

Update on Research in Alexander Disease (July 15, 2015)

Albee Messing

University of Wisconsin-Madison

amessing@wisc.edu

Alexander disease: where are we?

- mutations in GFAP in ~95% of patients - dominant
- prevalence ~ 1 in 2.7 million (Yoshida et al. 2011)
- wide variation in clinical severity
- onsets at all ages (prenatal through 60's)
- **major questions:**
 1. how do mutations cause disease?
 2. what accounts for the variability?
 3. what are the options for treatments?

topics

- sources of variability
 - environmental vs. genetic
- status of drug treatment studies
 - ceftriaxone and glutamate transport
 - Tecfidera (BG-12) and the Nrf2 stress pathway

Anne B. Johnson, M.D.

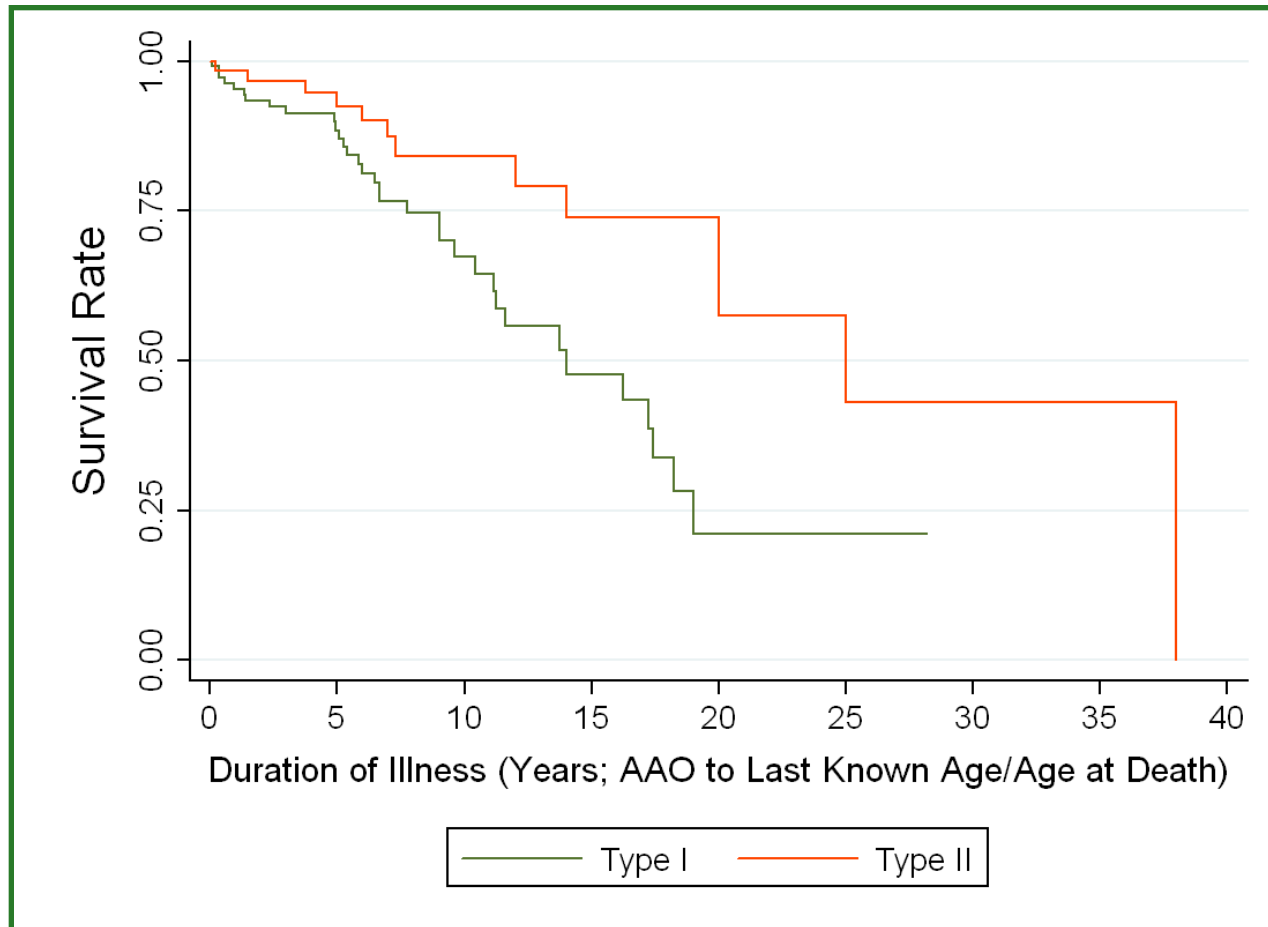
(1927-2015)

- Cornell University, B.A., 1948
- Cornell Medical School, M.D., 1951
- internships, residencies, fellowships, and children
- Albert Einstein College of Medicine, Assistant to Associate Professor in the Departments of Pathology and Neuroscience, 1970-2002



- pioneer in Alexander disease research
- the first to document GFAP in the core of Rosenthal fibers
- played a key role in the discovery of GFAP mutations as the cause of the disease

survival - Type I vs Type II



Prust M et al. (2011). GFAP mutations, age of onset, and clinical sub-types in Alexander disease. *Neurology*, **77**, 1287-1294.

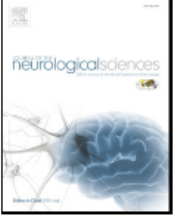
environmental modifier - alcohol?



Contents lists available at [SciVerse ScienceDirect](#)

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns



Short communication

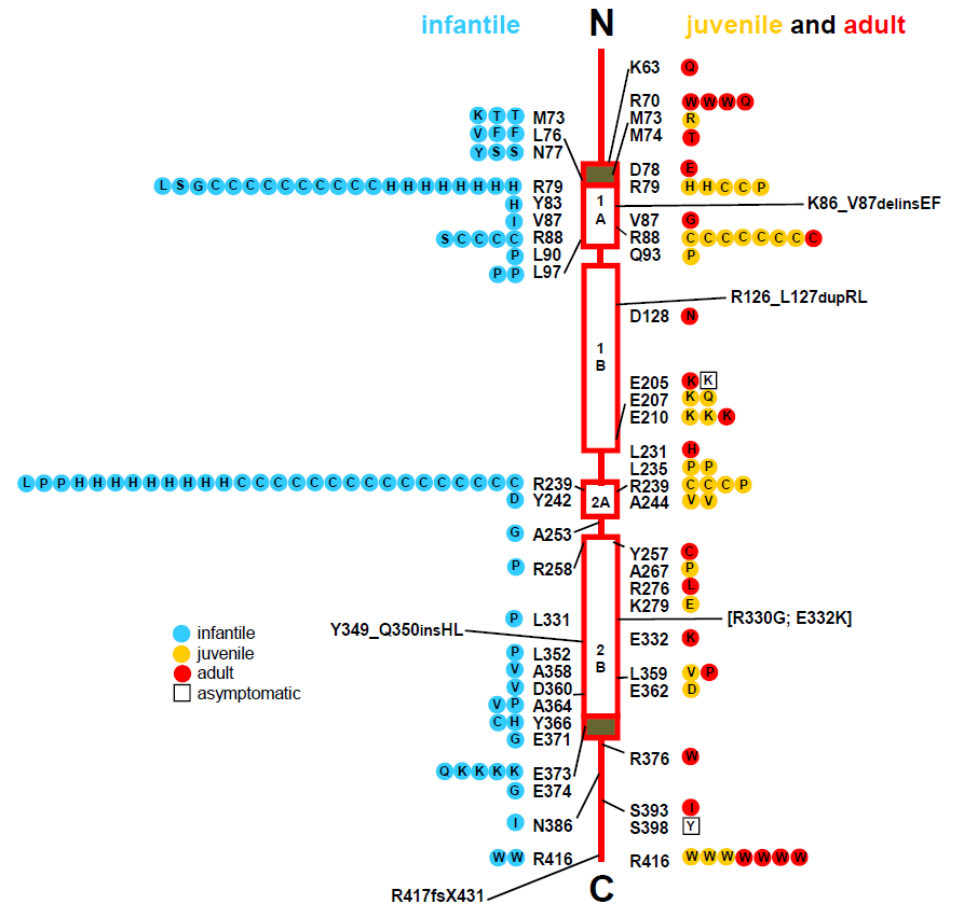
Acute onset of adult Alexander disease

Holger Schmidt ^{a,1}, Benedikt Kretzschmar ^a, Paul Lingor ^a, Silke Pauli ^b, Peter Schramm ^c, Markus Otto ^d,
Andreas Ohlenbusch ^e, Knut Brockmann ^{e,*}

- 32 yr old male, previously healthy
- consumed 3 L beer + several spirits (“more than his usual”)
- found prone, unable to stand or speak
- next morning eyes open and movable, but still couldn't speak or move limbs
- MRI features diagnostic for AxD, including tadpole sign in brainstem
- de novo 9 bp duplication-insertion in exon 1
- 3 mo. later - walking with cane, mild spasticity, psychomotor deficits

summary of genetics

- GFAP mutations account for >90% of patients
- all heterozygous, mostly de novo
- two hot spots at R79 and R239
- dominant, gain of function
- null or recessive mutations not found
- penetrance nearly 100%



Brenner et al. In: *Astrocytes in Pathophysiology of the Nervous System* (2009). Eds. Haydon & Parpura.

monozygotic twins

- boys, R79H
- hypotonia, dystonia - first months
- sitting - 12 mo, 25 mo
- first words - 3 yr, 4 yr
- walking - 3.5 yr, 6 yr
- plateau - 6 yr
- loss of speech and unsupported walking - 8 yr
- wheelchair dependent - 10 yr

(Meins et al., 2002)

monozygotic twins

- boys, R79C
- developmental delays - 1 yr
- febrile seizures, then persistent - 1.5 yr
- macrocephaly, spasticity, psychomotor and developmental delays
- independent walking - 2 yr

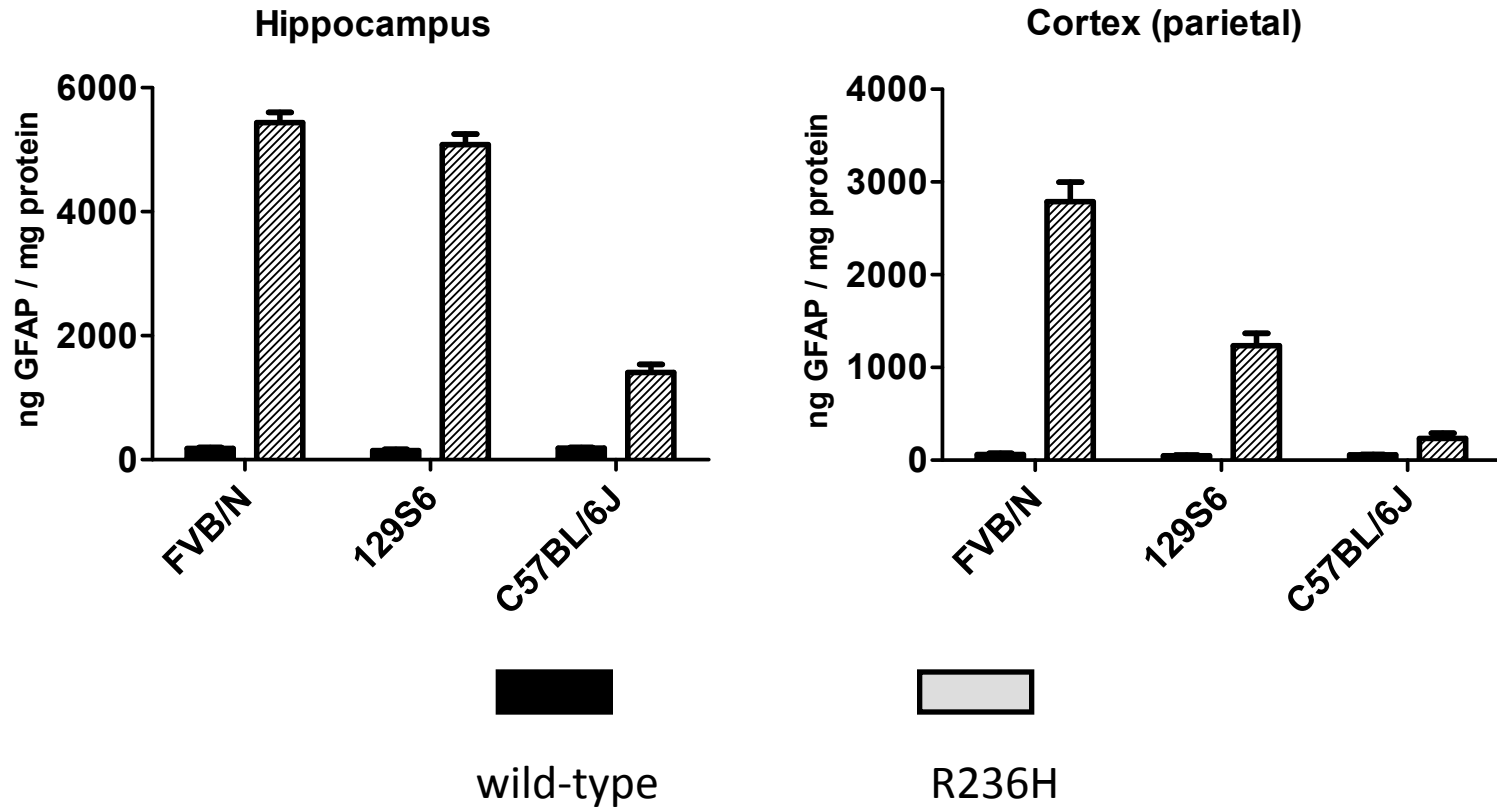
(Shiroma et al., 2003)

monozygotic twins

- boys, L235P
- onset (malnutrition, regurgitation) - 3 yr
- macrocephaly, seizures - no
- spasticity, ataxia - yes
- bulbar/pseudobulbar signs - yes
- cognitive deficits - no
- atypical MRIs (focal bulbar lesions)
- died - 8 yr, 10 yr

(Li et al., 2005)

mouse strain variation in GFAP response and the search for genetic modifiers



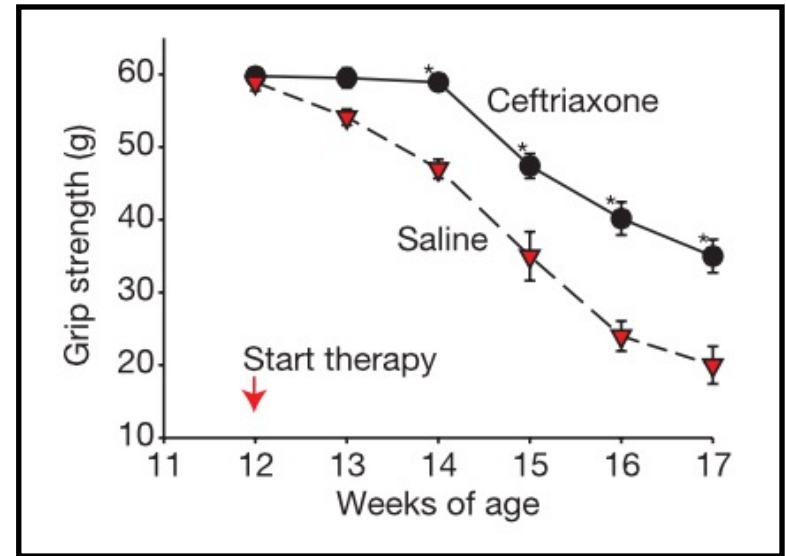
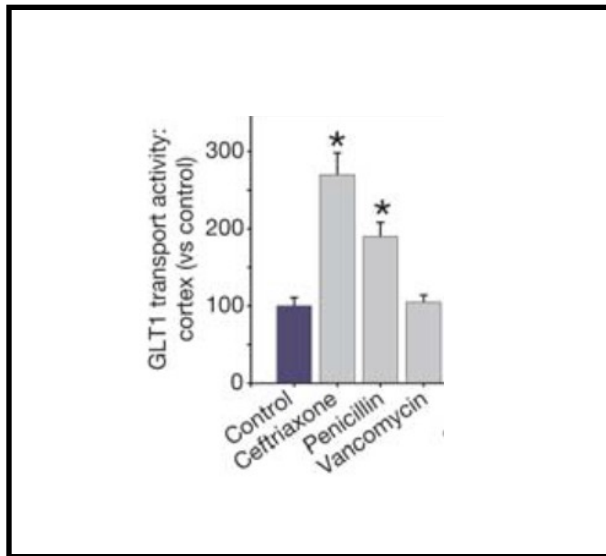
(Hagemann, unpublished)

glutamate transporters as therapeutic targets

β -Lactam antibiotics offer neuroprotection by increasing glutamate transporter expression

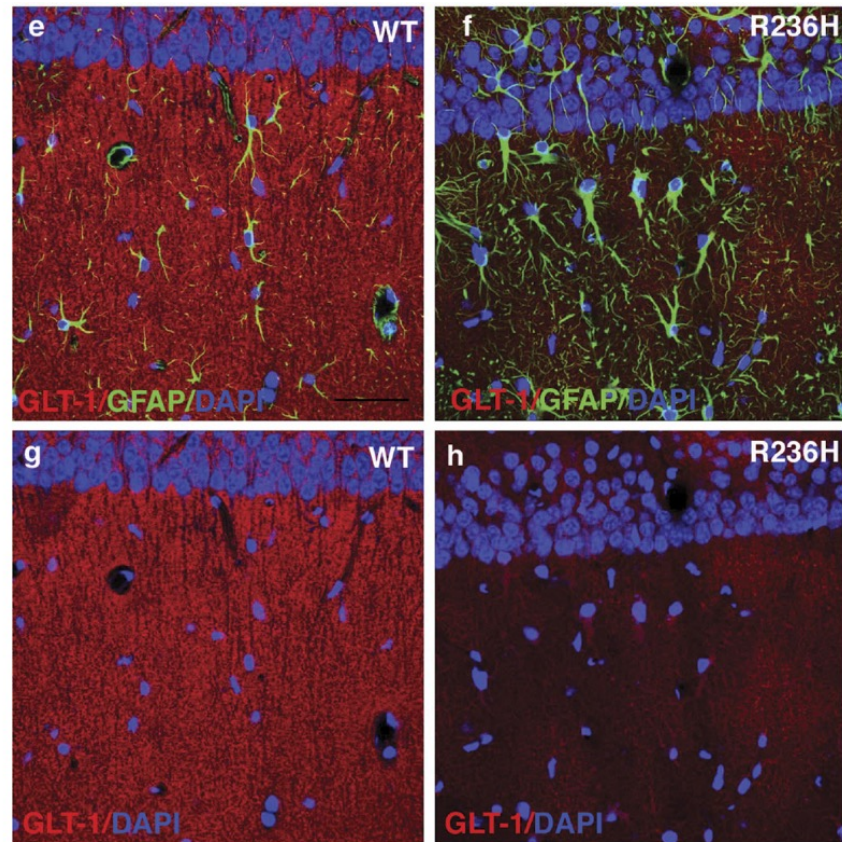
Jeffrey D. Rothstein^{1,2}, Sarjubhai Patel¹, Melissa R. Regan¹, Christine Haenggeli¹, Yanhua H. Huang², Dwight E. Bergles², Lin Jin¹, Margaret Dykes Hoberg¹, Svetlana Vidensky¹, Dorothy S. Chung¹, Shuy Vang Toan¹, Lucie I. Bruijn³, Zao-zhong Su⁴, Pankaj Gupta⁴ & Paul B. Fisher⁴

ceftriaxone

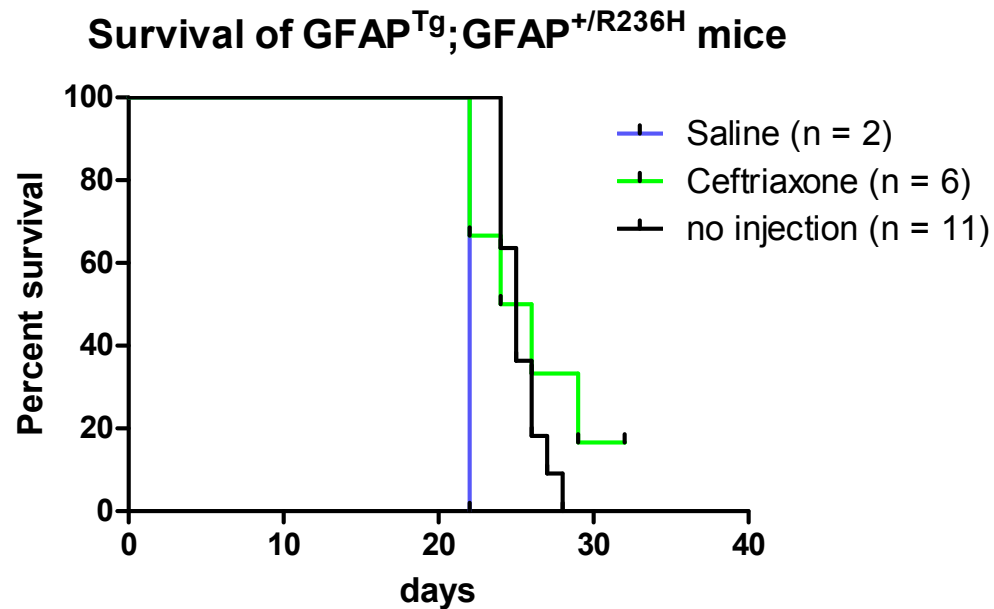


glutamate transport into astrocytes may be affected in AxD

- Glt-1 is a major glutamate transporter, primarily found in astrocytes
- Glt-1 expression is reduced in hippocampus in mouse models
- comparable findings in human tissues



ceftriaxone - our experience

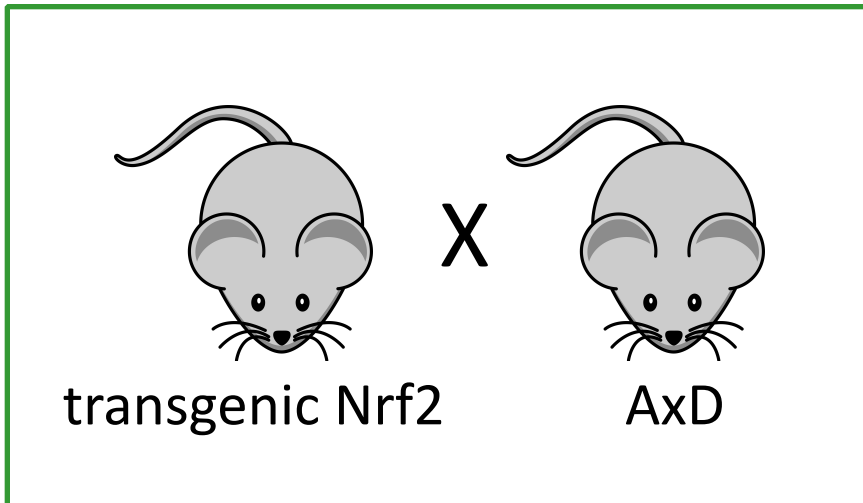


lab meeting 5/18/11

- no increase in expression:
 - alphaB-crystallin
 - Nrf2
 - Glt-1 transporter
- hence, we have no data to support its use in humans

is Nrf2 a useful target?

- Nrf2 is a transcription factor that regulates expression of many other genes
- Nrf2 is activated in both mouse and human AxD
- we tested whether forcing astrocytes to make even higher levels of Nrf2 is beneficial

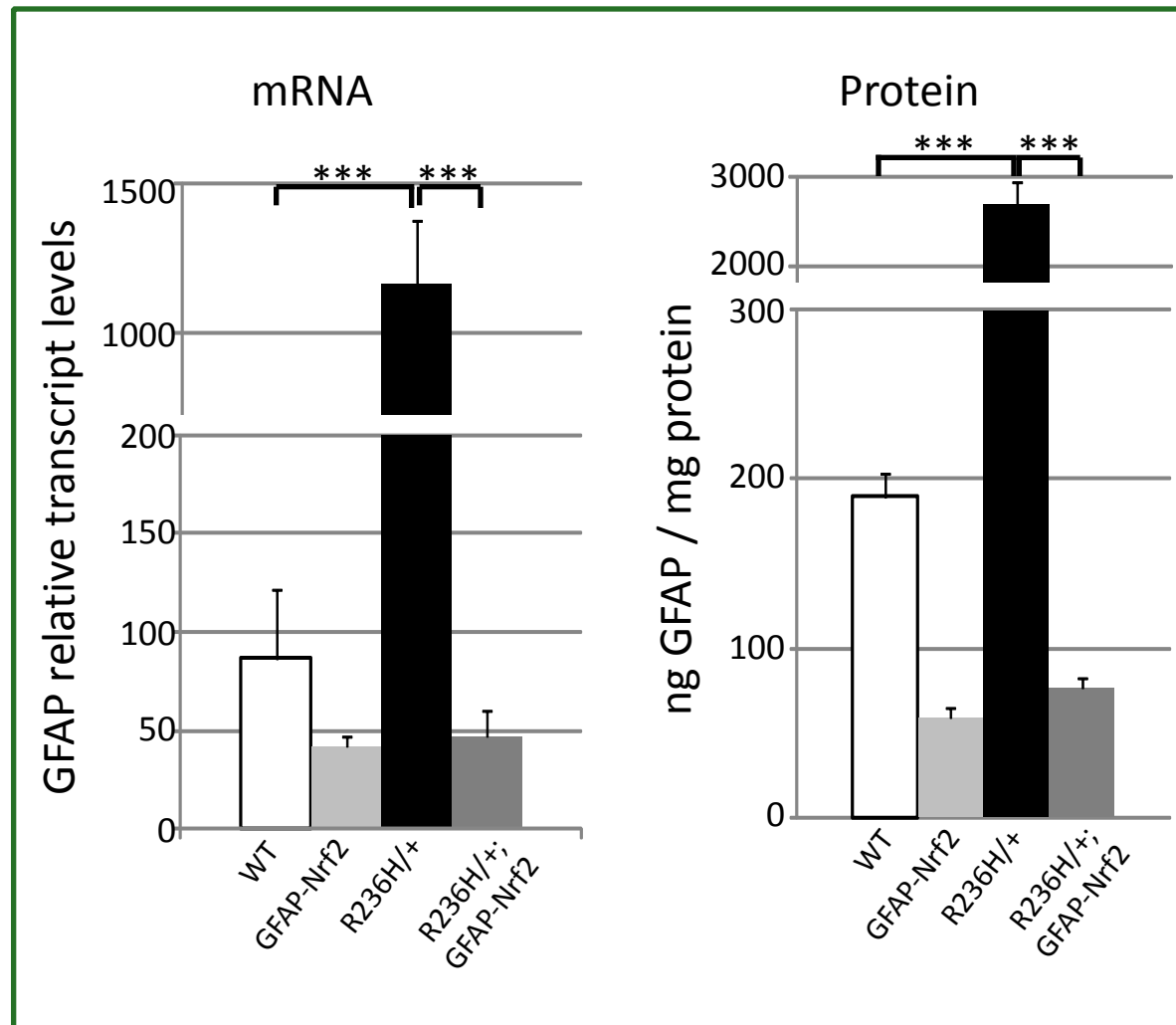


Results

reduces accumulation of GFAP

reduces or eliminates Rosenthal fibers

forcing astrocytes to make more Nrf2 reduces GFAP



dimethyl fumarate (BG-12) is an activator of Nrf2

doi:10.1093/brain/awq386

Brain 2011; 134; 678–692 | 678

BRAIN

A JOURNAL OF NEUROLOGY

Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway

Ralf A. Linker,^{1,*,+} De-Hyung Lee,^{1,*,+} Sarah Ryan,² Anne M. van Dam,³ Rebecca Conrad,⁴ Pradeep Bista,² Weiike Zeng,² Xiaoping Hronowsky,² Alex Buko,² Sowmya Chollate,² Gisa Ellrichmann,¹ Wolfgang Brück,⁵ Kate Dawson,² Susan Goelz,² Stefan Wiese,⁴ Robert H. Scannevin,² Matvey Lukashev² and Ralf Gold¹

BG-12 recently approved for use in MS

The New York Times

March 27, 2013

3rd Oral Drug to Treat MS Is Approved by the F.D.A.

By ANDREW POLLACK

A chemical once used to treat sofas — until it was found to cause rashes and blisters in people who sat on them — is now poised to become a major therapy for multiple sclerosis.



- but should this be tried in Alexander patients?
 1. questions remain about how much gets into the CNS, and whether it really activates Nrf2
 2. we do not know anything about dosing for children, and how to measure efficacy
 3. unfortunately, animal studies are no longer possible
 4. nevertheless, this is being tried in at least one or two patients

summary

- sources of variability
 - environmental vs. genetic (both are subjects of current investigation)
- status of drug treatment studies
 - ceftriaxone - mouse studies were done, but the results were negative
 - Tecfidera (BG-12) - mouse studies are not possible



Chrissie LaPash Daniels



Tracy Hagemann

Alexander Disease Research Project