



“Alexander Disease: a Guide for Patients and Families”

Appendix II Update – September 9, 2026

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(for Spanish translation, see ...)

INTRODUCTION

The first edition of “*Alexander Disease: a Guide for Patients and Families*” was published in early 2018, and updated with an Appendix in 2021. Spanish versions of both the main text and 2021 appendix are now available as free downloads at <https://alexander-disease.waisman.wisc.edu/axd-book/>.

Since August, 2021, 123 (last checked on 9.9.26) publications have appeared and it is now time for a second update. What have we learned?

GENETICS

The genetic landscape for Alexander disease (AxD) remains much as it was before – GFAP is the only known gene, and acts in a dominant fashion so that affected individuals are almost always heterozygous for the change in the DNA (i.e. only one of the two copies on chromosome 17 is altered). Minor updates to this picture consist of three single family reports where the affected individual was homozygous (both copies affected) for the particular GFAP variant (Fu et al. 2020; Rathod et al. 2025; Yoshida et al. 2021). In each of these reports, the parents were asymptomatic as heterozygotes, though in the case reported by Fu et al. (2020) the variant had previously been reported as capable of causing disease in the heterozygous state as well. In addition, the first example of germline mosaicism was described, in the mother of a child with the p.Arg79His variant who herself showed evidence of the same variant in ~12% of her blood cells (Grossi et al. 2021).

Sporadic reports of novel variants also continue to appear. Counting just the most common type, which involve changes of single amino acids, 167 have been reported to date, affecting 100 of the 432 amino acids in the major isoform, GFAP- α . Roughly 60% of these variants are “private” – that is, only one patient (or family, in inherited adult-onset forms) is known with that particular variant – which makes predicting disease course particularly challenging for this group.

Effort has now turned to the question of whether a specific GFAP variant predicts a specific outcome – that is, how severe will the disease be. The sheer number and diversity of known variants pose a challenge, since as noted they have only been reported in single individuals. One publication (Messing et al. 2025) addressed this challenge by concentrating just on the limited number of variants for which seven or more independent reports existed (the choice of seven being somewhat arbitrary) and focusing on just two aspects of the phenotype – age at onset of symptoms and survival. Some variants consistently caused early onset and rapid progression (N77S, R79C and L, and most of the variants involving R239), whereas others showed late onset and longer survival (R70W and N386S). Still others were extremely variable in their effects (particularly R416W). Similar conclusions regarding the effects of the common R79C and H compared to R239C and H variants were reached by Bachetti et al. (2026), who focused their analysis on early onset cases but added consideration of development of motor skills (ability to walk independently). This information should be useful for individuals or families affected by these variants.

Grossi and colleagues (2024) reported that variants that inherited from a parent (rather than those newly occurring, when both parents are negative, commonly referred to as *de novo*) were on the maternal chromosome twice as often as on the paternal. This is despite the well-known finding reported many years ago in Li et al. (2006) that nearly all newly occurring mutations occur on the paternal chromosome (i.e from the father), speculated as resulting from differences in the number of cell divisions that take place during the development of sperm vs eggs. At present there is no hypothesis to account for the propensity for maternal transmission of inherited variants, and this finding requires validation from future studies.

A third question is whether GFAP variants might cause problems other than Alexander disease. An interesting example is the change from aspartate to asparagine at position 295, otherwise designated as p.Asp295Asn or D295N. According to one large database (<https://gnomad.broad.institute.org/gene/ENSG00000131095>) this variant is found in approximately 8% of the general population (accepting that this database is skewed towards Europeans and the numbers might be somewhat different in other groups). Previously, when found in someone with presumed Alexander disease, D295N was considered benign and not related to that person's condition. Recently, two groups found a correlation between the D295N variant and other changes in the brain. Both studies utilized large databases that included individuals predominately of European ancestry, but some of Japanese ancestry as well. Durperon et al. (2023) found that D295N was associated with an increase in the perivascular space surrounding small blood vessels in the central nervous system, and Furuta et al. (2024) found an association with the presence of undefined “white matter lesions” seen in MRI. The relevance of these observations to the leukodystrophy that is the dominant feature of Alexander disease is not known.

Whether variants that are considered disease-causing always lead to clinical symptoms (i.e. penetrance) is a major topic of debate. The variants that were first reported in the original publications linking GFAP to Alexander disease in the early 2000's were thought

to have 100% penetrance. Now, with the identification of many more variants, the situation is less clear. A notable publication was that by Gagliardi et al. (2024) who examined the records of 470,000 adults (40-69 years of age) in the UK Biobank and found a large number of previously unreported variants. Based on these numbers, the investigators calculated the prevalence for adult-onset AxD in the UK at 68.5 per million. If one limits the calculation to just the variants for which there are previous reports in the literature, it is still 14.2 per million. These figures are significantly higher than previous estimates in earlier reports and in other countries [such as the widely cited 2.7 per million from Japan, only half of which were adult-onset, reported by Yoshida et al. (2011)]. The major conclusion from Gagliardi et al. is that many variants exhibit either reduced and/or underdiagnosis by physicians. These conclusions rest on the assumption that the new variants should all be classified as likely to cause disease, but this assumption is controversial and not yet widely accepted. Indeed, the consensus system for classifying novel variants on a 5-point scale (from benign to pathogenic), as outlined in 2015 by Richards et al. (2015), is not easily applied to Alexander disease, with a large number of new variants being classified in the middle category of “variants of unknown significance” (i.e. uncertain whether benign or pathogenic). Attempts are underway to update this classification system and improve its utility for interpreting variants in GFAP. The true prevalence of AxD in various populations remains a topic of investigation.

MECHANISMS

As commented upon many times before, a consistent feature of Alexander disease is an increase in the amount of GFAP. While expression of the variant GFAP clearly begins the process, the increased levels are expected to exacerbate whatever problems might be caused by the variant on its own. The increase in total GFAP can, in principle, result from an increase in synthesis (from increased mRNA allowing more translation into protein), a decrease in degradation, or both. We are learning more about the first side of this equation – what causes the increase. Using a variety of tools available from mouse genetics, Hagemann et al. (2023) found that the increase in expression of GFAP mRNA and protein requires the presence and activation of a protein known as STAT3, which belongs to a category of “transcriptional activators” that bind to the regulatory regions of genes and promote the transcription from DNA to RNA, the essential first step in gene expression. If ways can be found to safely suppress the expression or activation of STAT3, this pathway becomes a new potential therapeutic target in the search for effective treatments.

Once GFAP is expressed, what goes wrong within the astrocyte? Perng and colleagues identified several mechanisms by which GFAP variants interfere with assembly of the individual protein chains into the multi-subunit final form of a mature intermediate filament, as well as the incorporation of mature filaments into the cytoskeletal network of the cell (Lin et al. 2024; Yang et al. 2022). However, no common theme has yet emerged to explain how these changes lead to Rosenthal fibers, or even if the Rosenthal fibers themselves are toxic for the cell.

Nevertheless, we can now point to three aspects of astrocyte biology that become altered. First is the change in expression of specific genes that may significantly affect either astrocytes, oligodendrocytes, or both. YKL40, a protein secreted by astrocytes that can inhibit oligodendrocyte development, was discovered by Li et al. (2018). More recently, Heaven (2022) identified FABP7 as a second factor. We can expect more additions to this list as time goes on.

Second are changes in mitochondria, the energy-producing components of the cell, which under normal conditions are constantly undergoing periodic growth and division. Viedma-Poyatos and colleagues (2022) used astrocytoma tumor cell lines to show that 1) mitochondria co-localizes with GFAP, 2) the R239C variant causes oxidative stress, and 3) mitochondrial division (or “fission”) is reduced. However, Xiong and colleagues (Xiong et al. 2025), using the perhaps more relevant and less artificial system of patient-derived iPS cells, found the opposite result regarding mitochondrial fission – this phenomenon was increased by two different GFAP variants (R88C and R416W), it was decreased when GFAP was not present at all, and the association of GFAP to specific binding partners within the cell were responsible for mediating this effect on mitochondria. Changes in mitochondrial gene expression are also a clear feature of the rat model of AxD (Berman et al. 2025). The interactions of GFAP on mitochondria and the effects of the GFAP variants associated with AxD will be an interesting topic for future study, since mitochondrial dysfunction is a common feature of many disorders affecting the central nervous system.

A third question that is now being addressed is how astrocyte dysfunction in AxD impacts neurons. Wang et al used a combination of approaches, including the fly and rat models of Alexander disease, as well as human patient-derived iPS cells and brain, to detect a small population of astrocytes in the unusual state known as “senescence (stalled in the process of dying). Such cells are not innocuous, however, and begin secreting molecules that cause death of neighboring neurons (Wang et al. 2022). Berman et al. (2025) performed large scale gene expression profiling from brain of the rat model of AxD, and found not only the expected neuroinflammatory response but marked decreases in genes related to neuronal synaptic function.

Further links between AxD and other neurodegenerative diseases (typically associated with neuronal dysfunction and death) were demonstrated by two studies. Gammie et al. (2024) analyzed gene expression profiles from 505 animal models of neurodegenerative disease in an attempt to identify those that most closely resembled the expression profile found in human Alzheimer’s disease. The mouse model engineered to mimic the common human p.Arg239His variant by Hagemann et al. (2006) was ranked second overall, demonstrating remarkable overlap between the two conditions. In studies of human blood, Ashton et al. (2024) recently found that two proteins whose elevations are frequently associated with human neurodegeneration, neurofilament (light chain) and the phosphorylated forms of the protein known as tau, were also elevated in AxD, particularly in the early-onset form.

New information is now emerging for two protein biomarkers that are of particular relevance for AxD. First is GFAP. Previously, Jany et al. (2015) had shown that GFAP levels were elevated in CSF and blood in most individuals with AxD, but could not see a difference in those with onset as adults. Using newer and more sensitive methods for analysis, two studies have now documented that such adult-onset individuals also have elevated levels compared to controls (Ashton et al. 2024; Waldman et al. 2026). Waldman was also able to compare the GFAP levels over time in a subset of their cohort and made the interesting observation that the levels were rising in those examined before the age of 8 but remained relatively stable (though elevated) in those studied at later ages. This pattern over time resembles that seen in earlier studies using both the mouse and rat models (Hagemann et al. 2021; Jany et al. 2013). Separate from GFAP, again using the rat model, Hagemann et al. (2026) recently found marked elevations of the protein known as GDF-15, but only in CSF and not in blood. As a biomarker, it was also notable that GDF15 levels were dramatically reduced following treatment with an antisense oligonucleotide (ASO) that reduces GFAP. GDF-15 has received considerable attention due to its link to morning sickness in humans, and these findings may help in understanding the origins of nausea, vomiting, and failure to thrive in Alexander disease.

CLINICAL

Practical applications in clinical care

Several findings of practical significance for clinical care have emerged since 2021. First, new MRI features that are helpful during the initial diagnostic process were identified, perhaps the most useful being an MRI pattern described by Armange et al. (2024) which consists of a particular constellation of features in the brainstem involving the inferior olivary nucleus and nearby structures. This unusual MRI pattern was found in 48 of 55 individuals with AxD, equally distributed among those with Type I and Type II disease, although it was also found in 10 of 74 individuals with other leukodystrophies.

Second, analysis of 40 individuals seen at the Children's Hospital of Philadelphia revealed no evident risk associated with anesthesia for short-duration procedures, even general anesthesia, though nothing is yet known about anesthesia for longer-term procedures such as those involving major surgery (Berger et al. 2024). This finding is surprising in a way, given prior studies at the cellular level that implicated astrocytes as important regulators of the response to anesthesia. Third, cognitive deficits have been more carefully defined, particularly those associated with problems with speech and language (Levin et al. 2026). The main finding seems to be that there is no speech/language profile that is unique to AxD, nor do the different sub-types of AxD differ from one another (other than the expected general correlation with age of onset and frontal predominance). Instead, each patient must be evaluated as an individual and a personal treatment plan developed for their own constellation of symptoms.

Classification systems and natural history

Three classification systems are currently in use (neonatal-infantile-juvenile-adult, Type I vs Type II, and cerebral-bulbospinal-intermediate), with no clear consensus about which one is the best. Two new studies provide further detail about two of these systems, concentrating on the categories reflecting those at the more severe end of the spectrum (Type I and cerebral).

Mura et al. (2021) proposed a subdivision of Type I [as originally defined by Prust et al. (2011)] into four sub-types – Ia, Ib, Ic, and Id – based on a study of a pediatric cohort consisting of 21 children who had onset of symptoms from birth to 12 years. The distinctions between Types Ia-d hinge on a combination of 1) the age at which one achieves and/or loses motor milestones, 2) other developmental delays, and 3) particular focus on when one achieves and/or loses the ability to walk independent of any aids or assistance (aka “autonomous ambulation”). All four types shared the common feature of developmental delay, with 1a being the most severe (no postural control and short survival). Type Ib individuals achieve postural control, but not autonomous ambulation, and then begin to decline before the age of 5. Type Ic individuals do eventually achieve autonomous ambulation, but later than normal, and then begin to decline before the age of 6. Type Id individuals achieve autonomous ambulation, again with delay, but then remain stable after adolescence. Research is now aimed at finding ways, perhaps in combination with MRI, to predict in advance which of these distinct trajectories are likely to apply (Vaia et al. 2026).

Joung et al. (2023) provided more information on the natural history in a cohort of 51 children with the “cerebral” form of the disease (the definition of which overlaps to a considerable extent with Type I). The most common first symptom was developmental delay (motor control or acquisition of language) rather than seizures or macrocephaly (enlarged head). Autonomous ambulation was achieved by 67% of this group, with an additional 20% who could walk with assistance. For those who reached the ability to walk independently, 32% eventually lost that skill.

Two publications provide more detailed assessments of the cognitive deficits associated with AxD, a topic that surprisingly has not been well studied in the past. Kirsch et al. (2021) performed detailed longitudinal neuropsychological assessments of two individuals, one representing Type I and the other Type II AxD. Both experienced decline in functioning over the course of 4-6 years of follow-up. As expected, the Type I individual was more severely impaired than the Type II individual. As with the speech-language profiling described above, the main conclusion seemed to be that each person deserves thorough evaluation with treatment plans that are tailored to their particular deficits.

Based on a detailed study of 9 individuals, plus prior experience with other neurodevelopmental disorders, Kokaly et al. (2025) recently developed a measurement tool called the Alexander Disease Severity Score (ADSS). This score derives from ratings on just six aspects of the disease – problems with feeding, epilepsy, motor

function, failure to thrive, language, and apnea. Severity in each of these domains is rated on a scale of 0-2, and then the individual scores are added together to yield a final score ranging from 0 (severely affected in all domains) to 12 (no symptoms). Validation of this score in larger patient populations will be necessary to determine whether it will be useful for future clinical care and research.

Modifiers

Efforts to connect specific GFAP variants to the course of disease were described above. However, we and others have noted the likelihood that both genetic (i.e. other genes) and environmental (any external influence) modifiers exist that can impact the trajectory and severity of disease. To date, although no genetic modifiers have yet been identified in human, previous work in the *Drosophila* model (Wang et al. 2015; Wang et al. 2018), and as yet unpublished data from the mouse models, offer promise for progress on this front. With regard to environmental modifiers, no systematic studies have been done, but eight new case reports of head trauma are now added to the two that were mentioned in the first edition of the book (Ayaki et al. 2010; Benzoni et al. 2020; Chang et al. 2024; Godinho et al. 2023; Goertler et al. 2022; Kang et al. 2023; Matsuyama et al. 2020; Namekawa et al. 2010; Yousaf et al. 2025). All such incidents occurred in adults, were often described as “minor” trauma, and in one (Godinho et al. 2023) the head trauma resulted from a fall due to alcohol intoxication. The extent to which alcohol by itself can act as a modifier remains uncertain (there had been one previous report of such a case – see (Schmidt et al. 2013)). More recently, Kim (2022) described a patient whose symptoms may have resulted from a combination of alcohol spinal cord trauma.

Clinical trial of the antisense oligonucleotide (ASO) strategy for treatment

In 2018 and 2021 we published studies using the mouse and rat models that outlined a treatment strategy for AxS utilizing antisense suppression of GFAP (Hagemann et al. 2021; Hagemann et al. 2018). Based on this “pre-clinical” work, a phase I-III clinical trial (which combines evaluation of safety and efficacy) was initiated in 2021 and completed last year (NCT04849741)(publication pending). The trial included individuals ranging from 2-53 yr and with many different GFAP variants. The primary outcome measure (the symptom on which a determination of whether or not the treatment worked) was a test of motor function – how much time did it take to walk 10 meters. Hence the trial excluded those who were already severely impaired and unable to complete this task.

Those receiving the ASO over a period of 60 weeks displayed 10-meter walk times that were 33% better than those receiving the placebo. Several secondary outcome measures were also assessed that demonstrated suggestive (though not statistically significant) evidence for efficacy of the ASO, including such measures as stabilization or improvement in “the most bothersome symptom.” Despite the heterogeneity in the patient population and the exclusion of those with the earliest onsets, these results provided strong evidence that the ASO treatment produced a meaningful benefit.

Equally important is that no significant safety issues emerged. An unknown is exactly how much suppression of GFAP expression was actually achieved.

On Thursday, September 3, 2026, the FDA in the United States approved the *GFAP*-targeted antisense oligonucleotide as manufactured by Ionis Pharmaceuticals for use in Alexander disease, permitting use in all age groups affected. Ionis licensed the ASO (zilganersen, aka ZANVASTRO™) to Recordati, a pharmaceutical company based in Italy, for clinical implementation in all countries other than the U.S.

NEW RESOURCES

Several online resources now exist to help those who are interested to keep up with the recent research literature. One is a complete bibliography, listed in reverse chronological order with the most recent articles first, and the second is a comprehensive listing of all GFAP variants that have been published. Both files can be found at Zendodo.org.

Bibliography: <https://10.5281/zenodo.17253798>
GFAP variants: <https://10.5281/zenodo.14313058>

In 2021 we began recording periodic podcasts with the primary goal of interpreting recent research results for the patient family/community. Audio versions of these podcasts can be found at:

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

Video versions also exist for some of the podcasts, which can be found at:

<https://www.youtube.com/@Albee-pv5un>

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