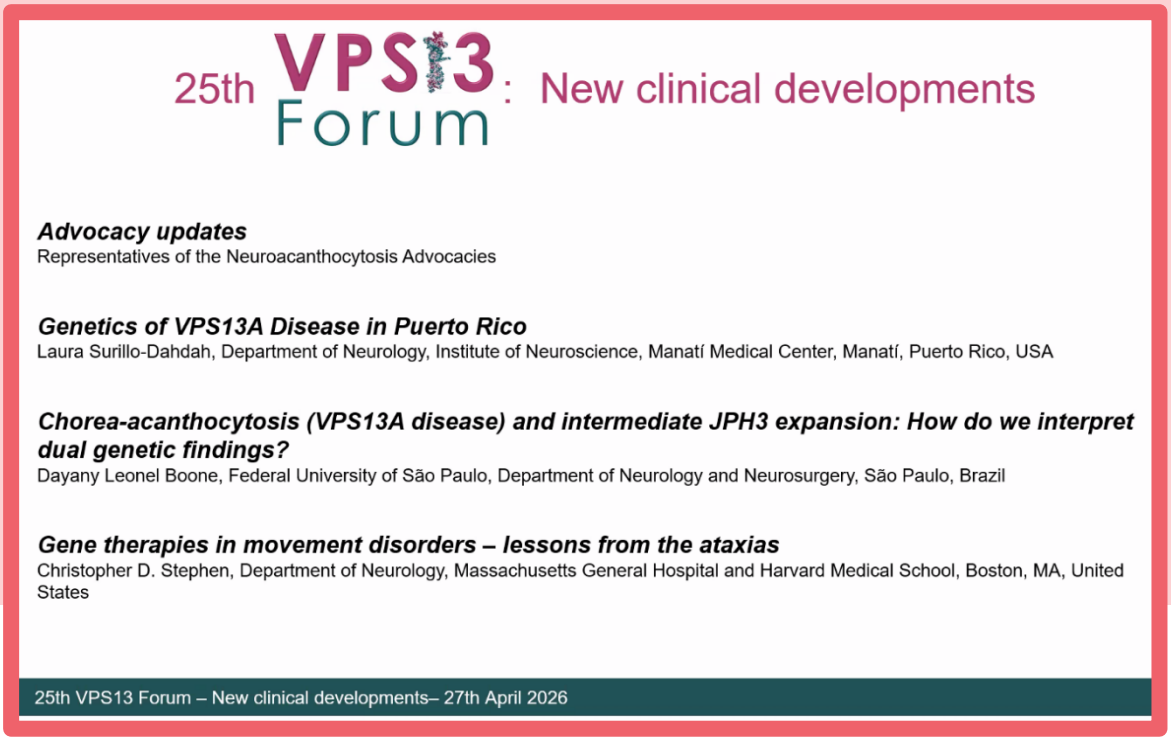

25thVPS13 Forum April 2026

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.

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INTRODUCTION

The Forum was moderated by Dr Kevin Peikert, University Medical Center, Rostock, Germany.

The focus was on clinical updates and the presentations were:

- **Advocacies updates**
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- ***Genetics of VPS13A Disease in Puerto Rico***
  Laura Surillo-Dahdah, Department of Neurology, Institute of Neuroscience, Manatí Medical Center, Manatí, Puerto Rico, USA
- ***Chorea-acanthocytosis (VPS13A disease) and intermediate JPH3 expansion: How do we interpret dual genetic findings?***
  Dayany Leonel Boone, Federal University of São Paulo, Department of Neurology and Neurosurgery, São Paulo, Brazil
- ***Gene therapies in movement disorders – lessons from the ataxias***
  Christopher D. Stephen, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

ADVOCACIES UPDATES

Despina opened with a brief introduction for newcomers, outlining the history of the NA Advocacy, founded in 2002 by Ginger and the late Glenn Irvine after their daughter Alex was diagnosed with VPS13A disease. The organisation was born from a need for information, connection, and support at a time when almost nothing was available. The close collaboration between the UK and US advocacy groups was highlighted, and the essential role of the VPS13 Forum in keeping families informed about scientific progress.

Rare Disease Day (28 February): Both organisations participated in global campaigns, supported by umbrella groups, which are helpful collaborations to ensure that the voices of ultra rare disease communities are heard in policy and research discussions.

Joy shared latest updates about the NA News, the 50th anniversary issue, which was published on RDD. The community's newsletter was first launched in 2003 and grew ever since into a unique global resource, connecting families with knowledge, community, and

hope. She expressed deep gratitude to donors, supporters, and fundraisers who make this work possible.

Joy also spoke about the latest grant awarded to the Icahn School of Medicine in New York, ensuring continued support for the ongoing research.

She also welcomed the new members of Research Advisory Committee, Professor Emerita Roberta Fuller and Professor Aaron Niemann, who join Professor Ruth Walker in guiding research priorities and ensuring alignment with patient needs.

Joy expressed heartfelt thanks to Professor Emeritus Adrian Danek, the longest serving member on the committee. His scientific expertise and personal commitment have shaped the NA community for decades, and he continues to serve as a Trustee of Na Advocacy.

Ginger shared a joyful update from Scotland, where long-time supporters Sheila Averbuch and her husband, Ralph hosted a two-day open garden and plant sale at Mercat Cottage under the Scottish Gardens Scheme. The event raised over £1,300, with additional funds from plant sales and copies of Alex's book. It brought together old friends, supporters, and new visitors, helping spread awareness even further. Ginger encouraged everyone to share the photos and updates on social media to help amplify the message.

SCIENTIFIC PRESENTATIONS

Laura Surillo-Dahdah (Institute of Neuroscience, Manati Medical Center, Puerto Rico)

Topic: Genetics of VPS13A Disease in Puerto Rico

What was it about? Working with Professor Ruth Walker and colleagues across Puerto Rico and the US mainland, Laura collected clinical and genetic data from 17 patients (15 families) of Puerto Rican origin. Their symptoms, family backgrounds, and genetic variants were analysed. The research team looked for patterns suggesting a founder effect (a mutation passed down through generations in an isolated population).
VPS13A disease's prevalence (around 1 in a million) makes it an extremely rare disease, but Laura's clinical experience told a different story. Within just six years of practice, she diagnosed four genetically confirmed patients, prompting her to investigate whether Puerto Rico might have a higher-than-expected prevalence.

Key points:

- In most isolated populations there is one gene mutation that gets passed down. However, in Puerto Rico the team found four mutations passed down through generations.
- Every patient had at least one of these variants. Half had two of them.
- A new deletion in exon 27 was identified in three patients, a variant not previously reported and possibly unique to Puerto Rico.
- Symptoms varied widely, but common early signs included: seizures, feeding difficulties, tongue and facial movements, elevated creatine kinase (CK) levels.

- Diagnosis was often delayed by 10 years or more, highlighting the need for greater awareness among clinicians.

Why it matters: These findings suggest that VPS13A disease may be under-recognised and subsequently under-diagnosed in Puerto Rico, and that several founder mutations are circulating in the population. Raising awareness could lead to earlier diagnosis, better care, and appropriate genetic counselling for families.

Laura emphasised her commitment to sharing these findings with clinicians across the country to improve recognition and support.

Dayany Leonel Boone (Federal University of São Paulo, Brazil)

Topic: Chorea-acanthocytosis (VPS13A disease) and intermediate JPH3 expansion: How do we interpret dual genetic findings?

What was it about? Dayany presented a fascinating and complex case involving a patient with two genetic findings:

- a likely pathogenic *VPS13A* mutation
- an intermediate-range expansion in the *JPH3* gene, which is associated with Huntington-disease-like 2 (HDL2). (Note: *JPH3* gene provides instructions for creating the junctophilin-3 protein, which is essential for linking cell surface channels with internal calcium stores in brain neurons)

Key points:

- The patient, a 42-year-old man, underwent neurological examination which revealed: severe involuntary mouth and tongue movements, chewing and biting causing repeated injuries, weight loss, and later, involuntary arm movements and toe-walking. Laboratory evaluation revealed elevated CK levels, and blood tests revealed acanthocytes, both classic features of *VPS13A* disease. Further complementary exams were taken.
- The *VPS13A* variant strongly supports a diagnosis of chorea-acanthocytosis. The *JPH3* expansion was in the intermediate range, which is not considered disease-causing, but its clinical significance is still debated.
- Could both genes be contributing?
    - Intermediate JPH3 expansions do not cause disease, but some researchers wonder whether they might subtly influence symptoms.
    - Both VPS13A disease and HDL2 affect the same brain region (the striatum), which complicates interpretation.
    - However, the presence of acanthocytes and the patient's overall presentation strongly point to *VPS13A* disease as the primary diagnosis.

Why it matters: The case highlights the challenges of interpreting multiple genetic findings, especially as genetic testing becomes more widely used. It also underscores the importance of combining: clinical features, imaging, blood tests, and genetics to reach the most accurate diagnosis.

Christopher D. Stephen (Massachusetts General Hospital and Harvard Medical School, USA)

Topic: Gene therapies in movement disorders – lessons from the ataxias

What was it about? Christopher provided an accessible overview of gene therapy and what it might mean for VPS13A and XK diseases in the future.

Forms of gene therapy in the context of ataxias:

- Antisense oligonucleotides (ASO) = uses short, synthetic strands of nucleic acids to bind specific ribonucleic acid (RNA) sequences, modulating gene expression by degrading toxic proteins, altering splicing, or increasing protein production.
- Adeno-associated virus (AAV)-mediated gene replacement = a leading, non-pathogenic, *in vivo* delivery tool used to introduce functional genetic material into human cells to treat inherited and acquired diseases.
- RNA Interference (RNAi) = a natural cellular process that regulates gene expression by silencing specific messenger RNA (mRNA) molecules, preventing them from producing proteins.
- CRISPR-Cas9 gene editing = a revolutionary, precise, and cost-effective gene-editing technology that allows scientists to edit parts of the genome by removing, adding, or altering sections of DNA.

Key points:

- Gene therapy aims to replace or repair faulty genes. It's tested for certain neurological conditions / movement disorders.
- Challenges for gene therapy in NA syndromes:
    - Gene sizes: VPS13A very large
    - Multi-system
    - Limited pathophysiological understanding
    - No validated biomarkers
    - Lack of natural history data
    - Limited animal models (mice).
- Gene therapy for ataxias:
    - Addresses the root cause
    - One-time treatment possible
    - Robust mouse models
    - Demonstrated benefits in some ataxias.

Why it matters: Gene therapy has advanced considerably over the past few decades. We can learn from the experience of the genetic ataxias which advanced to clinical-stage gene therapy. However, there are currently no gene therapy programs for either VPS13A or XK.

Before gene therapy becomes feasible for NA syndromes, the field needs: better biomarkers, clearer natural history data, validated animal models, and improved delivery technologies.

The small size of the XK gene makes is a possible candidate to consider in the future for AAY gene replacement or CRISPR editing.

VPS13A will require innovative large-gene delivery strategies.

In conclusion, gene therapy is a promising long-term avenue, but a lot more foundational work is needed before it can be applied to VPS13A and XK diseases.

NEXT VPS13 FORUMS

Dates for your diary:

- **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