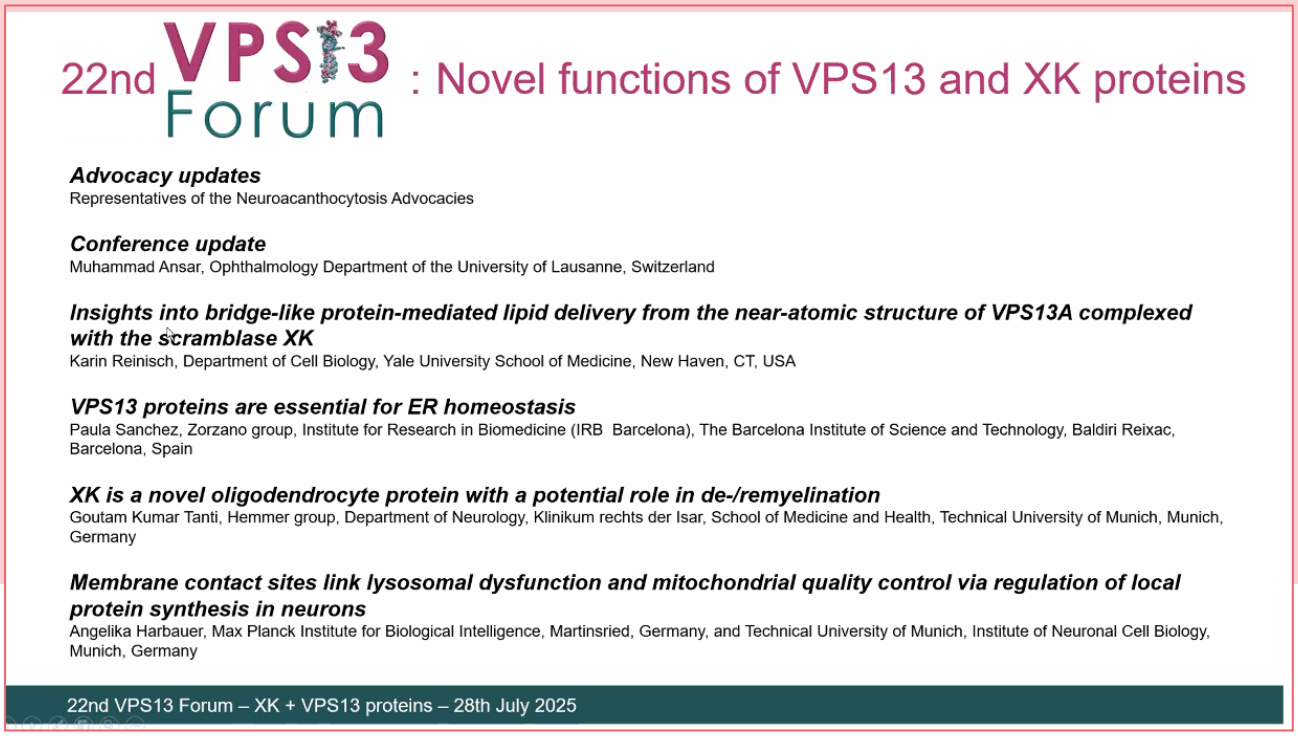

MEETING REPORT
July 2025

Thank you

To the organisers and hosts:

Dr. Kevin Peikert
Professor Ruth Walker
Professor Dr. Adrian Danek

To all the speakers!

To all attendees and everyone reading this report and helping to share the knowledge.

TABLE OF CONTENTS

INTRODUCTION

The Forum was moderated by Dr Kevin Peikert, Rostock University Medical Centre, Department of Neurology, Section for Translational Neurodegeneration "Albrecht Kossel", Rostock, Germany.

The focus was on the bench side of research, exploring novel functions and structures of VPS13 and XK proteins. It featured updates from advocacy groups and four scientific presentations, and there were over 60 attendees throughout.

The presentations were:

- **Insights into bridge-like protein-mediated lipid delivery from the near-atomic structure of VPS13A complexed with the scramblase XK**
  Karin Reinisch, Department of Cell Biology, Yale University School of Medicine, New Haven, CT, USA
- **VPS13 proteins are essential for ER homeostasis**
  Paula Sanchez, Zorzano group, Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Baldiri Reixac, Barcelona, Spain
- **XK is a novel oligodendrocyte protein with a potential role in de-/remyelination**
  Goutam Kumar Tanti, Hemmer group, Department of Neurology, Klinikum rechts der Isar, School of Medicine and Health, Technical University of Munich, Munich, Germany
- **Membrane contact sites link lysosomal dysfunction and mitochondrial quality control via regulation of local protein synthesis in neurons**
  Angelika Harbauer, Max Planck Institute for Biological Intelligence, Martinsried, Germany, and Technical University of Munich, Institute of Neuronal Cell Biology, Munich, Germany

ADVOCACY UPDATES

Despina Dinca, Charity Manager for NA Advocacy gave a brief overview of what NA Advocacy and NA Advocacy USA stand for and what they've accomplished in the past months since the Forum in April.

She summarised the new three-year Strategic Plan for 2025-28 which is launching in September and is focusing on:

- Strengthening support for patients, families and carers
- Raising awareness among clinicians and researchers
- Building capacity and growing income for programs

You can read more about the advocacies, our projects and their progress in NA News, where you can discover research-oriented articles as well as featured patient perspectives.

The advocacies are also supporting the development and progress of young scientists interested in NA related fields through the Glenn Irvine Prize in the amount of £5,000. The next Prize will be awarded at the 12th Symposium taking place Lausanne in September 2025. The event has a track dedicated specifically to the NA community of patients, families and carers with talks and activities.

Thank you for continuing to search for clues to a cure; we're honoured to be on this path together!

12TH SYMPOSIUM

There was an update from Fabrizio Vacca about the 12th International Symposium on Neuroacanthocytosis, Cohen Syndrome and Other VPS13-related Disorders, which will take place in Lausanne, Switzerland, from 12 -14 September 2025. The programme and the registration pages are live. The advocacies requested a better communication of the current registration status as we are keen to stay in touch with the members of our community who will be attending and update them accordingly, as they keep requesting updates on the accommodation status, which hasn't been communicated to them to the date.

The abstract submission and registration had been extended to 10 August 2025.

SCIENTIFIC PRESENTATIONS

Karin Reinisch (Yale University)

Topic: Understanding the structure of VPS13A and its partner protein XK

What was it about? Karin presented new research using a technique called cryo-electron microscopy (cryo-EM), which allows scientists to see proteins at near-atomic detail. She focused on VPS13A, a protein linked to chorea-acanthocytosis (now known as VPS13A disease), and how it interacts with another protein called XK linked to McLeod syndrome (now known as XK disease).

Key points:

- VPS13A acts like a "bridge" that helps move fats (lipids) between different parts of the cell.
- It connects directly to cell membranes and works with XK, a protein that helps shuffle lipids between the two layers of the membrane (a process called "scrambling").
- A new partner protein, calmodulin, was discovered. It might help regulate VPS13A's activity in response to calcium levels in the cell.
- The research suggests that VPS13A and XK work together to move lipids efficiently and may even change the shape of the membrane to make this easier.

Why it matters: Understanding how VPS13A and XK work together could help explain what goes wrong in VPS13A disease and potentially leads to new treatments.

Paula Sanchez (Zorzano Group, Barcelona)

Topic: How VPS13A and VPS13D affect the cell's stress response system

What was it about? Paula studied what happens when two versions of the VPS13 protein (A and D) are reduced in cells. She looked at how this affects the endoplasmic reticulum (ER) part of the cell that helps fold proteins and manage fats.

Key points:

- When VPS13A or D is missing, certain fats build up in the ER, especially a type called ceramides.
- This buildup stresses the ER, triggering a protective system called the unfolded protein response (UPR). Think of it like a factory alarm going off when machines are overheating.
- One specific branch of this alarm system, called IRE1-XBP1, was especially active.
- By blocking ceramide production, they were able to reduce the stress and even improve the shape and function of mitochondria (the cell's energy producers).

Why it matters: This shows that problems with fat handling in the cell can lead to stress and damage, which may contribute to diseases like VPS13A. Targeting ceramides might be a way to reduce this damage.

Goutam Kumar Tanti (Hemmer Group, Munich)

Topic: The role of XK in brain cells that make myelin

What was it about? Tanti et al. found for the first time that XK is oligodendrocyte enriched and it is expressed on the surface of these cells that are responsible for myelination (the protective coating around nerves, like insulation on wires). He used pig brain tissue and human samples to study this.

Key points:

- XK is found on the surface of oligodendrocytes and seems important for their survival.
- When XK was removed, these cells were more likely to die, especially during the process of remyelination (repairing damaged myelin).
- In brain samples from people with XK disease and VPS13A disease, there were fewer oligodendrocytes, suggesting a link to disease.
- He also showed that VPS13A and XK physically interact in the brain, and this partnership may be crucial for maintaining healthy myelin.

Why it matters: This research opens up a new area of investigation: how VPS13A and XK might affect myelin and contribute to neurological symptoms. It could also help explain some of the brain changes seen in these rare diseases.

Angelika Harbauer (Munich)

Topic: How cells make a key protein (PINK1) in the right place at the right time

What was it about? Angelika studies Parkinson's disease and focused on how cells make a protein called PINK1, which helps detect and remove damaged mitochondria (a process called mitophagy). She discovered that this process depends on contact between different parts of the cell.

Key points:

- PINK1 is made locally in nerve cell branches (axons), not just in the cell body.
- Its production happens at "hotspots" where mitochondria, the ER, and lysosomes (the cell's recycling centres) come into close contact.
- These contact sites are important for coordinating energy, nutrients, and protein production.

- The protein called VPS13C helps maintain these contact sites.
- This could help explain how problems with VPS13C contribute to Parkinson's disease.

Why it matters: This research links two key features of Parkinson's: mitochondrial damage and lysosomal dysfunction, and shows how VPS13C might be the missing link. It also highlights the importance of local protein production in nerve cells.

Looking Ahead

Together, these presentations paint a picture of a field that's evolving rapidly. Researchers are not just asking "what goes wrong?" they're asking "how can we fix it?". Whether it's through understanding protein structures, managing cellular stress, supporting brain repair, or restoring vital contact points, the science is moving forward with purpose and creativity.

The VPS13 / XK research community is clearly committed to finding answers faster. With collaboration, innovation, and continued support from all of us, we're getting closer to unlocking the mysteries of these rare conditions, and to building a future where patients feel less alone and more hopeful.

NEXT VPS13 FORUMS

Dates for your diary:

- **24 November 2025**
- **26 January 2026**
- **27 April 2026**
- **27 July 2026**
- **26 October 2026.**

The exact times and topics will be announced nearer the time in the email invitation you will receive from Dr Kevin Peikert and also on all our social media channels.

Thank you!

ADVOCACY FOR NEUROACANTHOCYTOSIS PATIENTS

NA ADVOCACY USA
NEUROACANTHOCYTOSIS ADVOCACY USA, INC.

info@naadvocacy.org

www.naadvocacy.org www.naadvocacyusa.org