Alexander Disease:

New Ideas Linking GFAP Variants & Leukodystrophy

reliable
Free Online Sources of^Information

Albee Messing, VMD PhD
University of Wisconsin-Madison
amessing@wisc.edu

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How do GFAP Variants Lead to Leukodystrophy?

GFAP variants -> astrocyte dysfunction ? myelin deficits

How do GFAP Variants Lead to Leukodystrophy?

GFAP variants -> astrocyte dysfunction ->

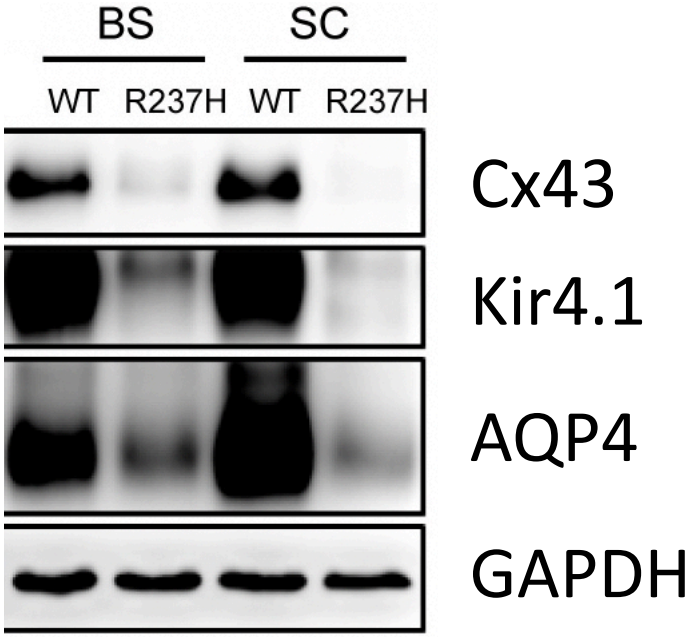
- Kir4.1
- connexin 43 (Cx43)
- aquaporin 4 (AQP4)

} myelin deficits

How do GFAP Variants Lead to Leukodystrophy?

GFAP variants -> astrocyte dysfunction ->

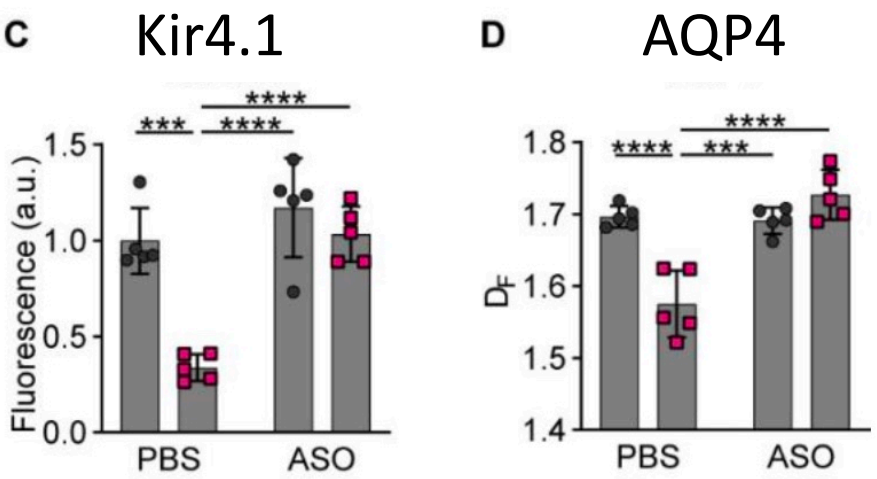
rat model



Hagemann et al., *Sci Transl Med* (2021)

Correction by ASO

GFAP variants -> astrocyte dysfunction ->



rat model

Hagemann et al., *Sci Transl Med* (2021)

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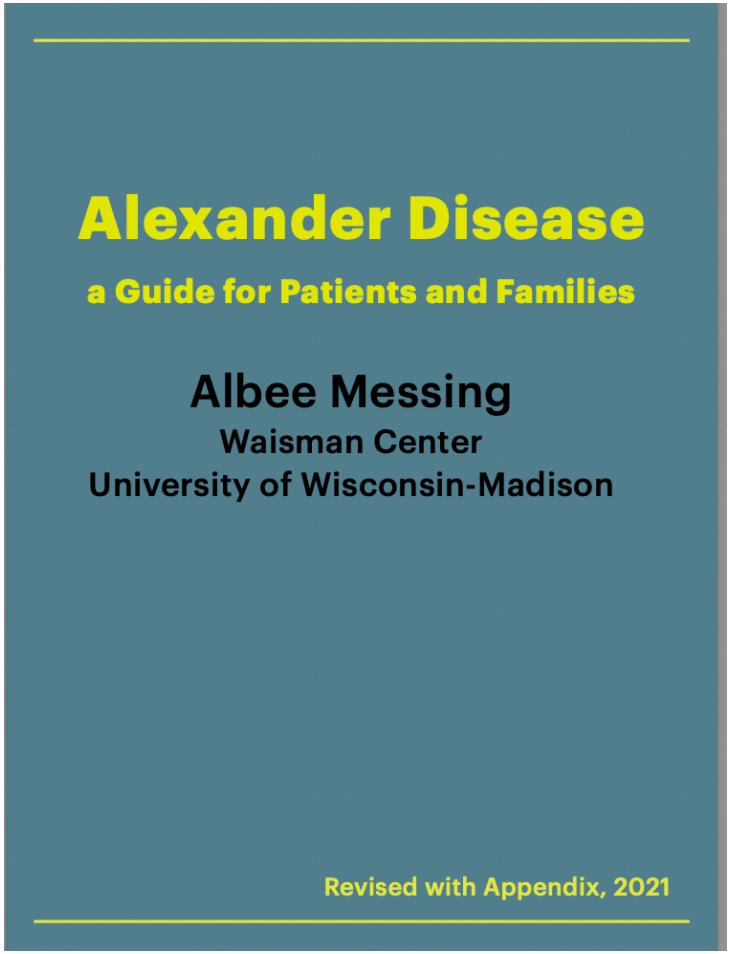

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https://alexander-disease.waisman.wisc.edu/axd-book/

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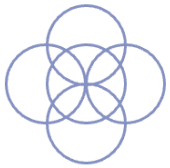

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Alexander Disease Research Bibliography
(updated June 16, 2022)

Recently added:

Arshiany H, Ezzatian B, Artounian V, Alizadeh F, Mohammadian F. (2022). Psychiatric Onset Alexander Disease: An Important Challenge in Neuropsychiatric Diagnosis.
Basic and Clinical Neuroscience 13, 269-274
[very misleading, contains many mistakes, Alexander disease should not be in the title]

Schlote W. (1966). Rosenthasche "Fasern" und Spongioblasten im Zentralnervensystem. II. Elektronenmikroskopische Untersuchungen. Bedeutung der Rosenthalschen "Fasern"
Beitrage zur Pathologischen Anatomie und zur Allgemeinen Pathologie 133, 460-480
[first ultrastructural description of Rosenthal fibers in Alexander disease]

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General Reviews:

Messing A (2018) Alexander Disease: a Guide for Patients and Families (updated 2021)
[overview on every aspect except symptom management] [full text]

Srivastava S, Waldman A, Naidu S (2020) Alexander disease. In: GeneReviews(®) (Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, eds). Seattle (WA): University of Washington, Seattle [focuses on clinical aspects] [full text]

Key publications (most available as free downloads):

Alexander WS. (1949). Progressive fibrinoid degeneration of fibrillary astrocytes associated with mental retardation in a hydrocephalic infant.
Brain 72, 373-381
[first description of a child with what later came to be called Alexander disease]

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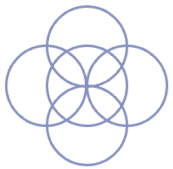

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REVERSE CHRONOLOGICAL LISTING

2022

Kang YR, Lee SH, Lin NH, Lee SJ, Yang AW, Chandrasekaran G, Kang KW, Jin MS, Kim MK, Perng MD, Choi SY, Nam TS. (2022). A novel in-frame GFAP p.E138_L148del mutation in Type II Alexander disease with atypical phenotypes. *European Journal of Human Genetics* (in press)

Wang L, Bukhari H, Kong L, Hagemann TL, Zhang S-C, Messing A, Feany MB. (2022). Anastasis drives senescence and non-cell autonomous neurodegeneration in the astrogliopathy Alexander disease. *Journal of Neuroscience* (in press)

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Abstract

Anastasis is a recently described process in which cells recover after late-stage apoptosis activation. The functional consequences of anastasis for cells and tissues are not clearly understood. Using *Drosophila*, rat and human cells and tissues, including analyses of both males and females, we present evidence that glia undergoing anastasis in the primary astrogliopathy Alexander disease subsequently express hallmarks of senescence. These senescent glia promote non-cell autonomous death of neurons by secreting interleukin family cytokines. Our findings demonstrate that anastasis can be dysfunctional in neurologic disease by inducing a toxic senescent population of astroglia.**SIGNIFICANCE STATEMENT** Under some conditions cells otherwise destined to die can be rescued just before death in a process called anastasis, or "rising from the dead." The fate and function of cells undergoing a near death experience is not well understood. Here, we find that in models and patient cells from Alexander disease, an important brain disorder in which glial cells promote neuronal dysfunction and death, anastasis of astrocytic glia leads to secretion of toxic signaling molecules and neurodegeneration. These studies demonstrate a previously unexpected deleterious consequence of rescuing cells on the brink of death and suggest therapeutic strategies for Alexander disease and related disorders of glia.

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- send me your email if you wish to be added (amessing@wisc.edu)
- simple to unsubscribe

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Jun 9, 2022	Alexander Disease Research Update - Episode #10: effects of variants in the rod domain on GFAP assembly and aggregation, new ideas about functions of intermediate filaments	34:04
Apr 12, 2022	Alexander Disease Research Update - Episode #9: new mechanisms of astrocyte dysfunction, case report with novel variant, commentary on head trauma as an aggravating factor	41:27

https://www.buzzsprout.com/1819681/

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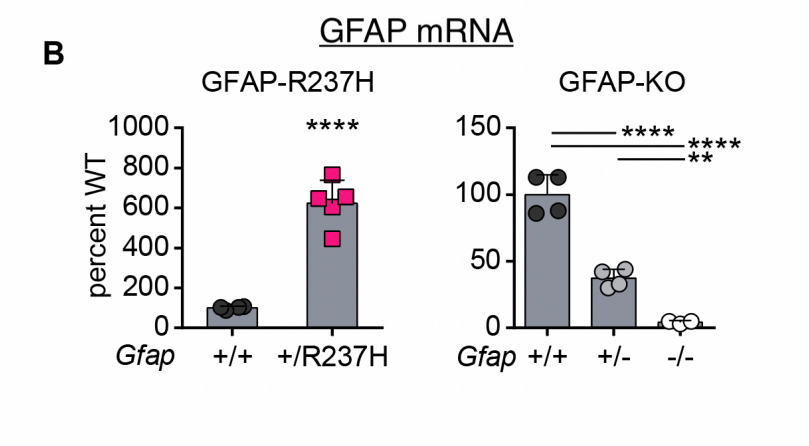

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- **Data Slide of the Week** series (figure from recent publication - now working our way through the rat model)

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bibliography	https://alexander-disease.waisman.wisc.edu
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