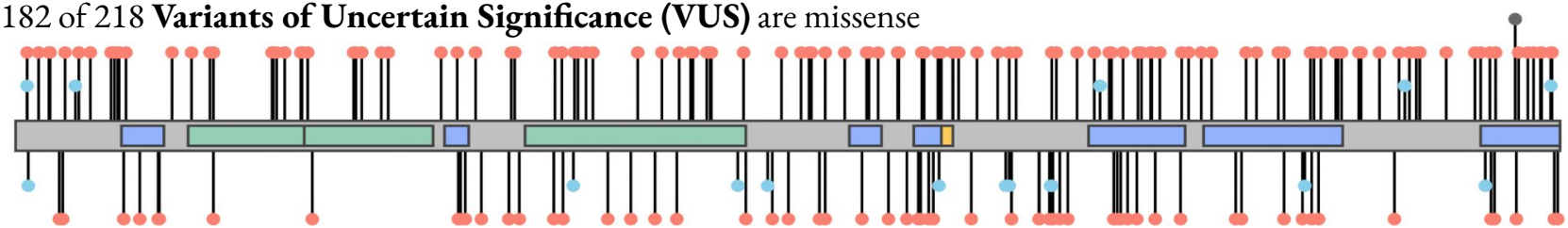
A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by de novo variants

⅔ of SYNGAP1 Missense Variants are VUS

39 of 221 **Pathogenic or Likely Pathogenic (PLP)** are missense



182 of 218 **Variants of Uncertain Significance (VUS)** are missense



Synonymous
Missense
PTV

JOURNAL ARTICLE

Atomistic simulations reveal impacts of missense mutations on the structure and function of SynGAP1

Aliaa E Ali, Li-Li Li, Michael J Courtney, Olli T Pentikäinen, Pekka A Postila

Briefings in Bioinformatics, Volume 25, Issue 6, November 2024, bbae458, https://doi.org/10.1093/bib/bbae458

Published: 23 September 2024 **Article history** ▾

https://simple-clinvar.broadinstitute.org/ accessed 2 Feb 2023

Features and Challenges of SynGAP1-RD

Core Features

Epilepsy
Multiple, evolving types
Prevalent absence seizures
Refractory epilepsy

ID
Global developmental delays (fine/gross motor, speech)
Limited range of capabilities

ASD
High incidence of severe autism
Narrow interest range
Limited self care
Difficult to diagnose

Maladaptive Behaviors
Aggressive and self-injurious
Limits community participation

Common

Sleep Problems
Difficulty falling & staying asleep with worse behaviors at night

Speech Problems
Delayed development
Range of capabilities from nonverbal to short sentences

Eating Problems
Food aversions
Poor oral intake/Packing
Healthy weight issues
If severe, GI tube needed

GI issues
Severe constipation
Gastroesophageal reflux disease
Decreased motility

Under studied

Psychiatry
Anxiety
OCD, ADHD and ADD
Associated with behaviors

Gait Problems
Mobility challenges
May need assistive devices

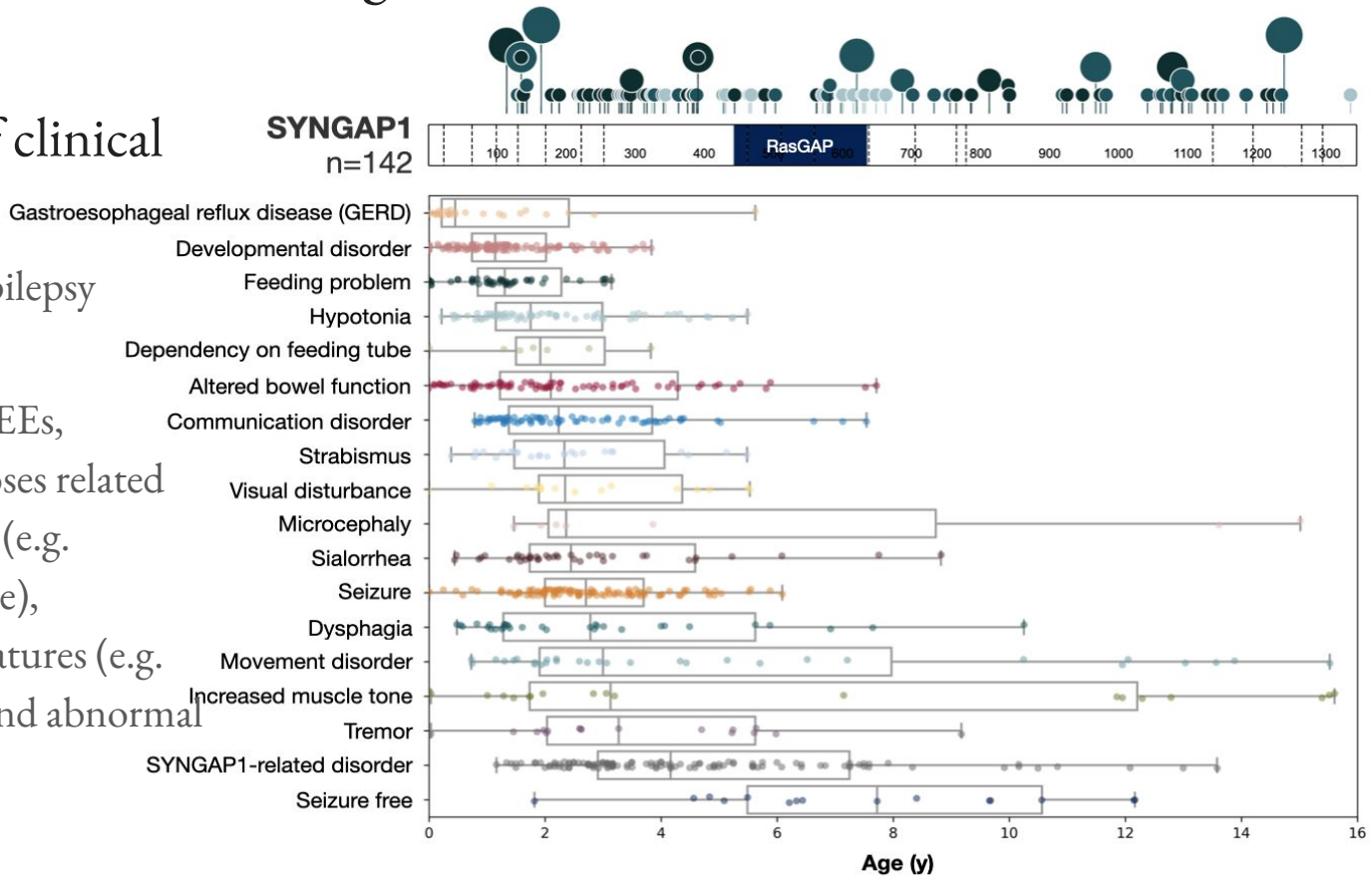
Hypotonia
Scoliosis/Imbalance
Overpronation/Flat feet
Delayed motor skill development

Sensory Processing Issues
High Pain Tolerance
Limited self preservation skills
Range of type and severity

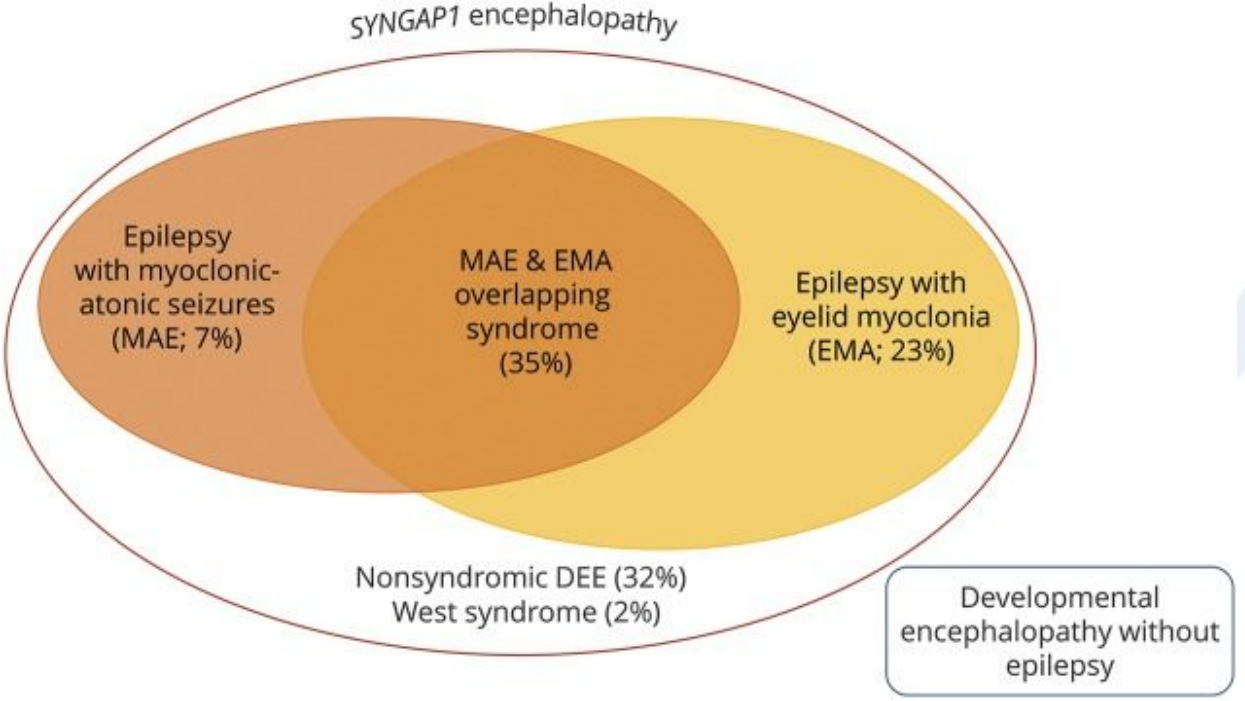
Citizen Health Data shows the gradual onset of disease

Sequencing onset of clinical phenotypes

- Childhood onset of epilepsy (median age 2.7 years)
- Compared to other DEEs, enrichment for diagnoses related to generalized seizures (e.g. atypical absence seizure), neuropsychological features (e.g. aggressive behavior), and abnormal gait

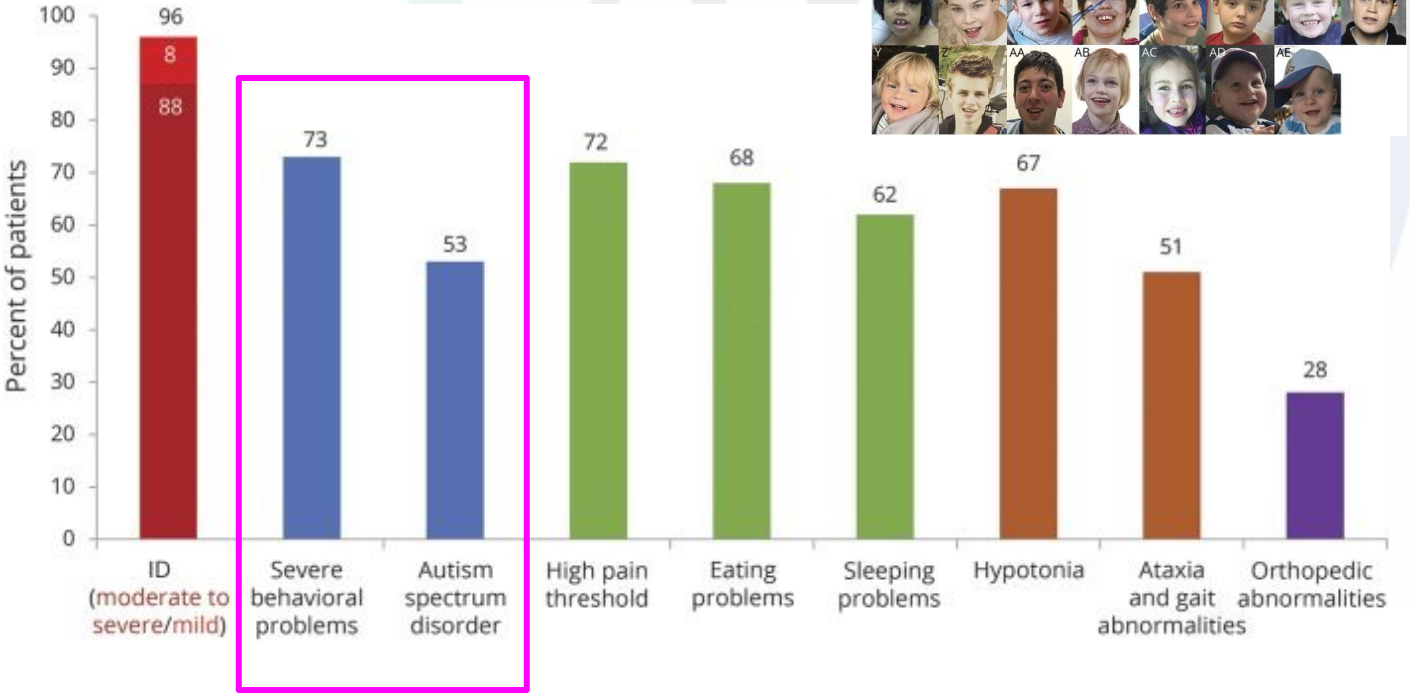


Original Natural History in 2019 – 99% had seizures, many of which are invisible to the untrained eye.



Syngap.Fund/Vlaskamp

Original Natural History in 2019



Syngap.Fund/Vlaskamp

#213

Reconstructing the longitudinal history of *SYNGAP1*-related disorders through data integration across healthcare resources

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Children's Hospital of Philadelphia
Epilepsy Neurogenetics Initiative

Introduction

- *SYNGAP1*-related neurodevelopmental disorder is one of the more common monogenic causes of generalized epilepsy, including myoclonic-astatic epilepsy (MAE, or Doose Syndrome), intellectual disability, and autism spectrum disorder.
- Clinical variation is wide, but poorly understood, and a better understanding of the phenotypic variation over time is needed for clinical trial readiness for the precision therapies currently under development.
- Here, we integrated data from 246 individuals with *SYNGAP1*-related disorders identified through healthcare claims data, spanning 1,321 cumulative patient-years, with reconstructed medical records from 158 individuals from the Ciitizen Natural History Registry and Children's Hospital of Philadelphia across 1,253 patient-years.

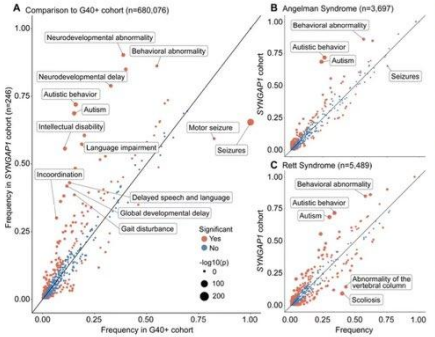

Figure 1: Clinical phenotypes enriched in individuals with *SYNGAP1* in comparison to other epilepsies and neurodevelopmental disorders. Individuals with *SYNGAP1*-related disorders were compared to a broader epilepsy cohort of 680,076 individuals with an epilepsy (G40+) diagnosis (**A**), as well as with syndromic comparator groups that phenotypically resembled *SYNGAP1*: 3,697 individuals with Angelman Syndrome (**B**) and 5,489 individuals with Rett Syndrome (**C**). Compared to a broader population of individuals with epilepsy, clinical characteristics including behavioral abnormalities (Odds ratio (OR) 12.35, 95% CI 9.21 – 16.78), generalized-onset seizures (OR 1.56, 95% CI 1.20 – 2.02), autism (OR 12.23, 95% CI 9.29 – 16.24), and abnormality of higher mental function (including intellectual disability, OR 6.38, 95% CI 4.89 – 8.37) were enriched in individuals with *SYNGAP1*. When comparing *SYNGAP1* with Angelman and Rett syndromes, behavioral features (AS OR 7.2, 95% CI 5.3 – 9.9, RS OR 5.0, 95% CI 3.7 – 6.8) and autism (AS OR 6.8, 95% CI 5.1 – 9.2; RS OR 4.4, 95% CI 3.3 – 6.8) were more common.

This work was supported by The Hartwell Foundation through an Individual Biomedical Research Award (IH), the National Institute for Neurological Disorders and Stroke (K02 NS112600), the Eunice Kennedy Shriver National Institute of Child Health and Human Development through the Intellectual and Developmental Disabilities Research Center (IDDRC) at Children's Hospital of Philadelphia and the University of Pennsylvania (U54 HD086984), the American Epilepsy Society, Pediatric Epilepsy Research Foundations (PERF) & *SYNGAP1* Research Fund through a Research Training Fellowship for Clinicians (JLM), intramural funds of the Children's Hospital of Philadelphia through the Epilepsy NeuroGenetics Initiative (ENGIN), and by Ambit, Inc.

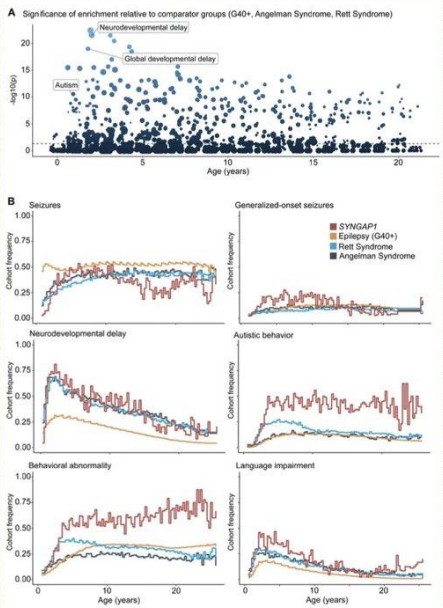

Figure 2: Age-related clinical features in *SYNGAP1* compared to longitudinal histories of other epilepsies and neurodevelopmental disorders. We assessed clinical features across the age span, demonstrating that the overall clinical presentation of *SYNGAP1*-related disorder begins to diverge from comparator groups by the second year of life. (**A**) The significance of enrichment of key features compared to comparator groups (G40+, Angelman Syndrome, Rett Syndrome) is plotted across the lifespan. (**B**) The frequencies of selected features across the lifespan are shown for individuals with *SYNGAP1*-related disorder (red) compared to all individuals with a G40+ diagnosis (orange), and those with Angelman Syndrome (dark blue) and Rett Syndrome (light blue). When compared to the general epilepsy cohort, we found that individuals with *SYNGAP1* were more likely to have behavioral abnormalities, first significant between 27 and 30 months (OR 3.00, 95% CI 1.50 – 5.68) and persisting throughout the lifespan. Autistic behavior also became prominent between 27 and 30 months (OR 5.71, 95% CI 2.44 – 11.9). Generalized-onset seizures became significantly enriched (OR 4.05, 95% CI 2.02 – 7.59) after 3 years of age.

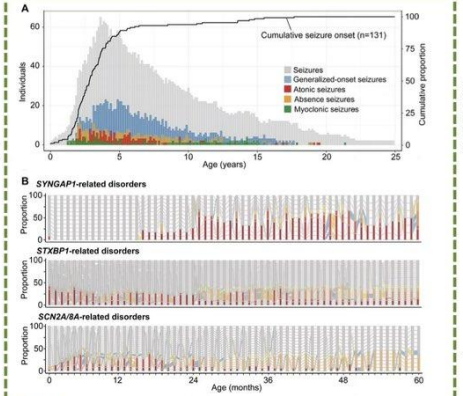

Figure 3: Seizure landscape and epilepsy onset in *SYNGAP1*-related disorders differs from other common genetic epilepsies. (**A**) Generalized-onset seizures occur in up to 70% (frequency range 66.5%, n=107/161 claims data to 69.5%, n=91/131 medical records). The frequency of bilateral tonic-clonic seizures ranged between 16.8% (n=22/131 in medical records) to 46.6% (n=75/161 in claims data), absence seizures in 18.0% (n=29/161) to 54.2% (n=71/131), atonic seizures in 32.9% (n=53/161) to 42.0% (n=55/131) and generalized myoclonic-atonic seizures in up to 43.5% (n=70/161). (**B**) The median age of seizure onset was 2.8 years (IQR 2.0–3.8 years), later than other common genetic epilepsies.

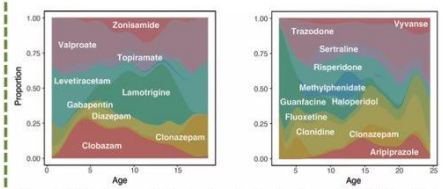

Figure 4: Anti-seizure and behavioral medication landscape in *SYNGAP1*-related disorders demonstrates varied treatment strategies across the lifespan. Longitudinal reconstruction of medications for epilepsy management (left) and behavioral features (right), including sleep disturbance and attention-related concerns, demonstrates age-related treatment strategies in individuals with *SYNGAP1* with predominance of valproic acid (OR 2.26, 95% CI 1.29 – 3.70) and clobazam (OR 2.58, 95% CI 1.55 – 4.09) for epilepsy and risperidone (OR 5.43, 95% CI 3.47 – 8.18), aripiprazole (OR 3.52, 95% CI 2.05 – 5.69) and guanfacine (OR 2.97, 95% CI 1.76 – 4.75) for behavior, which contrasted from treatment strategies frequently used in the broader epilepsy population.

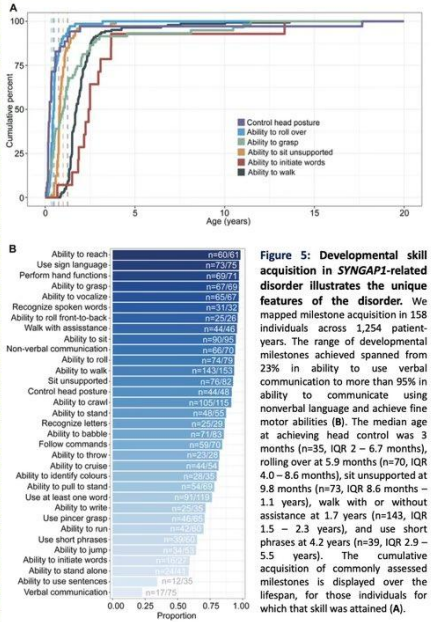

Figure 5: Developmental skill acquisition in *SYNGAP1*-related disorder illustrates the unique features of the disorder. We mapped milestone acquisition in 158 individuals across 1,254 patient-years. The range of developmental milestones achieved spanned from 23% in ability to use verbal communication to more than 95% in ability to communicate using nonverbal language and achieve fine motor abilities (**B**). The median age at achieving head control was 3 months (n=35, IQR 2 – 6.7 months), rolling over at 5.9 months (n=70, IQR 4.0 – 8.6 months), sit unsupported at 9.8 months (n=73, IQR 8.6 months – 1.1 years), walk with or without assistance at 1.7 years (n=143, IQR 1.5 – 2.3 years), and use short phrases at 4.2 years (n=39, IQR 2.9 – 5.5 years). The cumulative acquisition of commonly assessed milestones is displayed over the lifespan, for those individuals for which that skill was attained (**A**).

Discussion

- We characterized the landscape of *SYNGAP1*-related disorders across >2500 patient-years, leveraging data from healthcare resources with varying scopes of clinical documentation and identified clinical signatures specific to *SYNGAP1*.
- Clear delineation of epilepsy and developmental trajectories will improve the prognosis and clinical care of individuals with *SYNGAP1*-related disorders and facilitate clinical trial readiness for future precision medicine approaches.

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https://x.com/cureSYNGAP1/status/1711855442895446320

#213 Recor

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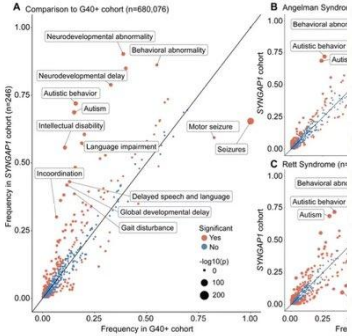

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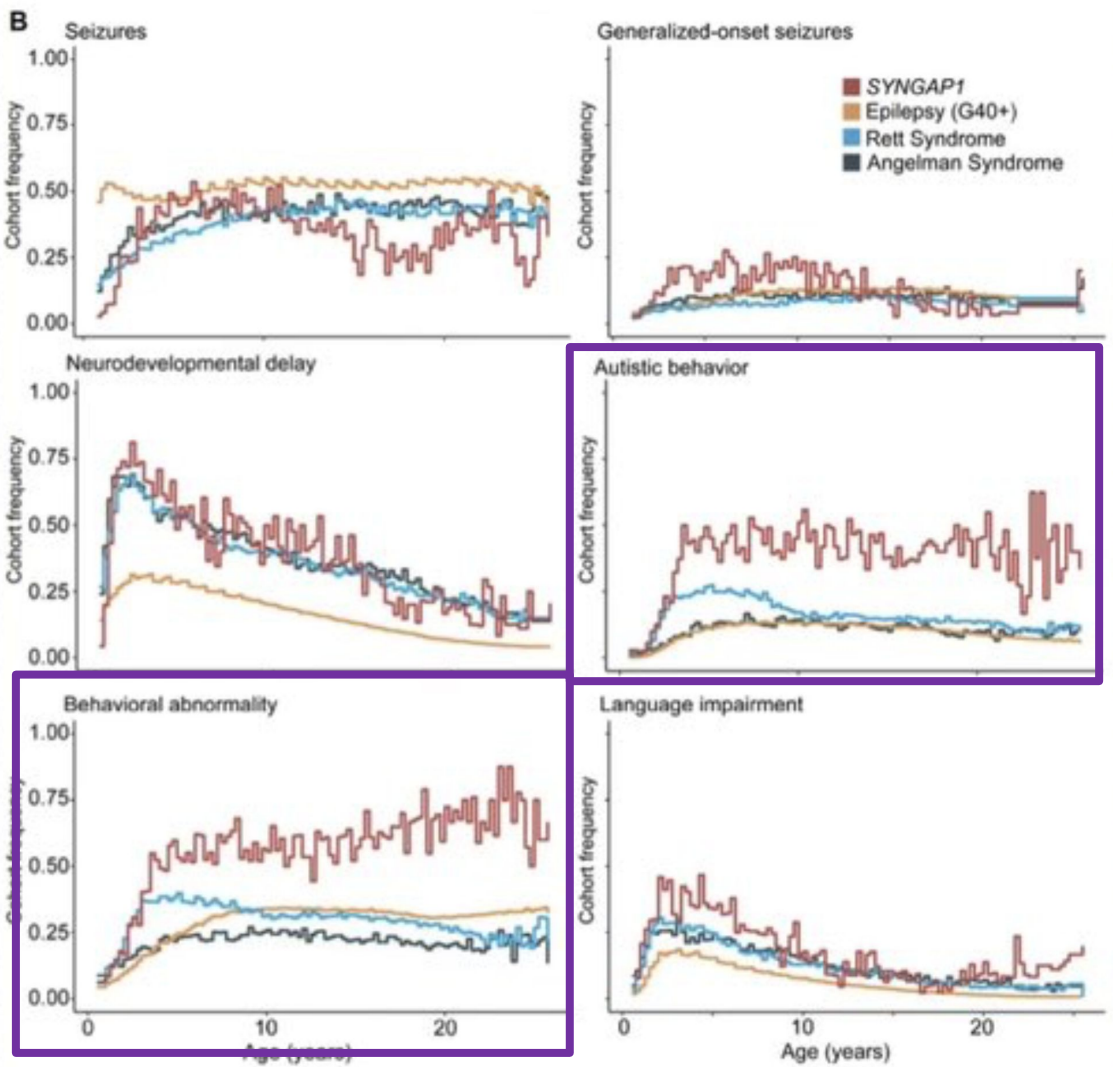

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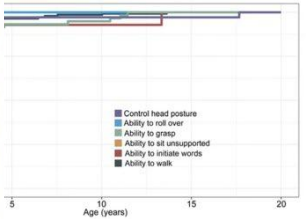

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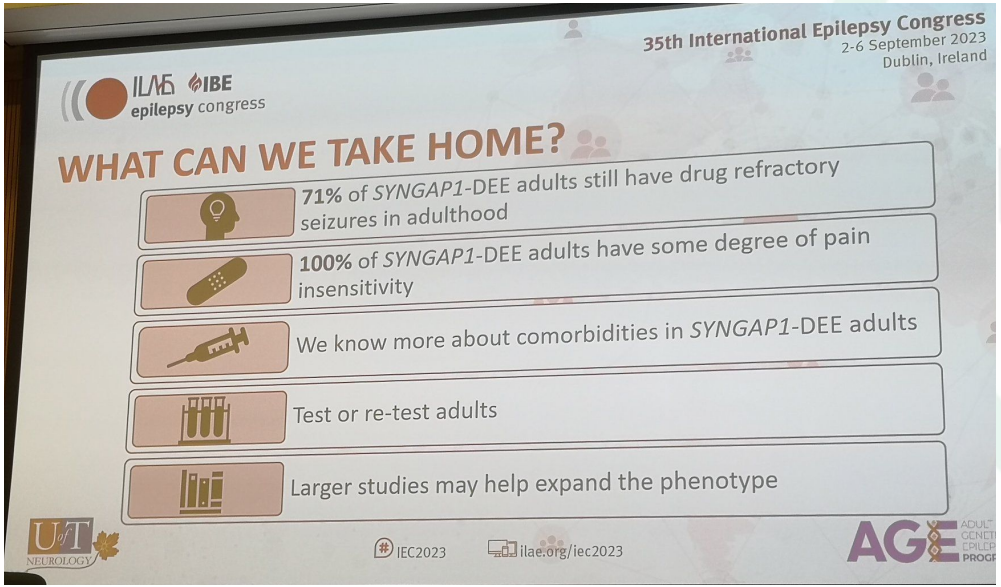
Life with Tony is not easy and getting harder

Spontaneous aggression (seizures maybe?) leads to bruises and scary moments for family member, makes it very challenging to find childcare or ABA and requires transferring to a special school this year.

Tony is getting stronger and the future is scary.

Syngap.Fund/NW

SYNGAP1 patients live a long time

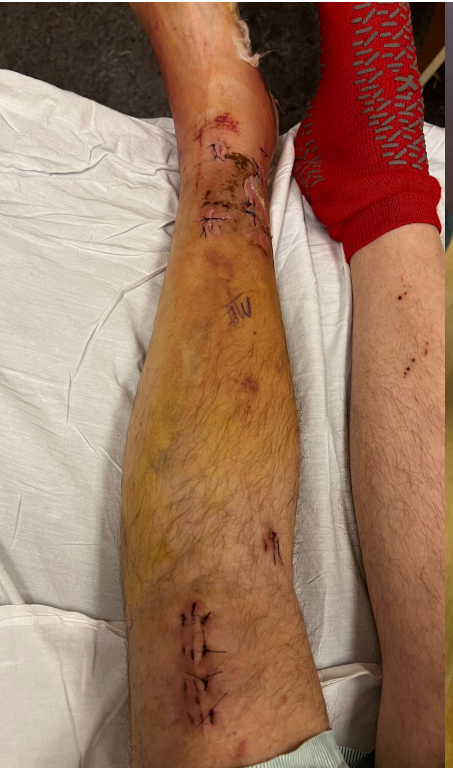
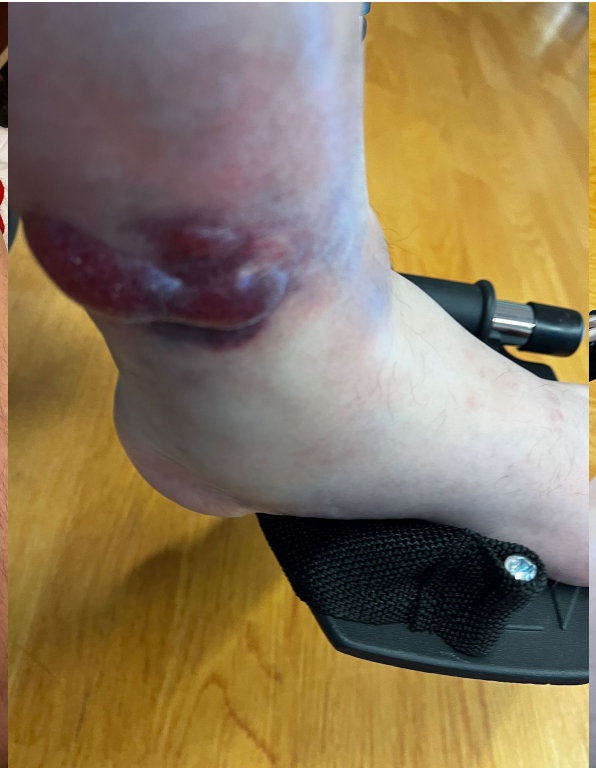
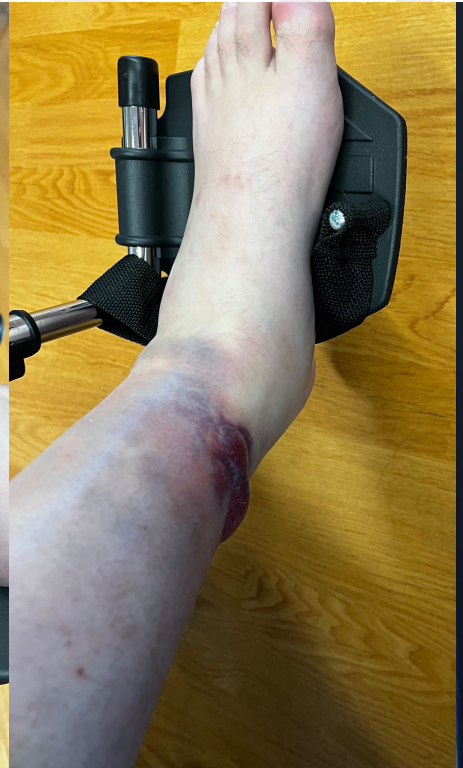
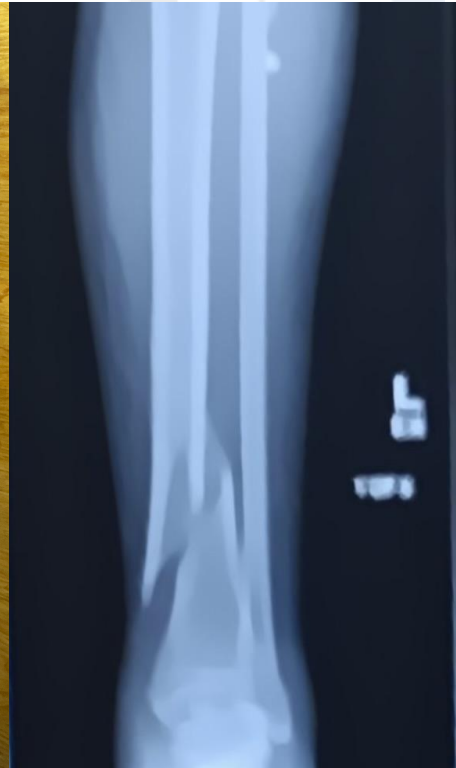


https://twitter.com/AleRossiNeuro/status/1699993470151151621

https://syngap.fund/caren

Adults have severe complications of lifelong treatment

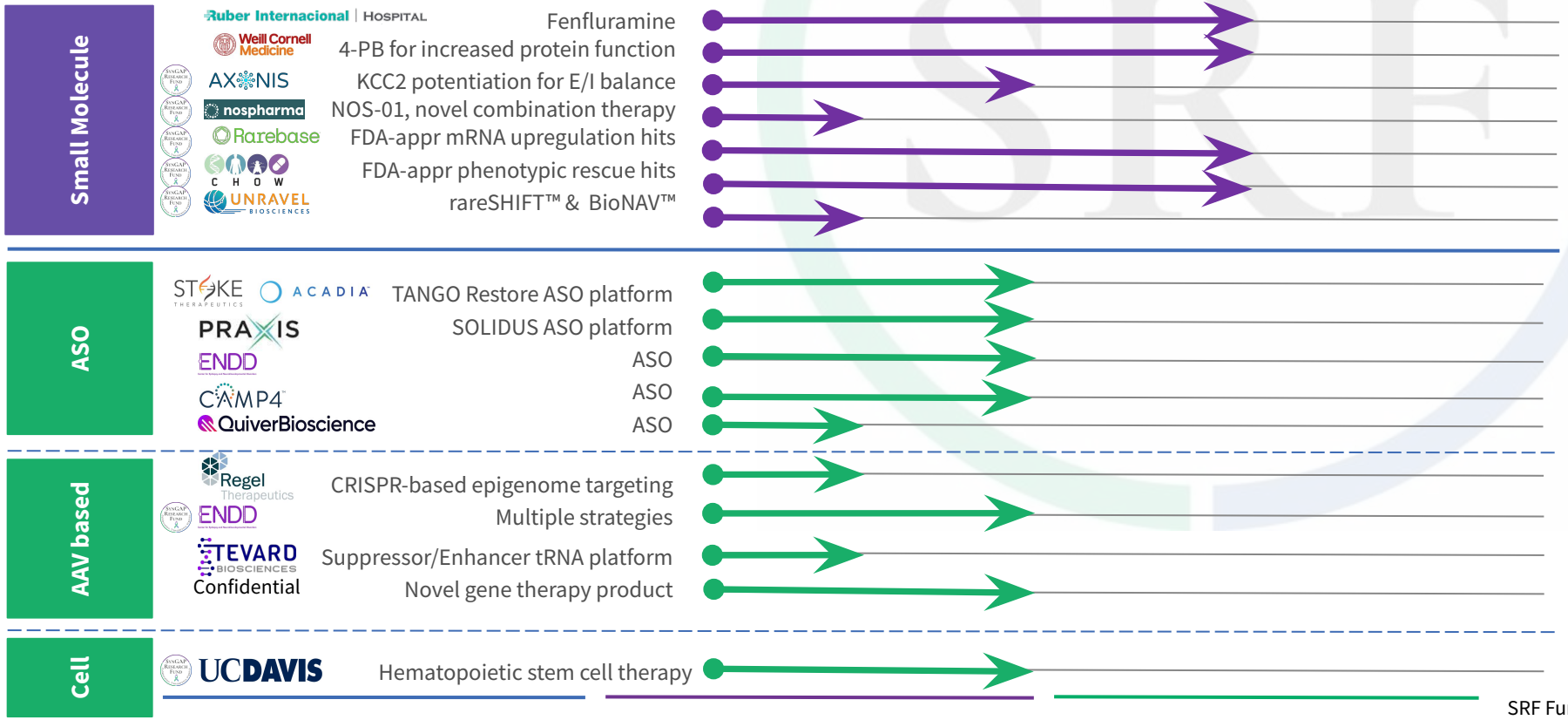
Refractory drop seizures + with weak bones from decades of ASMs = Severe Fractures

SYNGAP RESEARCH FUND
cureSYNGAP1.org

SYNGAP1 THERAPEUTIC PIPELINE | 2024

DISCOVERY | PRECLINICAL | IN HUMAN | FDA REVIEW & APPROVAL



SRF Funded

We believe that SYNGAP1 is rescuceable... (and have shown this in adults mice[1])

"Neurons want their SYNGAP back"

- Researcher, SRF Conference 2022

"We had no idea how plastic the brain was."

- Clinician re Stoke ASO results in Dravet

"The change in my child was amazing the day after the drug, I never thoguht I would see them do..."

- SRF Parent re small molecule trial

1. Thomas K Creson, Camilo Rojas, Ernie Hwaun, Thomas Vaissiere, Murat Kilinc, Andres Jimenez-Gomez, Jimmy Lloyd Holder Jr, Jianrong Tang, Laura L Colgin, Courtney A Miller, Gavin Rumbaugh (2019) **Re-expression of SynGAP protein in adulthood improves translatable measures of brain function and behavior**

...but what will we measure when seizures are not obvious?

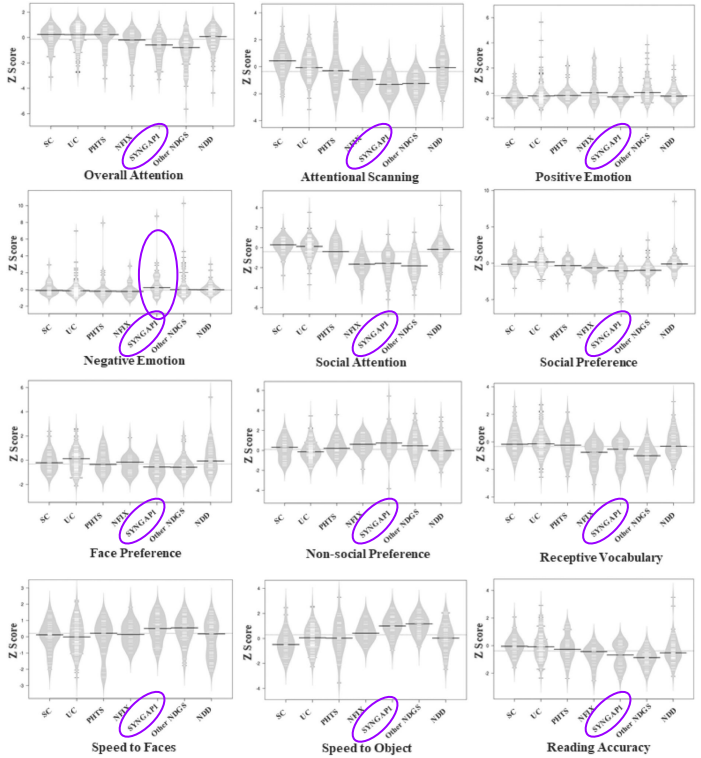
- CHOP/CHOC/Stanford NHS are testing multiple validated scales
- Eye Tracking and ORCA (FDA) are being developed and validated for S1
- SRF & CB are looking for biomarkers via separate proteomic studies
- Number of ASMs that can be removed could be a good endpoint
- "Improved sleep is a viable endpoint for future clinical trials for these neurodevelopmental disorders (SYNGAP1 & SHANK3)" [1, 2, 3] GI too!
- EEG biomarkers are being identified, but we need an easier way to test frequently.[4,5]

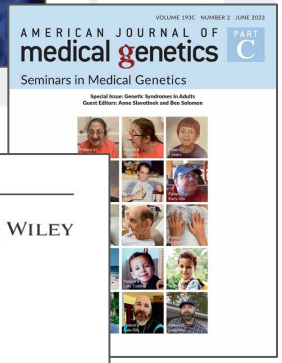
1. Smith-Hicks, Constance et al. "Sleep Abnormalities in the Synaptopathies-*SYNGAP1*-Related Intellectual Disability and Phelan-McDermid Syndrome." *Brain sciences* vol. 11,9 1229. 17 Sep. 2021
2. Mosini, Amanda et al. "Subjective sleep assessment in individuals with SYNGAP1–associated syndrome" Journal of Clinical Sleep Medicine, online. 3 Jul. 2024
3. Paasch,Valerie et al. "An exploratory study of sleep quality and quantity in children with causal variants in *SYNGAP1*, an autism risk gene" Sleep Medicine, vol. 107, 2023
4. Gonzales-Sulser, Alfredo. "Learning EEG Biomarkers in *SYNGAP1* Rodent Models and Patients" *SYNGAP1* Conference 2023. https://www.youtube.com/watch?v=NfMpgF19crI
5. Levin, April. "Using EEG to understand 'how the brain works' in *SYNGAP1*" *SYNGAP1* Conference 2023. https://www.youtube.com/watch?v=WdcURdASE2s

Scales being used at CHOP for *SYNGAP1* NHS

- Modified Checklist for Autism in Toddlers (MCHAT), participants 16-30 months
- Computerized Pediatric Evaluation of Disability Inventory (PEDI-CAT)
- Observer-Reported Communication Ability (ORCA)
- Sensory profile 2
- Quality of Life Inventory-Disability (QI Disability)
- Developmental Disability-Clinical Severity Assessment (DD-CSA)
- Vineland Adaptive Behavior Scales (VABS-III)
- Aberrant Behavior Checklist (ABC-2)
- Child Behavior Checklist (CBCL), participants ≥ 18 months
- Children's Sleep Habit Questionnaire (CSHQ), participants > 2 years
- Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)
- Vanderbilt ADHD Diagnostic Teacher Rating Scale (VADTRS)
- Emotional Dysregulation Inventory (EDI) - PROMIS
- Anxiety Scale – PROMIS
- Repetitive Behaviors Scale (RBS-R)
- Social Responsiveness Scale (SRS-2)
- CDD Clinical Severity Assessment (CCSA-Caregiver)

Eye tracking tool just published by SRF grantee





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ORIGINAL ARTICLE

American Journal of medical genetics Part A WILEY

Development of informant-report neurobehavioral survey scales for PTEN hamartoma tumor syndrome and related neurodevelopmental genetic syndromes

Thomas W. Frazier[1,2] | Robyn M. Busch[3,4] | Patricia Klaas[3] | Katherine Lachlan[5] | Shafali Jeste[6] | Alexander Kolevzon[7] | Eva Loth[8] | Jacqueline Harris[9] | J. Michael Graglia[1] | Jenine Beekhuyzen | Charis Eng[4] | A

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[5]Human Genetics and Genomic M
[6]Division of Neurology, Children's
[7]Departments of Psychiatry and
[8]Department of Forensic and Ne
[9]Krieger Institute and Johns Hop
[10]Department of Psychology, Fra
[11]PTEN Research Foundation, Ch
[12]PTEN Hamartoma Tumor Synd
[13]SYNGAP Research Fund, Palo A
[14]Malan Syndrome Foundation, C
[15]ADNP Kids Foundation, Brush
[16]Adroit Research, Brisbane, Que
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RESEARCH ARTICLE

American Journal of medical genetics Part C Seminars in Medical Genetics WILEY

Development of webcam-collected and artificial-intelligence-derived social and cognitive performance measures for neurodevelopmental genetic syndromes

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[2]Departments of Pediatrics and Psychiatry, SUNY Upstate Medical University, Syracuse, New York, USA
[3]Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, Ohio, USA
[4]Genomic Medicine Institute, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA
[5]Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton and Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[6]Division of Neurology, Children's Hospital of Los Angeles, Los Angeles, California, USA
[7]Departments of Psychiatry and Pediatrics, Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York, New York, USA
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Duke & FDA expanding ORCA from Angelman to SYNGAP1 & other DEES

ORCA

Observer-Reported Communication Ability Measure

FDA

Department of Population Health Sciences
Duke University School of Medicine

COMBINED


Tony, 7


Tony, 10

thank you

mike@cureSYNGAP1.org

SYNGAP 1 SRF

10 minute updates with mike graglia

@cureSYNGAP1