Characterizing the CSF Biomarker Signature of Calpain-2 Activity in ALS and the Biomarker Impact of Calpain-2 Inhibition in a Preclinical Model of ALS

Robert Bowser, PhD

Barrow Neurological Institute; nVector, Inc.

Additional Authors: Jiyan An; Pavol Zelina; Carola Kusserow; R. Jeroen Pasterkamp; Lauren Kett, MD, PhD; Evan Mizerak; Jamie Timmons, MD; Sabrina Paganoni, MD, PhD

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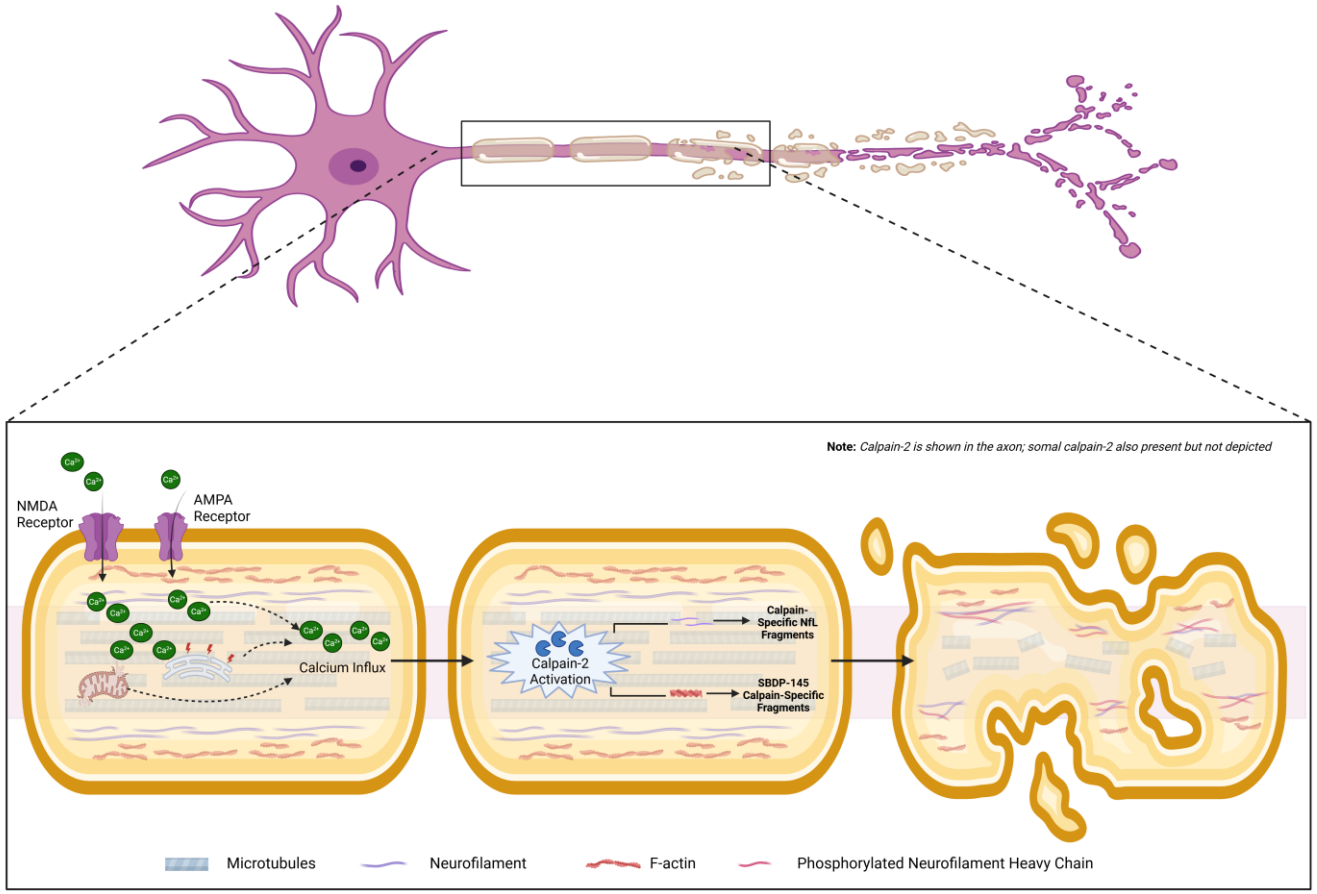
Calpain-2 Drives Axonal Degeneration and Contributes to the Pathogenesis of ALS

Background

- Axonal degeneration has been increasingly recognized as a key early contributor to the clinical presentation and pathogenesis of ALS[1,2]
- Activation of calpain-2, a calcium-dependent protease, is considered one of the critical effectors of this axonal degeneration[1-4]
- Calpain-2 targets multiple substrates within the axonal skeleton including alpha II-spectrin and neurofilament light chain (NfL):[2,4-7]
  - **SBDP-145** is a calpain-specific alpha II-spectrin breakdown product

Representative Schematic of Select Calpain-2 Substrates and Breakdown Products[7-8]



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1. Moloney EB, et al. Front Neurosci. 2014;8:252. **2**. Ma M. Neurobiol Dis. 2013;60:61-79. **3**. Asakawa K, et al. Cell Mol Life Sci. 2021;78(10):4453-4465. **4**. Wang Y, et al. Cells. 2020; 9(12): 2698. **5**. Ono Y, Saido TC, Sorimachi H. Nat Rev Drug Discov. 2016;15(12):854-876. **6**. Ma M, et al. Neurobiol Dis. 2013;56:34-46. **7.** Yamashita, T et al. Nat Commun. 2012; 3:1307. **8**. Tadic V, et al. Front. Cell. Neurosci. 2014; 8.

Levels of SBDP-145, a Calpain-Specific Breakdown Product, Were Significantly Higher in CSF from People Living with ALS Compared to Controls

Methods

107 CSF Samples
NEALS Biorepository, n=47
Target ALS Biorepository, n=60

- **Healthy Controls (HC) n=42**
- **Sporadic ALS (sALS) n=44**
- **Familial ALS (fALS) n=9[a]**

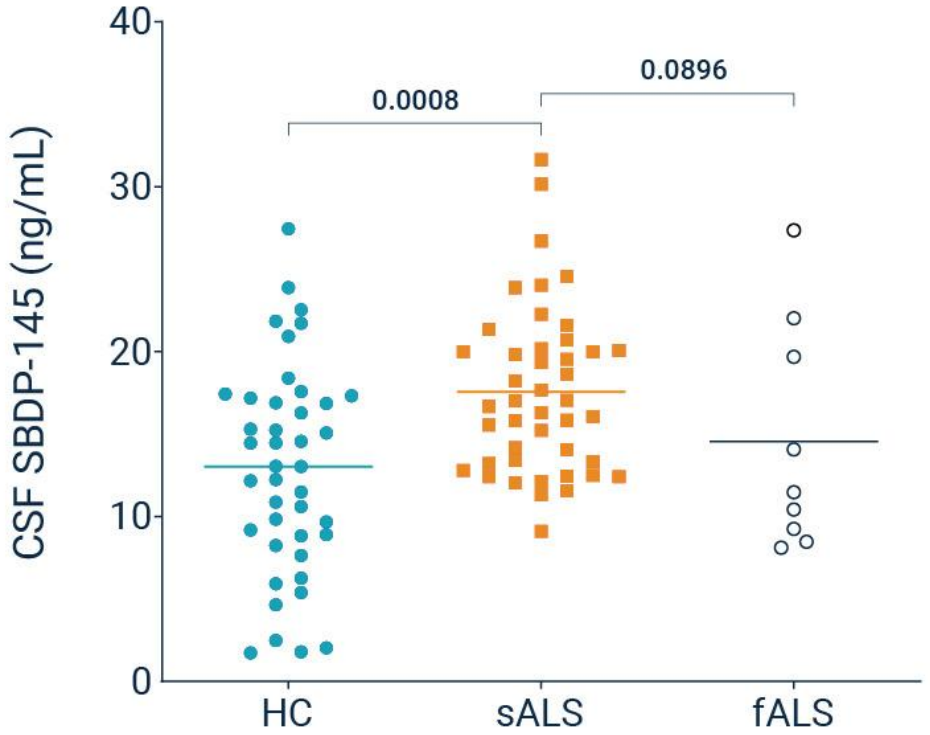
Assay Details:

- CSF SBDP-145 level quantification using ELISA (Biomatik)
- All samples run in duplicate
- Standard curves (0-40 ng/mL) generated per plate
- Individual values and median calculated per diagnostic group

[a]Seven C9orf72, one SOD1, and one TAF15 mutation carriers

CSF SBDP-145 Levels

by disease group



Levels of SBDP-145 were significantly higher in CSF from people living with ALS compared to controls (***p*=0.0029**)

Key Takeaways

- Activation of calpain-2 is considered a critical effector of axonal degeneration
- **SBDP-145 could be a promising biomarker for calpain-2 activity and axonal injury** in ALS given its significant elevation in CSF from people living with ALS vs healthy controls

Visit Poster #11 to Learn More:

- SBDP-145 **assay details**
- **Nuanced insights** into SBDP-145 differences in ALS vs healthy control CSF
- **New AMX0114 data showing in vitro reduction of SBDP-145** by this ASO inhibitor of calpain-2 – supporting SBDP-145's potential as a marker of target engagement

AMX0114 is an investigational drug and has not been approved by any health authority