

TIMOTHY SYNDROME ALLIANCE (TSA)



ANNUAL REPORT

FOR FINANCIAL PERIOD

1 DECEMBER 2020 TO 30 NOVEMBER 2021



WELCOME



Vision:

Our vision is a world where shared knowledge and understanding lead to a cure for everyone with a *CACNA1C* genetic variant.

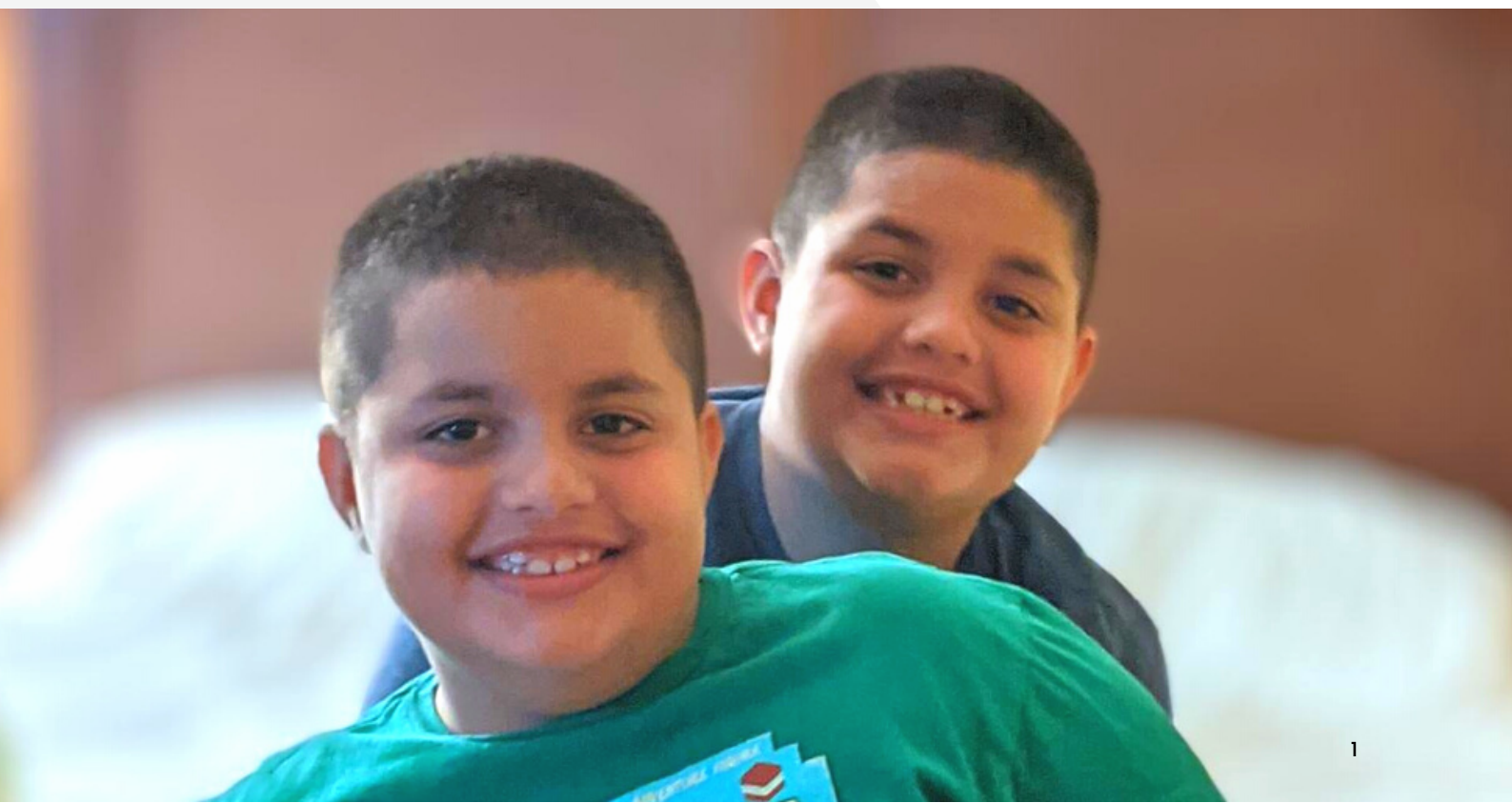
Mission:

Our mission is to improve the diagnosis, treatment and care of individuals with *CACNA1C*-related disorders, including Timothy Syndrome and LongQT8, and to support the families and carers of those diagnosed.

Our values:

Our values combine to form a solid foundation for the way in which we do things and what we believe in. We are **determined, supportive, empowering** and **a community**.

CACNA1C-related disorders, including Timothy Syndrome and LongQT8, do not have geographic boundaries. TSA has no boundaries. We support families wherever they are in the world. Why? Because we are **#strongertogether**



CACNA1C

What is CACNA1C?

CACNA1C is a gene that provides the code for a protein found in cells throughout the body. This protein manages the movement of calcium in and out of the cell, which is critical for many cells' function. Changes to the gene can cause changes to the protein and its ability to manage calcium movement, making it work more, less, or not at all.

What is Timothy Syndrome?

Timothy Syndrome (TS) is caused by specific changes to the *CACNA1C* gene. There are two types of TS: TS1 and TS2.

Most common symptoms include: abnormal heart function, irregular heart beat, abnormal heart structure, neuronal developmental delays, immunodeficiencies, endocrinological dysfunction, gastrointestinal concerns, effects on smooth muscle, effects on skeletal muscle, facial anomalies, syndactyly (joined fingers or toes), mild dental, skin, eye and hair anomalies.

Some individuals have: significant episodes of low blood sugar levels (hypoglycemia), seizures, an unusually low body temperature (hypothermia).

What is a CACNA1C-related disorder?

A novel variant in the *CACNA1C* gene - individuals have some but not all symptoms typical of Timothy Syndrome. Some affected individuals may present with multisystem health concerns that overlap entirely with Timothy Syndrome.

What is Non-syndromic LongQT8?

Non-syndromic LongQT8 overlaps with Timothy Syndrome in that the affected individual has LongQT (a prolonged QT interval on an ECG). There are many variants throughout the *CACNA1C* gene that appear to cause non-syndromic LongQT8.

**Increase in Support Group members
between
1 December 2020 and 30 November 2021
+44**

ACHIEVEMENTS AND PERFORMANCE

Raising Awareness

Our first **film** from 2019 continues to raise awareness and to signpost families to TSA to connect with the CACNA1C Community for knowledge and support. Film festivals widen our audience; this year we were a finalist at the International Rare Disease Festival (Berlin) and Uno Sguardo Raro Festival - The Rare Disease International Film Festival (Rome). The film took Silver in the Best Creative Campaign category at the PM Society Awards 2021 (UK), whose audience is the pharmaceutical and healthcare industry.

To coincide with Rare Disease Day on the 28th February we made a film called 'Rare Strikes Back' with aligned aims of improving knowledge amongst the general public of rare diseases whilst encouraging researchers and decision makers to address the needs of those living with rare disease. It signposts to both the TSA and the Rare Disease Day websites.

The film was launched on all our social media channels and has been viewed over 11,000 times on Twitter alone. 'Rare Strikes Back' went on to win Best Storytelling by a Voluntary Group at the Rare Reach Festival - Rare Disease UK 2021 and Gold at the Charity Film Awards (UK) £0 - £100,000 Turnover Category. It won Bronze at the PM Society Digital Awards - Effectiveness Category, was a finalist at Uno Sguardo Raro



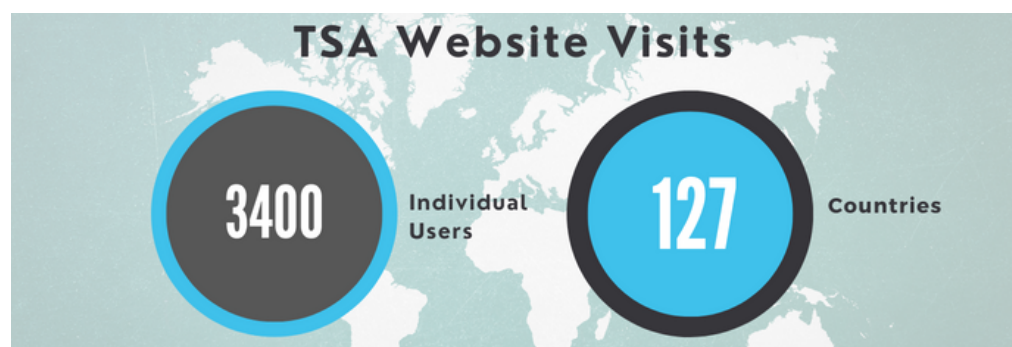
ACHIEVEMENTS AND PERFORMANCE

Festival - The Rare Disease International Film Festival, QIFF: Quarantine International Film Festival (India)) and PM Society Digital Awards 2021 - Craft category. The film is also available on The Disorder Channel streaming through Amazon Fire and Roku.

Our next film will be a deeper dive into *CACNA1C* aimed at healthcare professionals.

'OPEN Health is a leading Global healthcare communications agency with extensive scientific expertise. It's a pleasure to work with the team at TSA following their deserved award at the 2021 Rare Reach festival. It's always wonderful working with a talented team that are collectively dedicated to better patient outcomes where there is such unmet need. OPEN Health are committed to providing expert pro bono resources to play a part in making this important and much needed film a success. Our role is to identify and validate the key clinical messages that the film needs to convey and create a script that makes both impact and mobilises healthcare professional into positive change. To enable this we have assembled a team of both scientific experts and project managers to ensure the film is scientifically robust, has the necessary impact and that we deliver on our promise.' Gavin Jones | Global Advisor | Rare Diseases

The TSA **website** continues to grow and is now available in the German language via a simple flag click. Our presence on **social media** forums such as Facebook, Instagram, Twitter and LinkedIn also show steady growth in supporters. With repeated use of hashtags we were delighted when a new family found us having seen **#CACNA1C** on Rare Disease Day. **#TSAawareness21**, our first **awareness day** was successfully celebrated on 1st October with many posts shared globally as well as awareness support from Congenica, Rare Revolution and Genetic Alliance UK.



ACHIEVEMENTS AND PERFORMANCE

Community



Timothy Syndrome Alliance (TSA) and the Neuroscience and Mental Health Research Institute (NMHRI) hosted online the Brain Research **Conference** online on 25th June 2021. The conference gave over 70 registered attendees 4 hours of the latest insight into *CACNA1C* research delivered by seven leading figures in this field.

A worldwide attendance saw families with TS or *CACNA1C* gene variants and researchers drawn in from as far east as Malaysia to as far west as California.

"It's a great privilege to be able to host the TSA annual meeting again. These events offer an opportunity for families with this rare disorder to come together from around the globe, make connections and hear about the latest advances in understanding it."

Dr Jack Underwood

**Wellcome Trust GW4-CAT Clinical Research Fellow,
NMHRI**

The conference began with a talk from Gemma Wilkinson, who discussed using patient-derived calls to investigate *CACNA1C*. Talks throughout the conference focused on research within *CACNA1C*, including a session from Dr. Underwood, before a concluding discussion from Dr Rebecca Levy. Questions from attendees were taken in between talks, sparking in-depth conversation and constructive interaction between speakers and guests.

"The Brain and TSA research conference was wonderful, with four hours of the newest research information on *CACNA1C* and Timothy Syndrome shared. I've waited for years for researchers to study neuronal issues observed in TS in-depth and I'm very pleased with the collaborative efforts now being undertaken with Dr. Jeremy Hall and his associates, Dr. Liz Turnbridge and the Stanford University group."

Katherine Timothy

Dr. Underwood highlighted, "Meeting the families and hearing their thoughts and hopes provides meaning to our research, and is leading to discussions, partnerships and international collaborations among researchers investigating TS and *CACNA1C*-related disorders."



ACHIEVEMENTS AND PERFORMANCE

Every session of this conference was **transcribed and translated** into Brazilian Portuguese to ensure the information was accessible to our families.

Early and accurate diagnosis

TSA has submitted an application via NHS England and NHS Improvement to update the 2021/22 National Genomic Test Directory. The application is to update the nomenclature to include 'CACNA1C-related disorders' on existing panels and to include CACNA1C on a new panel 'Early onset or syndromic epilepsy'.

The Genomics England PanelApp, a publicly-available knowledgebase used by experts throughout the worldwide scientific community relates to genomic tests listed in the NHS National Genomic Test Directory. Clinicians and other healthcare professionals use PanelApp to view and interpret a panel that has been applied to their patient and to look at the evidence for the inclusion of a gene(s) in their patient report during a Multidisciplinary Team (MDT). If successful these changes will make a difference to improving early and accurate diagnosis.

Research and education

In October 2020 TSA entered The Student Voice Prize, an annual international essay competition that raises the profile of rare disease within the medical field, particularly with medical students, nurses and scientists who may have never come across rare diseases in their training. We worked with our amazing student Zoe who has been a TSA advocate ever since and even translated our website into German. Our German based families have also now worked with Zoe participating in a rare disease neonatology and paediatrics university scheme.


TSA were delighted to be invited by Cambridge Rare Disease Network (CRDN) to take part in the inaugural Patient Group and Industry Partnering event. This event brought together 10-12 rare disease patient groups alongside a similar number of companies working in the orphan drug space with the

ACHIEVEMENTS AND PERFORMANCE

goal of finding new avenues for collaboration between individual companies and patient groups towards the development of new treatments.

A dissertation study looking at the psychosocial impact of living with *CACNA1C*/TS/LongQT8 diagnosis has begun for a MSc Genetic & Genomic Counselling student we are working with at Cardiff University.

Recruitment of *CACNA1C* families has begun for the first international study investigating the effects of *CACNA1C* variants on brain development and mental health (Cardiff University and Stanford University). We look forward to better understanding *CACNA1C* as a result of this collaboration.



Cardiff University
Neuroscience & Mental Health Research Institute
Safonidol Vintchall y Neurowyddrau ac Iechyd Meddal

Examining the symptom spectrum of *CACNA1C* gene variants

We are a genetic research group based in the Division of Psychological Medicine and Clinical Neurosciences in Cardiff University's School of Medicine, dedicated to understanding the effects of having a *CACNA1C* gene variant.

We would be really grateful if you and your family would consider taking part in our research

investigating Timothy Syndrome and *CACNA1C* gene variants.

In brief, taking part in this research will involve researchers contacting you and your family first with a short survey, and then a via video call.

If you would like to be involved in this international effort to understand Timothy Syndrome please contact us.

WHO WE ARE

Our researchers are based in purpose-built research laboratories in the Hadyn Ellis Building, part of Cardiff University's Maindy Road campus.

This £30m investment houses neuroscientists from the Research Institute, the MRC Centre for Neuropsychiatric Genetics and Genomics, the National Centre for Mental Health, the BRAIN Unit. Bringing together genetics, neuroscience and clinical research on a single site.

The Research Institute comprises over 100 neuroscientists and researchers from other disciplines who are actively engaged in neuroscience research.


CONTACT US

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neuroscience@cardiff.ac.uk
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@neuroscienceccu


Neuroscience and Mental Health Research Institute
Hadyn Ellis Building
Maindy Road
Cardiff CF24 4HQ

We are a group of researchers investigating the effects of *CACNA1C* variants on brain development and mental health as part of an international study with Stanford University.


If you would like to take part in our research, please contact us:



Professor Jeremy Hall
hallj10@cardiff.ac.uk



Dr Kathryn Peall
peallkj@cardiff.ac.uk

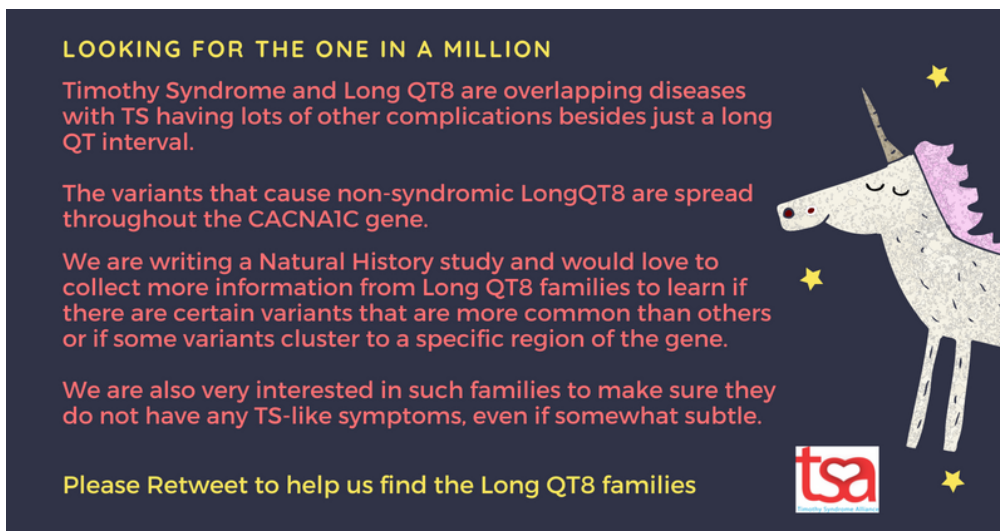
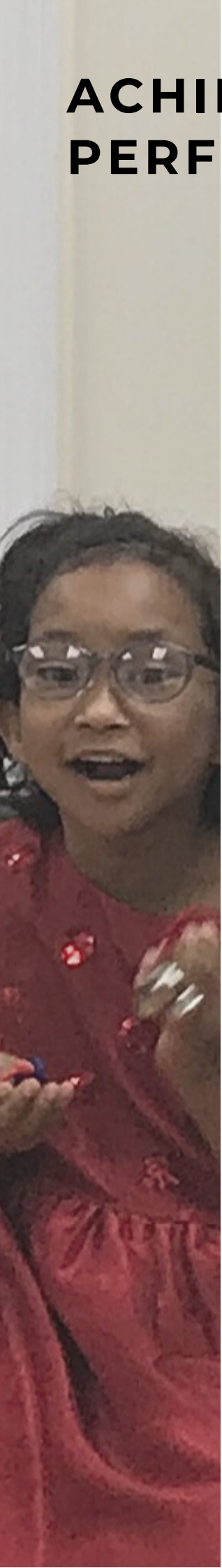


Dr Jack F G Underwood
underwoodj4@cardiff.ac.uk

We are working with Cardiff University on The Rare Disease Research Journey project which aims to create a short film with global reach showcasing the importance of public engagement in research, and the research journey from an individual's involvement through clinical research to changes in practice and understanding. The project is a collaboration between the Neuroscience and Mental Health Research Institute (NMHRI) and TSA, with combined academic, charity and public involvement in production.

ACHIEVEMENTS AND PERFORMANCE

In September we ran a campaign on our social media channels which was successful in signposting new LongQT8 families to our support group.



LOOKING FOR THE ONE IN A MILLION


Timothy Syndrome and Long QT8 are overlapping diseases with TS having lots of other complications besides just a long QT interval.

The variants that cause non-syndromic LongQT8 are spread throughout the CACNA1C gene.

We are writing a Natural History study and would love to collect more information from Long QT8 families to learn if there are certain variants that are more common than others or if some variants cluster to a specific region of the gene.

We are also very interested in such families to make sure they do not have any TS-like symptoms, even if somewhat subtle.

Please Retweet to help us find the Long QT8 families



Published papers of note:

- Bauer, R., Timothy, K. and Golden, A. (2021). Update on the Molecular Genetics of Timothy Syndrome. *Frontiers in Pediatrics*, 9. <https://doi.org/10.3389/fped.2021.668546>
- Rodan, L. H., Spillmann, R. C., Kurata, H. T., Lamothe, S. M., Maghera, J., Jamra, R. A., Alkelai, A., Antonarakis, S. E., Atallah, I., Bar-Yosef, O., Bilan, F., Bjorgo, K., Blanc, X., Van Bogaert, P., Bolkier, Y., Burrage, L. C., Christ, B. U., Granadillo, J. L., Dickson, P., ... Shashi, V. (2021). Phenotypic expansion of CACNA1C-associated disorders to include isolated neurological manifestations. *Genetics in Medicine*, 1-11. <https://doi.org/10.1038/s41436-021-01232-8>

Support

'having the TSA Facebook group has helped massively in understanding that we aren't alone in this, and that we all can support each other even at a distance.'

TSA administers an online Facebook Support Group for individuals and families of CACNA1C-related disorders including Timothy Syndrome and LongQT8, offering 24/7 access to emotional and practical support and information via our families. The benefits of this are huge, enabling:

- meeting and befriending other people with the same rare disease and similar experiences from across the world



ACHIEVEMENTS AND PERFORMANCE

- learning about the disease
- giving and receiving emotional support
- having a place to speak openly about the disease and one's feelings
- learning coping skills
- feeling empowered and hopeful
- advocating to improve healthcare.

'like minded people who don't judge and are always there if you have a lot of questions'

The support group is growing in size as is the spectrum of affectedness as we find more families. Identified previously as a need, TSA began Support Each Other 'drop in' Zooms which were well attended. This support has now progressed to working with Rareminds which is an organisation that specializes in providing counselling and emotional wellbeing services for the rare disease community.

'Not being alone is a tremendous help.'

Sometimes other forms of support can help our community. Donations have enabled cardiac equipment – a defibrillator – to be donated to a family and, sadly, contributions have also helped another family towards unexpected funeral expenses for their child.

'Just beyond wonderful to be connected with other families.'

Fundraising

'I feel seen (you see us as others cannot)'

Every donation we receive goes to help fund the vital work that we do as a charity.

We:

- support and connect the CACNA1C community
- improve CACNA1C diagnosis, outcomes and quality of life
- support CACNA1C research initiatives

The impact of the pandemic accompanied by low awareness of rare diseases and TSA makes fundraising a challenge however by widening our digital reach and using creative ways to engage audiences we are continuing to connect and

ACHIEVEMENTS AND PERFORMANCE

actively grow our support base.

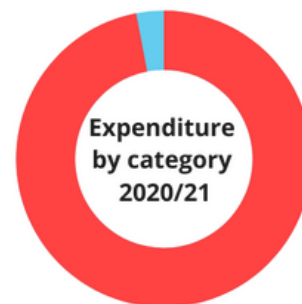
We have only one volunteer managing TSA full time which means the amount of time available to specifically fundraise is limited due to the other mission based activities. The generosity of your support has been amazing. Whether it be regular monthly donations, a one off gift, creating a birthday fundraiser on Facebook or sponsorship from running a marathon our heartfelt thanks goes to each and every one of you.

'TSA is the conduit of all the advances in medical research, care, and quality of life support.'



Voluntary Receipts 100%

Total income £6084



Charitable Activities 97%

Charity costs 3%

Total expenditure £3226

Special thanks to the following for your support and projects: Limestone Media, the teams at the NMHRI Cardiff University, Department of Psychiatry, Oxford University and Stanford University, OPEN Health and Charity Translators. Dmitry Kran, Zoe Shaked, Bhavna Vadukul and our students Tali Feen, Laurel Mangelsdorf and Raivat Shah from Muhlenberg College.

It really is chicken and egg. We know it's an important gene, and there are people out there, but we have to find the people, to publish the papers proving it's important, to persuade people it's important to identify the gene, to help find the people, to get them involved, to publish the papers to show it's important...





**The trustees present
their report for the
period
1 December 2020 to
30 November 2021.**

TIMOTHY SYNDROME ALLIANCE (TSA) TRUSTEES' REPORT General Information

REGISTERED CHARITY NUMBER: 1185523

TRUSTEES:

Sophie Muir – Chairperson

Galina Gardiner – Treasurer

Meg McLoughlin - Secretary

Nick Muir

Katherine W Timothy (Appointed 14 December 2020)

Andy Golden (Appointed 14 December 2020)

Sally Johns (Appointed 8 September 2021)

REGISTERED OFFICE:

8 Butt Street, Minchinhampton, Gloucestershire GL6 9JP

Objectives: To relieve the needs of those affected by *CACNA1C*-related disorders including Timothy Syndrome and LQT8, their families, friends and carers. Promote greater understanding of the causes, symptoms and treatment. Raise public awareness of the symptoms, needs and related medical conditions.

Structure, governance and management: Timothy Syndrome Alliance (TSA) is a registered charity number 1185523, governed by the Charities Act 2006. The charity is a Charitable Incorporated Organisation registered on 27 September 2019 under the Foundation Governing Document. New trustees are appointed by the serving trustees, considering the skills required by the board.

Public Benefit: The Trustees confirm that they referred to the Charity Commission's general guidance on public benefit when reviewing the Charity's aims and objectives for the year. Public benefit has been achieved as per the activities outlined in the Achievements and Performance section of this report.

Trustees' responsibilities statement

The trustees are responsible for preparing the trustees' report and the financial statements in accordance with applicable law and United Kingdom Accounting Standards (United Kingdom Generally Accepted Accounting Practice).

The trustees are required to prepare accounts for each financial year, which reflect the receipts and payments of the charity and of the surplus or deficit of income against payments for the year.

The trustees are responsible for:

- keeping proper accounting records which disclose with reasonable accuracy at any time the financial position of the charity; and
- safeguarding the assets of the charity and hence for taking reasonable steps for prevention and detection of fraud and other irregularities.

The trustees annual report was approved on and signed on behalf of the board of trustees by

Sophie Muir Chair of Trustees



CHARITY COMMISSION
FOR ENGLAND AND WALES

Timothy Syndrome Alliance

1185523

CC16a

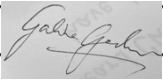
Receipts and payments accounts

For the period from	01/12/2020	To	30/11/2021
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Section A Receipts and payments

	Unrestricted funds to the nearest £	Restricted funds to the nearest £	Endowment funds to the nearest £	Total funds to the nearest £	Last year to the nearest £
A1 Receipts					
Voluntary Receipts	6084.2	-	-	6,084	-
		-	-	-	-
		-	-	-	-
		-	-	-	-
		-	-	-	-
		-	-	-	-
		-	-	-	-
		-	-	-	-
Sub total (Gross income for AR)	6,084	-	-	6,084	-
A2 Asset and investment sales, (see table).					
	-	-	-	-	-
	-	-	-	-	-
Sub total	-	-	-	-	-
Total receipts	6,084	-	-	6,084	-
A3 Payments					
Cost of Charitable Activities	3127.8	-	-	3,128	-
Governance Costs	98.6	-	-	99	-
	-	-	-	-	-
	-	-	-	-	-
	-	-	-	-	-
	-	-	-	-	-
	-	-	-	-	-
	-	-	-	-	-
Sub total	3,226	-	-	3,226	-
A4 Asset and investment purchases. (see table)					
	-	-	-	-	-
	-	-	-	-	-
Sub total	-	-	-	-	-
Total payments	3,226	-	-	3,226	-
Net of receipts/(payments)	2,858	-	-	2,858	-
A5 Transfers between funds	-	-	-	-	-
A6 Cash funds last year end	-	-	-	-	-
Cash funds this year end	2,858	-	-	2,858	-

Section B Statement of assets and liabilities at the end of the period

Categories	Details	Unrestricted funds to nearest £	Restricted funds to nearest £	Endowment funds to nearest £
B1 Cash funds	Bank balance	2,843	-	-
		-	-	-
		-	-	-
	Total cash funds	2,843	-	-
	(agree balances with receipts and payments account(s))	Agreement Error	OK	OK
B2 Other monetary assets	Details	Unrestricted funds to nearest £	Restricted funds to nearest £	Endowment funds to nearest £
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
		-	-	-
B3 Investment assets	Details	Fund to which asset belongs	Cost (optional)	Current value (optional)
			-	-
			-	-
			-	-
			-	-
B4 Assets retained for the charity's own use	Details	Fund to which asset belongs	Cost (optional)	Current value (optional)
			-	-
			-	-
			-	-
			-	-
			-	-
			-	-
			-	-
			-	-
B5 Liabilities	Details	Fund to which liability relates	Amount due (optional)	When due (optional)
			-	
			-	
			-	
			-	
Signed by one or two trustees on behalf of all the trustees		Signature	Print Name	Date of approval
			Galina Gardiner	17 March 2022