This is a Language Accessible Virtual Event

Language Accessibility

Powered by Wordly.ai

CONNECT CACNA1C GLOBAL NETWORK CONFERENCE

TSA Scientific Advisory Board

Dr. Jack Underwood
Wellcome Trust GW4-CAT Clinical Research Fellow, NMHII, Cardiff University

Dr. Rebecca Levy
Clinical Scholar, Neurology & Neurological Sciences.
Postdoctoral Scholar, Neurology & Neurological Sciences
Stanford Medicine

Dr. Gemma Wilkinson
Research Associate, NMHII, Cardiff University

Dr. Nicola Hall
Postdoctoral Researcher, University of Oxford

Dr. Anwar Baban
Bambino Gesù Children Hospital and Research Institute, IRCCS, Rome

Dr. Wilfried Haerty
Group Leader of Evolutionary Genomics, Earlham Institute

23 JUNE 2023

3PM-7:30PM BST

Register : timothysyndrome.org/conference

CONNECT CACNA1C GLOBAL NETWORK CONFERENCE

Welcome!

We are thrilled to gather our global CACNA1C community, spread across different parts of the world, in this virtual language-accessible conference. By embracing this digital platform, we ensure that everyone, regardless of their geographic location, has the opportunity to join us. Thanks to the inclusive Wordly Translation app, participants can engage in real-time, listening or reading along in their preferred language. Additionally, all presentations will be available after the conference for educational purposes.

We invite you to share this conference invitation with anyone interested in learning more about CACNA1C. There is no registration fee.

This conference serves as an opportunity for CACNA1C individuals, families, caregivers, researchers, scientists, healthcare professionals, advocates, and supporters to come together. We will collectively share current knowledge, and ongoing studies, exchange ideas, and foster collaborations that will help shape the future of CACNA1C research, improved diagnosis, and care.

Our programme features presentations by members of our Scientific Advisory Board and guest speakers, all experts in their respective fields. In addition, we have arranged two breakout discussion rooms and a dedicated Q&A session where speakers will be readily available to address your questions.

We hope that this conference will leave you feeling inspired and well-informed about the latest advancements in the field of CACNA1C. Together, we can turn hope into action, driving advocacy forward and creating a significant impact on the lives of those affected.

Thank you for joining us, we look forward to meeting you. ❤

Any queries? Please email sophie@timothysyndrome.org

TABLE OF CONTENTS

CONFERENCE PROGRAMME

3:00 PM Event Opens (Times BST)

3:10 PM **Welcome & Introduction**


Speakers: Sophie Muir & Jack Underwood (NMHII, Cardiff University)

3:15 PM **The Impact of CACNA1C Real-World Data: CCR Registry Update and Vision**


Speakers: Sophie Muir & Joshua Henderson (Pulse Infoframe)

3:40 PM **Differences in the expression of CACNA1C between the brain and the heart**

Speaker: Dr Nicola Hall (Department of Psychiatry, Oxford University)

4:00 PM **Discussion Rooms: Global Family Connect & Global Researchers Connect**

4:30 PM BREAK

4:45 PM **Using patient-derived stem cells to investigate CACNA1C-related disorders**

Speaker: Dr Gemma Wilkinson (NMHII, Cardiff University)

CONFERENCE PROGRAMME

5:05 PM	**Multiple beta cell-independent mechanisms drive hypoglycemia in Timothy syndrome**  Speaker: Dr Maiko Matsui (Cardiovascular Research Institute, Weill Cornell Medicine)
5:30 PM	BREAK
5:45 PM	**Heart and Beyond Heart: clinical spectrum of CACNA1C variants, literature revision**  Speaker: Dr Anwar Baban (Bambino Gesù Children Hospital and Research Institute, IRCCS, Rome)
6.15 PM	**Predicting functional effects of genetic variants in calcium and sodium channels such as CACNA1C**  Speaker: Dr Henrike Heyne (Hasso-Plattner-Institute, Potsdam, Germany and Mount Sinai School of Medicine, NY)
6:45 PM	**Discussion Rooms: Ask Anything (two researchers per room, multiple rooms open)**
7:30 PM	**Final Q&A**
7:30 PM	Event Close

OUR SPEAKERS

JACK UNDERWOOD

I am a Forensic Psychiatry Registrar Doctor on the Welsh Clinical Academic Track, currently undertaking a PhD in Neuroscience on a Wellcome Trust GW4-CATFellowship. My work predominantly focusses on rare and common genetic variants associated with autism and neurodevelopmental conditions, using a range of genetic and epidemiological techniques. My interest in CACNA1C is predominantly around characterising the genotype-phenotype relationship, with a goal of targeted therapeutics in the future alongside greater understanding of the neurobiology. I sit on the Scientific Advisory Board of the TSA, and have organised or presented at several international meetings on the topic of CACNA1C and rare gene variants.

JOSHUA HENDERSON

Joshua Henderson's expertise is in building relationships and fostering collaboration across diverse groups of stakeholders, with a specific focus on supporting underrepresented populations and advancing the development of treatments for underserved diseases. He is currently the Head of Rare Diseases at Pulse Infoframe, responsible for partnering with patient advocacy groups and biopharma companies globally to streamline fit-for-purpose, regulatory-grade real-world data. He is also a co-founder of the NW Rare Disease Coalition, the founder of StageNext Fund, investing in seasoned women entrepreneurs, and a Venture Partner & Healthcare Due Diligence Committee at NextGen Venture Partners. Previously, Joshua was the Vice President of Springboard Enterprises, a non-profit venture catalyst, where over 12 years he established its annual life science and health technology programs and led the efforts to recruit, select, and advise nearly 400 women-led healthcare and technology companies in the Springboard portfolio.

OUR SPEAKERS

NICOLA HALL

Dr Nicola Hall is a postdoctoral researcher at the University of Oxford, Department of Psychiatry and completed her PhD in 2017 at the University of Oxford, Department of Biochemistry. She is using her background in molecular biology and RNA sequencing to investigate how genes linked to brain disorders are expressed in the human brain. When a gene is expressed, an RNA copy of the gene is made, and that RNA message is used to make the protein that functions in the body. But most genes do not make only one protein product. The RNA message copied from the gene can be cut and stuck together in different ways to make slight changes in the way the final protein product is made and, therefore, in how the protein functions. Nicola's current work uses targeted RNA sequencing to read the RNA messages, comparing the differences in the RNA made from a gene in different brain regions and different tissues, which can tell us about how the gene acts in these different body locations.

GEMMA WILKINSON

My research involves using induced-pluripotent stem cells to investigate changes in neurodevelopment and neuron function in neurodevelopmental disorders, including CACNA1C-related disorder. Blood samples from patients are turned into stem cells (iPSCs) and from this we can grow brain cells or neurons. I then investigate changes that occur during the development of neurons and the effects on functional neuronal activity once they mature. By identifying what causes these changes, we hope to find new targets for treatment of neurodevelopmental disorders and test whether the changes can be rescued in the neurons.

OUR SPEAKERS

MAIKO MATSUI

Maiko Matsui is a scientist in the Cardiovascular Research Institute at Weill Cornell Medicine. She is interested in understanding causes of Timothy Syndrome (TS). Specifically, she studies how the normal and mutation of CACNA1C gene contribute to glucose regulation as well as metabolism in general and brain development in TS. Her broader research interests include metabolic regulation, cardiovascular diseases, and neuroscience. She received her Ph.D. from Duke University, and lives in Manhattan with her toddler daughter and husband.

ANWAR BABAN

Dr. Anwar Baban, MD, PhD, is a consultant Cardiogeneticist from Bambino Gesù Children Hospital and Research Institute (OPBG) in Rome – Italy. Founder and project lead of Cardiogenetic Centre which is part of Pediatric Cardiology, Cardiac Surgery, Heart and Lung Transplant Department. Dr Baban is a board member of ERN GUARD-HEART. The main fileds of interest are congenital heart defects (both isolated and multisystemic), channelopathies – genetically determined arrhythmias, Cardiomyopathies, aortopathies (Marfan S and related conditions), and pulmonary hypertension. The main fields of interest of the Cardiogenetic center is to offer tailored personalized multidisciplinary evaluations and whenever indicated molecular genetics diagnostic tests.

OUR SPEAKERS

HENRIKE HEYNE

Henrike Heyne is a research group leader at the Hasso-Plattner-Institute (HPI) Potsdam (Germany) and adjunct assistant professor at HPI Mount Sinai (NY, US) since 2021. Before that she was a postdoctoral researcher with Mark Daly at the Institute for Molecular Medicine Finland and before at the Massachusetts General Hospital/Broad Institute of MIT and Harvard. Dr. Henrike Heyne studied medicine at Leipzig University and obtained her doctoral degree at the Max Planck Institute for Evolutionary Anthropology (doctoral mentors: F. Albert, S. Pääbo). In her research, she is interested in genomic/personalized medicine; with a focus on ion channel related diseases such as epilepsy. With research training in computational and clinical genetics labs and an MD degree she aims for clinical applications of her predominantly computational genetics research.

SOPHIE MUIR

After a nearly decade-long diagnostic odyssey, my middle son Calvin was diagnosed with CACNA1C in 2016 through the DDD study and the 100,000 Genomes Project. With only 43 known living CACNA1C individuals worldwide, I registered Timothy Syndrome Alliance (TSA) as a charity in 2019. Leading the charity's day-to-day operations, we've focused on increasing awareness and signposting to grow our global community in size thereby improving our understanding of this gene and generating research interest. Today, our community has increased to over 120 individuals and I'm excited to bring together those with whom we collaborate to share the very latest knowledge on CACNA1C. Committed to improving the information and support for families and individuals with CACNA1C gene changes, I'm fortunate to be working with dedicated researchers and clinicians who share my enthusiasm for understanding CACNA1C.

DISCUSSION ROOMS/Q&A - HOW WILL IT WORK?

We will open two discussion rooms at 4:00 PM

The first will be for families and individuals from across the world to connect, as an opportunity for people to meet, and share stories and experiences.

The second room will be for researchers, clinicians and scientists, to share their own experiences and work on the CACNA1C, with an aim to forge links and connections for future work.

Attendees will be free to choose which room they wish to enter within the Zoom software, so we ask you to attend the room suitable for your background.

At 6:45 PM we will open a further set of rooms.

Speakers and attending Scientific Advisory Board members will split into separate rooms, offering attendees the opportunity to ask questions and discuss in smaller groups.

Does the Wordly App for Zoom work in breakout rooms?

Unfortunately, the Wordly App for Zoom does not support Zoom breakout rooms at this time. In order to provide translations, Wordly needs access to the audio stream, which Zoom does not make available in breakout rooms.

CACNA1C-related disorders (CRD) & Timothy Syndrome Alliance (TSA)

INTRODUCTION TO TSA

Timothy Syndrome Alliance (TSA) registered as a UK charity in 2019:

- Raises awareness of *CACNA1C*-related disorders including Timothy Syndrome and LongQT8 to improve the diagnosis, treatment and co-ordination of care
- Shares expertise and best practice - Scientific Advisory Board established January 2023
- Maintains a global *CACNA1C* Community Registry to improve the understanding of the epidemiology of *CACNA1C* to accelerate and support clinical and basic research
- Promotes research on treatment options and diagnostics
- Facilitates a global support network for individuals, families and carers of those diagnosed

INTRODUCTION TO *CACNA1C*

CACNA1C is a gene that provides the code for a protein found in the walls of 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 affect the protein's structure and its ability to manage calcium movement, making it work more, less, or not at all. Variants in the gene are associated with *CACNA1C*-related disorders including Timothy Syndrome (pathognomonic p.G406R protein change)[2] and LongQT8 (non-syndromic cardiac-only).[3] As we identify more individuals with *CACNA1C* variants there is considerable variability in the phenotype (ranging from severely affected with serious cardiac events to apparently mildly affected with only a few features). These phenotypes are multi-system, but typically individuals present with autism spectrum disorder, developmental delay, prolonged cardiac QT interval, syndactyly/ hip dysplasia, hypotonia, epilepsy and hypoglycaemia.

Due to low awareness, phenotypic variability, a lack of genotype-phenotype correlations for atypical variants, and no extant multicentric *CACNA1C* cohorts, clinical genetic testing results are not influencing clinical management, with many classified as Variants of Uncertain Significance (VUS).

It is now recognised that *CACNA1C* variants result in a spectrum of phenotypes[4], from neurodevelopmental through cardiac and musculoskeletal. *CACNA1C* studies have highlighted substantial advances in our understanding of *CACNA1C*. TSA and the *CACNA1C* community have been collaborating on research with NMHII, Cardiff University, University of Oxford and Stanford University for the past 3 years.

CACNA1C COMMUNITY REGISTRY

This registry went live June 2022 and collects information from *CACNA1C* individuals and caregivers worldwide to serve as a research platform of real-world data.
Comprehensive multisystemic characteristics and symptomology data including variant, age at diagnosis plus full demographics data are collected upon enrollment and yearly thereafter.

"*Clinical importance* of ***screening*** *and therapeutically addressing* ***neuropsychiatric*** *symptoms in* ***all*** *individuals with* ***CRD.***" [1]

Phenotypes include Epilepsy[5] / Seizures...

Caregiver-reported survey-based data (TSA Nov 2022) representing n=18; 17 CRD, 1 TS and 1 LQT8 individuals from our *CACNA1C* community (global support network comprising ~120 individuals with identified CRD in which n=19 are known to have presented with seizures/epilepsy - in some cases this may be just one occasion). Final survey awaiting translation.

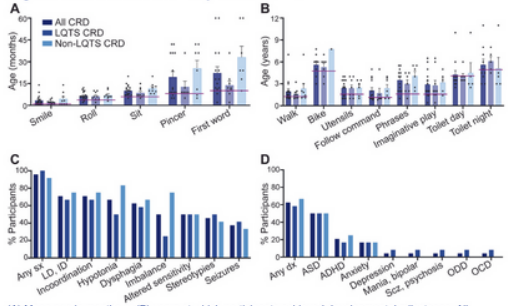
- Typical absence (very brief lapse in awareness, sometimes with staring)
- Tonic (body, arms, or legs suddenly stiff or tense)
- Automatisms (such as lip smacking, finger rubbing, chewing)
- Clonic (sustained, rhythmic jerking of part or the whole body)
- Myoclonic (brief, shock-like jerks)
- Infantile spasms
- Atypical absence (some or no lapse in awareness, sometimes with staring. Individual may be able to respond a bit)
- Behaviour arrest (movement stops, sometimes called a freeze or pause)
- Eyelid myoclonia (rapid blinking or jerks of one or both eyelids, sometimes with eyeball movements)
- Cognitive (such as impaired language, confusion, feeling of deja vu, illusions, or hallucinations)
- Autonomic (such as increased heart rate or blood pressure, sweating, facial flushing)
- Emotional (such as sudden fear or joy)
- Atonic also known as drop (sudden loss of muscle tone causing body to go limp and fall down)
- Restless leg syndrome (RLS) or the urge to move the legs
- Hyperkinetic (such as thrashing legs, pedaling, or rocking back and forth)
- Sensory (such as tingling or numbness, visual symptoms, smells, sounds)

...developmental delay, incoordination, hypotonia, autism spectrum disorder (autistic features) and attention deficit hyperactivity disorder with and without prolonged QT.

SCAN ME

PHENOTYPE

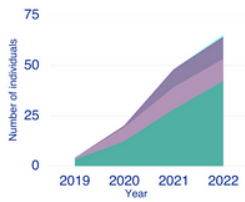
Developmental, neurologic, and psychiatric symptoms are highly prevalent in CRD but do not differ by history of LQTS. Figure and data from Levy et al 2022.[1]



(A) Mean age in months or (B) years at which participants achieved developmental milestones. All participants are depicted next to participants with and without LQTS. There were no significant differences between subgroups. Age at achievement in 50% of typical population denoted by purple lines derived from the Denver II Developmental Scale.42 Error bars show standard error of the mean. (C) Percent of participants who reported the most common neurologic symptoms. There were no significant differences between subgroups. (D) Percent of participants who reported the most common psychiatric diagnoses. There were no significant differences between subgroups. Abbreviations: ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; CRD: *CACNA1C*-related disorder: dx: diagnosis; ID: intellectual disability; LD: learning disability; LQTS: long QT syndrome; OCD: obsessive compulsive disorder; ODD: oppositional defiant disorder; Scz: schizophrenia; sx: symptoms.

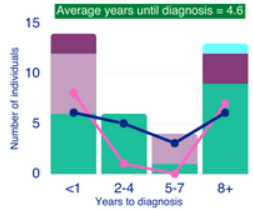
COMMUNITY

Cumulative yearly increase of individuals joining our *CACNA1C* Community (global support network) since registration of TSA as CIO on 27 September 2019 (CRDs represented not caregivers)



DIAGNOSIS

***CACNA1C* Community survey based data (TSA Aug 2022) indicating time to accurate diagnosis (survey completed by 34 individuals representing a total of 37 CRD individuals)**



CACNA1C-related disorder | Timothy Syndrome | Long QT8 | Short QT | Male | Female

Abbreviations: CIO: Charitable Incorporated Organisation.

Common misdiagnoses reported by *CACNA1C* Community (TSA March 2022)

Fragile X syndrome	Muscular dystrophy
Angelman syndrome	Down syndrome
DiGeorge syndrome	Myotonic dystrophy
Cystic Fibrosis	Cardiomyopathy
Coeliac disease	Failure to thrive (FTT)
Prader-Willi syndrome	
Ehlers-Danlos syndrome	
Glycogen storage disease	
Wolff-Parkinson-White syndrome	

CACNA1C Clinical significance on ClinVar submitted records (SCV)[6]

REFERENCES

1. Levy RJ, Timothy KW, Underwood JFG, Hall J, Bernstein JA, Paşca SP. A cross-sectional study of the neuropsychiatric phenotype of *CACNA1C*-related disorder. Pediatr Neurol [Internet]. 2022;102542. Available from: https://doi.org/10.1016/j.pediatrneurol.2022.10.013
2. Bauer R, Timothy KW, Golden A. Update on the Molecular Genetics of Timothy Syndrome. Front Pediatr. 2021;9(May).
3. Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, et al. CaV1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell Cell Press; Oct 1, 2004.
4.Rodan LH, Spillmann RC, Kurata HT, et al. Phenotypic expansion of *CACNA1C*-associated disorders to include isolated neurological manifestations. Genet Med 2021
5. Bozarth X, Dines JN, Cong Q, et al. Expanding clinical phenotype in *CACNA1C* related disorders: From neonatal onset severe epileptic encephalopathy to late-onset epilepsy. Am J Med Genet A 2018;176(12):2733–9.
6. https://www.ncbi.nlm.nih.gov/clinvar/?gr=1&term=cacna1c%5Bgene%5D&redir=gene (Accessed 3 January 2023)

Author: Sophie Muir, Chair
Timothy Syndrome Alliance (TSA)
sophie@timothysyndrome.org

Registered Charity no: 1185523

EMPOWERING CACNA1C THROUGH COLLABORATION

This conference is a product of collaboration and passion to understand CACNA1C.

For transparency the only costs incurred are those to The Stanley Grundy Foundation in funding the Wordly.ai translation service, for which we are immensely grateful. Their generous support has enabled this conference to be inclusive, accessible and global.

A heartfelt thanks go to all speakers and Scientific Advisory Board members who are giving their time so generously to share their latest knowledge and understanding of CACNA1C.

Big thanks also go to NMHII, Cardiff Univeristy for hosting through their conference Zoom subscription.

To the CACNA1C families and individuals attending - you are not alone on this journey!

WAYS YOU CAN HELP

Join the registry

Share our posts

Volunteer

Donate to support our work

Like our posts

Tag a friend

Start a fundraiser

Feedback on how we can help you

Learn more about our work. Read our latest Annual Report at https://timothysyndrome.org/about-us/#report

This conference programme was designed and created in house at no cost to TSA

TIME ZONES

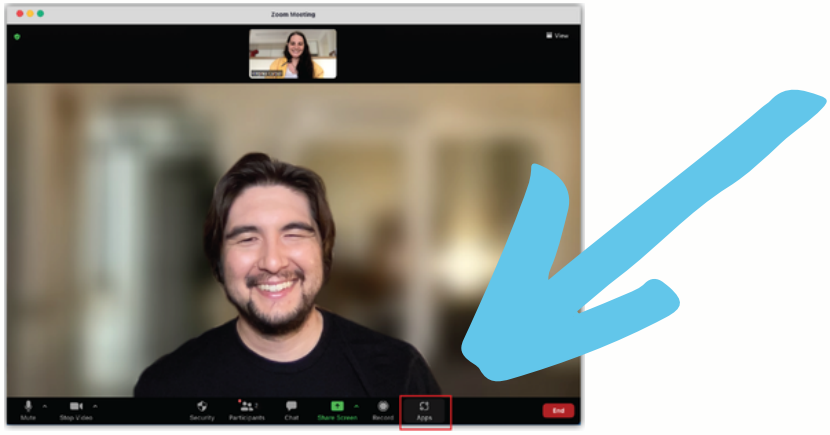
3:00 PM - 7:30 PM	British Summer Time (BST) (example: London, UK)
7:00 AM - 11:30 AM	Pacific Daylight Time (PDT) (example: Los Angeles, USA)
8:00 AM - 12:30 PM	Mountain Daylight Time (MDT) (example: Denver, USA)
9:00 AM - 1:30 PM	Central Daylight Time (CDT) (example: Chicago, USA)
10:00 AM - 2:30 PM	Eastern Daylight Time (EDT) (example: New York, USA)
11:00 AM - 3:30 PM	Atlantic Time (AT) (example: Halifax, Canada)
11:30 AM - 4:00 PM	Newfoundland Time (NT) (example: St. John's, Canada)
4:00 PM - 8:30 PM	Central European Summer Time (CEST) (example: Paris, France)
5:00 PM - 9:30 PM	Eastern European Summer Time (EEST) (example: Athens, Greece)
7:00 PM - 11:30 PM	Moscow Time (MSK) (example: Moscow, Russia)
7:30 PM - 12:00 AM	Indian Standard Time (IST) (example: Mumbai, India)
10:00 PM - 2:30 AM	China Standard Time (CST) (example: Beijing, China)
11:00 PM - 3:30 AM	Japan Standard Time (JST) (example: Tokyo, Japan)
24 JUNE - 4:30 AM	Australian Eastern Standard Time (AEST) (example: Sydney, Australia)
2:00 AM - 6:30 AM	New Zealand Standard Time (NZST) (example: Auckland, New Zealand)

WORDLY AI TRANSLATION

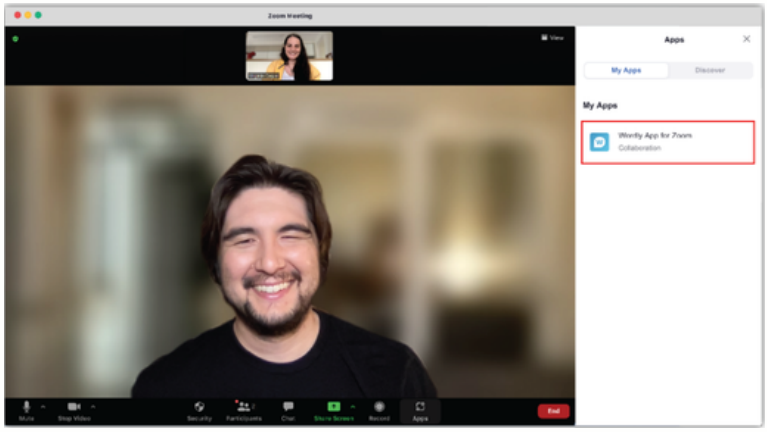
Do I need a Wordly account to use the Wordly App for Zoom?
As you are joining a Wordly translation session hosted by us a Wordly account is not needed.

Joining a Session

- Click on the “Apps” button after joining our conference on Zoom.



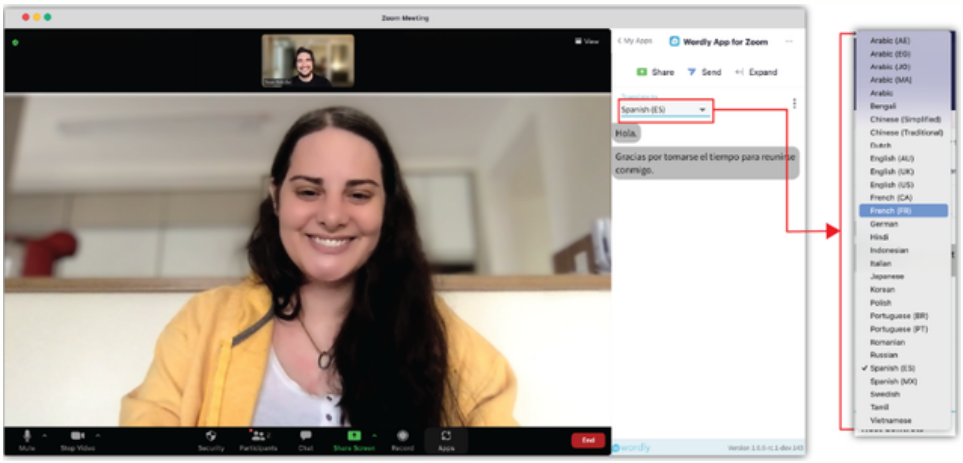
- Click on “Wordly App for Zoom.”



As soon as the app starts up in your meeting, it will automatically join the translation session started by the Zoom host (ie.us). After joining, you will begin seeing translations in the language you have chosen.

Choosing a Language
The Wordly App for Zoom allows participants to view translations in a large number of different languages, depending on their preference.
To change the translation language, click on the “Translate To” control near the top of the Wordly App for Zoom window:

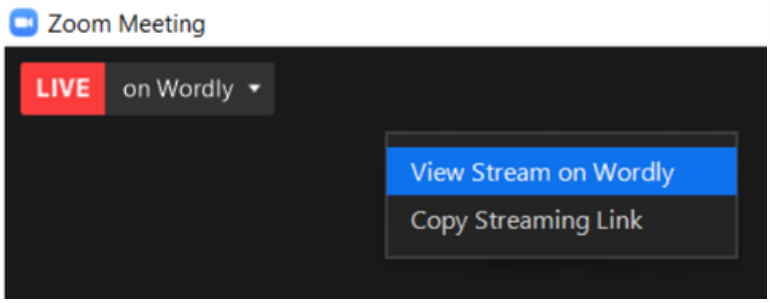
WORDLY AI TRANSLATION



The new translation language should take effect as soon as it is selected.

Rejoining a Session
In rare circumstances, you may be inadvertently disconnected from an ongoing Wordly session and taken back to the session lobby.
You can rejoin the ongoing session by clicking on the “Join” button

Wordly in a Browser
If you cannot install the Wordly App for Zoom, there is an alternate way to access translations using a Web browser.
After a Wordly session starts and “Live Streaming” begins, all participants can access a streaming menu in Zoom:



Select “View Stream on Wordly”. This will open the Wordly session in a Web browser and you can select the translation language you prefer.

Does the Wordly App for Zoom work in breakout rooms?
Unfortunately, the Wordly App for Zoom does not support Zoom breakout rooms at this time. In order to provide translations, Wordly needs access to the audio stream, which Zoom does not make available in breakout rooms.