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Analysis of GFAP variants in UK Biobank suggests underdiagnosis or incomplete penetrance of adult-onset Alexander disease

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ABSTRACT

Background Alexander disease is an autosomal dominant leukodystrophy caused by heterozygous pathogenic variants in the glial fibrillar acidic protein (GFAP) gene. Although increasingly recognised, there is evidence that Alexander disease, particularly later-onset disease, is significantly underdiagnosed and its true prevalence is unknown (the only population-based prevalence was estimated at one in 2.7 million). Using the extensive UK Biobank dataset, we analysed the frequency of pathogenic and likely pathogenic variants, *GFAP* variants, within the UK population and identified clinical and radiological phenotypes linked to these variants.

Methods Pathogenic, likely pathogenic and *GFAP* variants of uncertain significance were identified in the UK Biobank whole-exome sequencing data (n=4 70 000). Demographic information, previous medical history—including symptoms associated with Alexander disease—collected from self-reported data and hospital records, family history and various MRI metrics were compared between variant carriers and controls.

Results We identified 36 unique pathogenic and likely pathogenic *GFAP* variants in 106 carriers, yielding a carrier frequency of approximately 1 in 4435. Modelling based on the UK population estimated a prevalence of 6.8 per 100 000. Carriers of pathogenic and likely pathogenic *GFAP* variants had higher odds of bladder dysfunction (OR 3.17, p<0.0001), upper airway dysfunction (OR 7.82, p=0.004) and psychiatric conditions (OR 1.51, p=0.04). Additionally, carriers were more likely to report a paternal history of dementia (OR 2.79, p<0.0001). MRI data revealed significant atrophy in brainstem regions among variant carriers.

Conclusion Pathogenic and likely pathogenic *GFAP* variants are more prevalent in the general population than previously expected and are associated with clinical and radiological characteristics of Alexander disease. This study indicates that Alexander disease may be under-reported, misdiagnosed, or exhibit reduced penetrance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Later onset Alexander disease is underdiagnosed due to mild and heterogeneous disease presentations, and its true prevalence is unknown. A study based on a large population dataset is needed to explore the frequency of this disease in the general population.

WHAT THIS STUDY ADDS

⇒ This study shows that damaging glial fibrillar acidic protein variants are more common than expected and the estimated number of people with Alexander disease in the UK population is 6.8:100 000, which is much higher than previous figures.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings have important implications for global health and suggest that a greater number of patients can benefit from forthcoming clinical trials.

INTRODUCTION

Alexander disease is an autosomal dominant leukodystrophy caused by heterozygous pathogenic variants in the glial fibrillar acidic protein (*GFAP*) gene. Pathogenic variants in GFAP are thought to confer cytotoxicity through gain-of-function mechanisms resulting in the development of protein aggregates (Rosenthal fibres) in astrocyte cytoplasm, producing a progressive astrogliopathy, which induces secondary changes in neurons and other types of glia.[1]

Traditionally, four subtypes of Alexander disease (neonatal, infantile, juvenile and adult) are recognised, depending on the age of onset, though more recently, Prust *et al* proposed a two-group revised system based on clinical and imaging features.[2 3] The more common type I Alexander disease describes earlier onset cases—usually before aged 4—and so encompasses neonatal and infantile onset and is a predominantly frontal leukodystrophy presenting with seizures, macrocephaly and developmental delay. Prognosis is invariably poor, and death occurs within weeks to short years. Type II manifests later—usually after aged 4—thus generally referring to those with juvenile and adult onset, and presents differently, with bulbar dysfunction (dysphagia, dysarthria, dysphonia), eye movement abnormalities and dysautonomia, often with no or only mild neurocognitive deficits.[3] Other clinical features can include pyramidal and gait abnormalities, cerebellar ataxia, sleep/respiratory disturbances (sleep apnoea), bladder dysfunction and frontotemporal psychiatric symptoms.[4–6] Symptoms are generally milder with older onset—in fact in some

cases, the patient is asymptomatic and diagnosed following an abnormal scan—and prognosis is generally better, with median survival reported as 11–25 years after diagnosis.[7–9] MRI findings generally reflect the differences between the two phenotypes. In type I cases, there is macrocephaly, and predominantly frontal white matter abnormalities or involve the periventricular rim, in type II disease, abnormalities can be restricted to the posterior fossa, particularly with atrophy of the medulla and cervical spinal cord.[3 6 10]

Diagnosis at a younger age, where a striking and rapidly deteriorating clinical and radiological picture results in genetic testing, is more straightforward and commonplace than in adulthood, where the subtle signs and symptoms and broad age of onset generate a wider differential diagnosis and delayed or missed diagnoses.

As a result, true incidence of Alexander disease is unknown—with the only population-based prevalence estimate at one in 2.7 million.[11 12] To further our understanding of the prevalence of pathogenic and likely pathogenic variants (P/LP) *GFAP* variants in the UK population, we examined the whole-exome sequences (WES) of 470 000 UK Biobank participants. We used phenotypic data and MRI data to determine whether these variants were associated with evidence of disease activity.

METHODS

The UK Biobank is a prospective study of 502 493 volunteers aged 40–69 years, recruited across the UK between 2006 and 2010.[13] Participants attended longitudinal visits undergoing extensive phenotyping, provide biological sample—including a subset of 470 000 who underwent WES—and a further subset (45 000 or ~10%) of participants underwent MRI.

Ascertainment of GFAP pathogenic variants

All missense variants in *GFAP* with a minor allele frequency of <0.001 were extracted from WES data of 470 000 individuals in the UK Biobank dataset. Annotation was performed using Intervar to assess variant type, frequency in genomic population datasets and pathogenicity prediction using in silico tools (MetaSVM, GERP++, dbscSNV).[14] Synonymous and untranslated region variants were excluded.[15] Variants were classified as pathogenic, likely pathogenic and of uncertain significance according to the American College of Medical Genetics (ACMG) criteria.[16] Two experts in clinical genetics (DG and DSL) reviewed Intervar annotation and ACMG classification for variants already described in literature or causing a different amino acid substitution at a position previously reported as pathogenic for adult-onset Alexander disease. For assignment of PP3 criteria, all in silico tools must be in agreement; otherwise, PP3 is not assigned. Likely pathogenic variants with either multiple submissions to ClinVar as benign or uncertain pathogenicity according to the Waisman centre were removed.[17]

Disease modelling

To estimate the prevalence of adult-onset Alexander disease, we modelled the number of people affected by age on the UK population using a previously described method.[18] In the model, we accounted for the *GFAP* carrier frequency in the UK Biobank, the UK population count by age (taken from the Office of National Statistics), the distribution of the age at onset from patients with adult-onset Alexander disease, and the median survival time for the disease (25 years) to account for mortality.[19 20]

The *GFAP* carrier frequency in the UK Biobank was calculated as the number of exomes with a P/LP variant in *GFAP* over the total number of sequences (470 000). A more narrowed *GFAP* carrier frequency was calculated considering only P/LP variants found in the UK Biobank *and* already reported in literature. 95% Confidence Interval (95% CI) was calculated as previously described.[21 22]

The distribution of the age at onset for patients with adult-onset Alexander disease was obtained through literature review. Using PubMed, the following search terms were used 'Alexander disease' AND 'adult onset'.

Phenotypic data fields

Numerous demographic and phenotypic data were extracted and analysed for both the variant subjects and a 20 000-person cohort of random controls. We looked for evidence of disease manifestation using both International Classification of Diseases-10th Edition (ICD-10) codes and self-reported diagnoses. Patients with one or more codes for each medical condition or symptom were considered positive for that condition. We deliberately examined for common signs and symptoms of Alexander disease but looked extensively for wider neurological and psychiatric manifestations. Frequency of cognitive disease was also collected using the UK Biobank's algorithmically defined outcomes, which are obtained through combinations of coded information from UK Biobank's baseline assessment data collection (which included data from participants on their self-reported medical conditions, operations and medications), along with linked data from hospital admissions (diagnoses and procedures) and death registries. The use of UK Biobank algorithmically defined outcomes in dementia has been validated elsewhere. Family history (including age of death of parents and history of illness in parents and siblings) was also extracted. Logistic regression was then used to calculate ORs, which represent the probability of each condition occurring in the *GFAP* variant group, relative to the control group.

MRI was only performed in a limited subgroup of participants. As well as access to raw imaging data, processed UK Biobank neuroimaging working group-derived, quantitative MRI metrics including brain volume, regional brainstem volumetric data and white matter hyperintensity (WMH) volume and were compared between a subset of variant subjects and controls. Total brain volume (including grey and white matter, normalised for head size) was calculated using the FMRIB Software Library (FSL), which provides automated segmentation of brain structures and tissue types.[23] Regional posterior fossa volumes, including subsegmentation of brainstem structures, were derived from FreeSurfer, which performs detailed cortical and subcortical parcellation based on T1-weighted MRI images. The brainstem was an area of particular focus given it is classically affected in late-onset Alexander disease.[24] WMH volume was quantified on Fluid-attenuated inversion recovery (FLAIR) images using the Brain Intensity Abnormality Classification Algorithm within FSL, incorporating both T2-FLAIR and T1-weighted data.[25] This provided three specific imaging-derived phenotypes: total WMH volume, periventricular WMH volume (lesions within 10 mm of the ventricular mask) and deep WMH volume (lesions more than 10 mm from the ventricular mask).[26] No further delineation (eg, cerebellar white matter or dentate nuclei involvement) is possible. Qualitative review of available images was then undertaken by a neuroradiologist with significant experience in the imaging of leukodystrophy (FB).

RESULTS

The prevalence of pathogenic and likely pathogenic variants GFAP variants

We identified 36 P/LP *GFAP* variants (35 unique likely pathogenic and one pathogenic *GFAP*) across 106 carriers (affecting between 1 and 15 subjects each). These variants are listed in online supplemental table 1. Ten of them (present across 22 individuals) have been previously reported as pathogenic for Alexander disease, and 25 of the variants (present across 83 individuals) were in positions where different substitutions have previously been reported as pathogenic. One variant (present in one individual) has not previously been reported. Additionally, across 3591 individuals, we identified 277 variants of uncertain significance and three likely pathogenic variants, which we determined unlikely to be pathogenic, due to multiple submissions to ClinVar as benign and/or unpublished and of unknown pathogenicity according to Waisman centre (online supplemental table 2).

Given that adult-onset Alexander disease is under-recognised and prevalence data are lacking, we set out to estimate the number of affected people using genetic data. Considering only pathogenic and likely pathogenic variants, we calculated a *GFAP* variant frequency of 1/4 435 (95% CI 1/5 608 −1/3 666), while the carrier frequency of already reported variants is 1/21 363 (95% CI 1/35 895–1/12 736).

Disease modelling was performed using age at onset data from 138 patients over 18 years of age and affected by Alexander disease, derived from 67 different studies (online supplemental table 3).[6 9 27–90] The number of people affected by later onset Alexander disease was estimated to be around 6.85 in 100 000 individuals, which is much higher than previously reported figures.[11 12] When considering only carriers of variants previously reported in association with the disease, we estimated a prevalence of 1.42 in 100 000, which is over 38 times the literature prevalence (figure 1).

The clinical impact of pathogenic GFAP variants

The demographic profile of cases with P/LP *GFAP* variants and a random control group (n=20 000) are shown in online supplemental table 1 (ancestry and location) and online supplementaltable 4 (age, sex). The *GFAP* variant cohort mirrors the demographic profile of the UK Biobank, and there were no significant differences between groups with regard to age, sex or ancestry. The *GFAP* variant cohort was more likely to have hypertension (OR 1.52 (95% CI 1.15 to 2.06, p=0.004)), but there was no difference otherwise in terms of other cardiovascular risk factors including body mass index, hypercholesterolaemia, HbA1C or smoking status (online supplemental table 5, 6).

Regarding ICD-10 diagnoses, logistic regression analysis revealed statistically significant associations for bladder dysfunction codes with an OR of 3.17 (95% CI 1.87 to 5.35, p<0.0001), upper airway dysfunction with an OR of 7.82 (95% CI 1.95 to 31.30, p=0.004), and psychiatric codes with an OR of 1.51 (95% CI 1.02 to 2.24, p=0.04) within the *GFAP* variant cohort (online supplemental table 7, **figure 2**). These results suggest a significantly increased likelihood of these conditions among individuals carrying P/LP *GFAP* variants. There was no significant difference between the two groups in terms of self-reported diagnoses or algorithmically defined diagnoses (online supplemental table 8, 9).

In terms of family history (online supplemental table 10), **figure 3**), participants in the *GFAP* variant cohort were significantly more likely to have a paternal history of Alzheimer's disease/dementia compared with the control group (OR 2.79 (95% CI: 1.54 to 5.04, p<0.0001)).

Six MRI brain scans were available for carriers of P/LP *GFAP* variants (two with variants previously reported and four with unpublished variants), while 1895 scans were available for the control cohort. The P/LP *GFAP* variant cohort exhibited significantly reduced total brainstem volume (p=0.038) and pontine

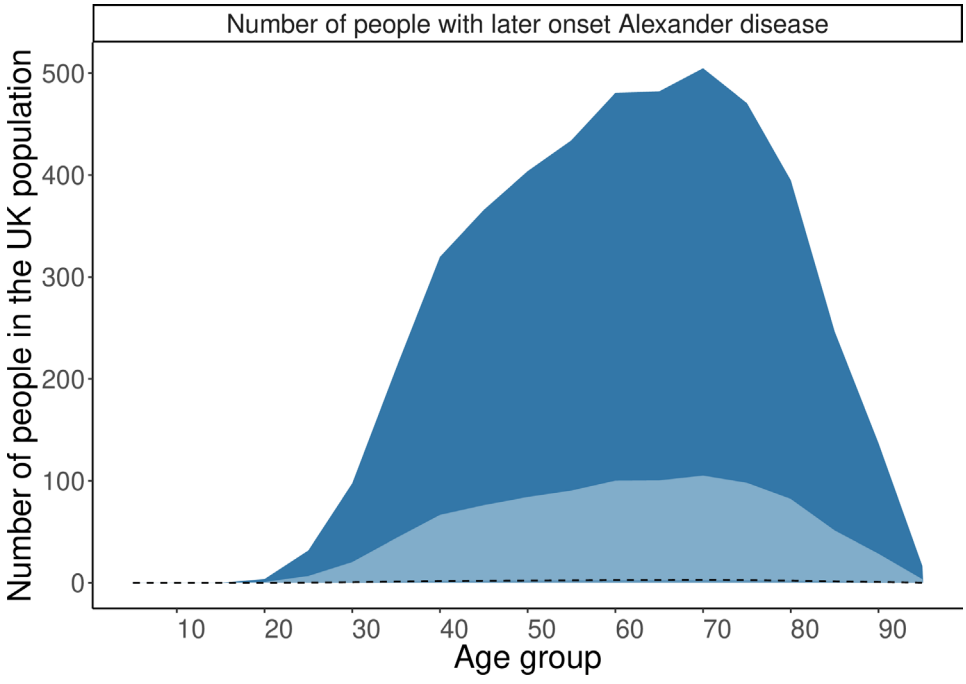

Figure 1 Estimated number of people affected by later onset Alexander disease due to all *GFAP* pathogenic and likely pathogenic variants in the UK Biobank (dark blue area) and to previously described variants (light blue area). Clinical prevalence from the literature is shown as a dashed line. Age bins are 5 years each. GFAP, glial fibrillar acidic protein.

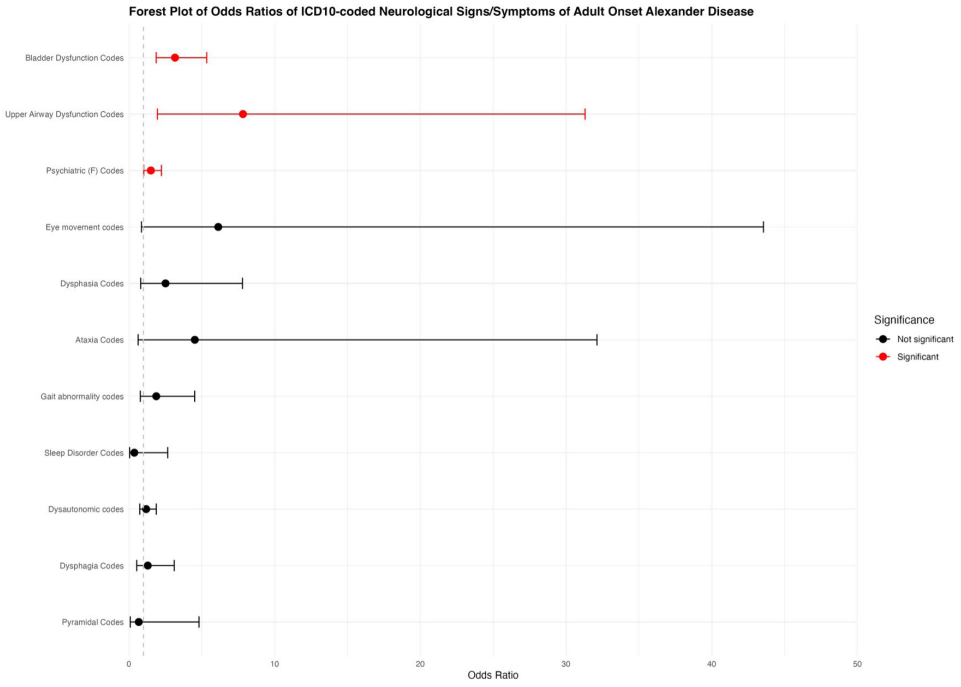

Figure 2 Forest plot showing the association of P/LP GFAP variants with various ICD10-coded diagnoses, when compared with a random control cohort through logistic regression. Significance at p<0.05. GFAP, glial fibrillar acidic protein; P/LP, pathogenic and likely pathogenic variants.

volume (p=0.049) when compared with the control (online supplemental table 11, figure 4). The two scans from participants that had variants previously been reported as pathogenic show radiological changes associated with Alexander disease on qualitative image review (figure 5). The remaining four scans available were for participants with variants where different substitutions in the same position have previously been published as pathogenic are all normal appearing. There were no significant differences found on MRI measures of white or grey matter volume or white matter hyperintensities, midbrain or medullary volumes between the P/LP *GFAP* variants cohort and the control group.

DISCUSSION

In this study, leveraging WES data from nearly 500 000 individuals, we demonstrate that P/LP variants in the GFAP gene are more frequent than expected in the general population.

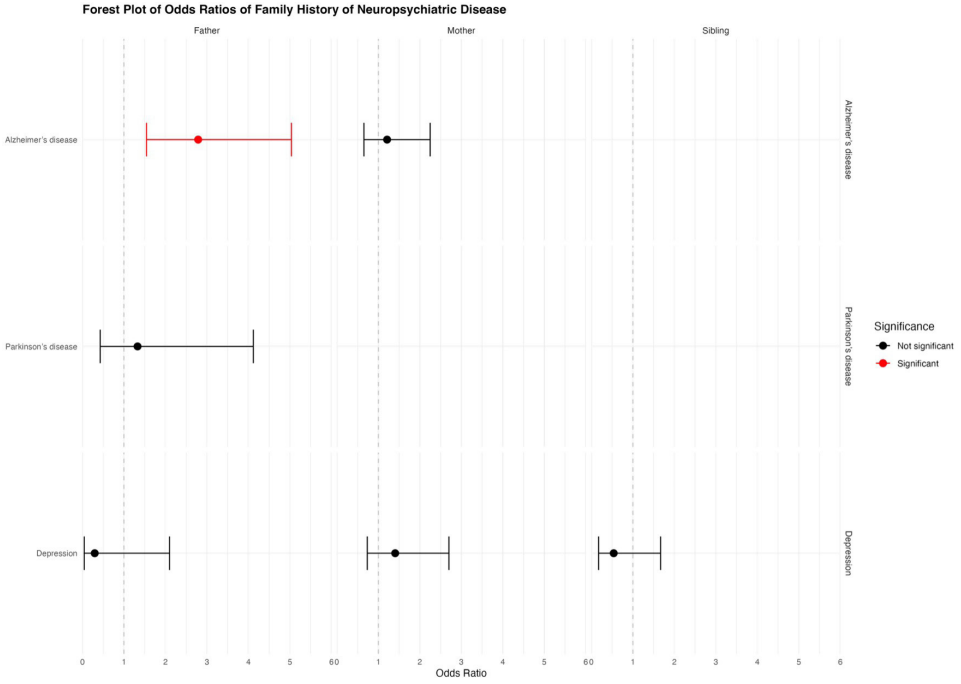

Figure 3 Forest plot showing the association of P/LP GFAP variants with family history of disease, when compared with a random control cohort through logistic regression. Significance at p<0.05. GFAP, glial fibrillar acidic protein; P/LP, pathogenic and likely pathogenic variants.

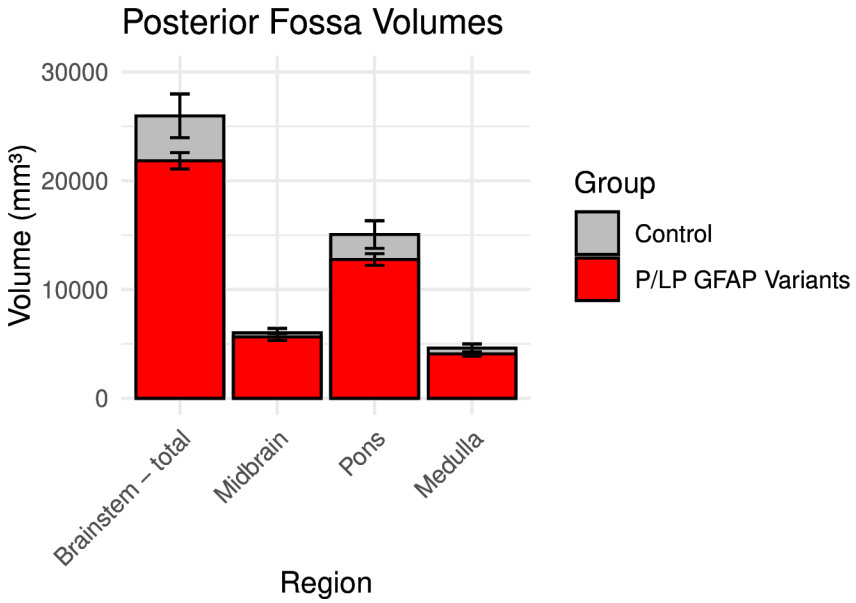

Figure 4 Bar plot with error bars comparing posterior fossa volumes (in mm³) between a random control cohort and P/LP GFAP variant carriers across different regions. Error bars represent the IQR. Significant differences ($p<0.05$) are marked with asterisks. GFAP, glial fibrillar acidic protein; P/LP, pathogenic and likely pathogenic variants.

Moreover, they are associated with some of the typical and signs and symptoms of Alexander disease as well as with an increased family history for dementia.

At the time of writing, nearly 150 different *GFAP* variants have been reported to be associated with Alexander disease—including missense, nonsense, splicing, regulatory and small indels—though missense mutations make up the vast majority.[17 91] In a large latent class analysis of 30 new cases and reviewed 185 previously reported cases of Alexander disease, Prust *et al* report that more than half (50.7%) of the subjects

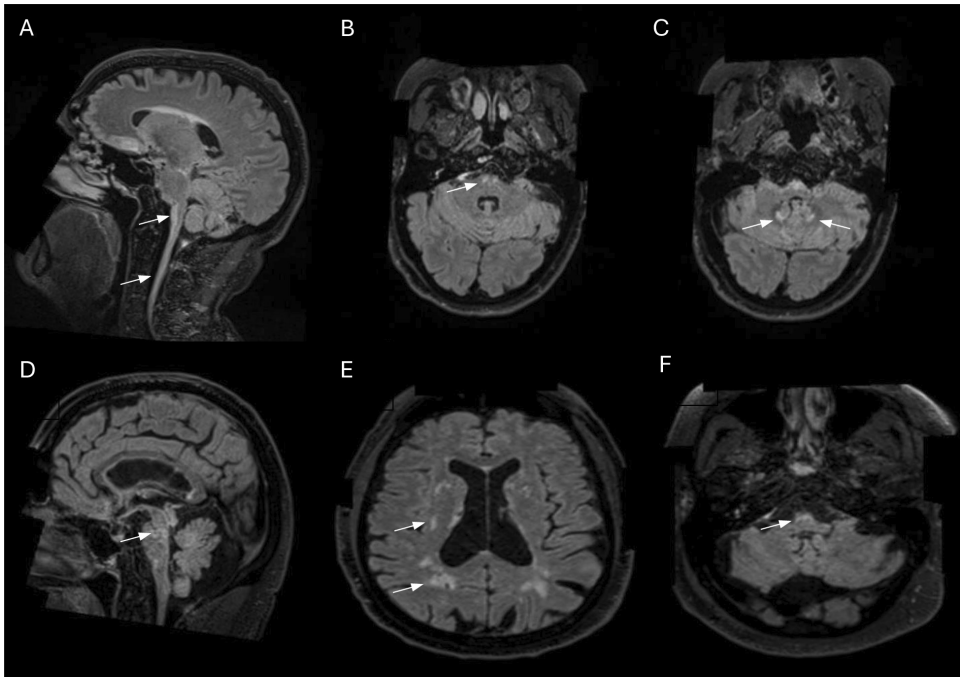

Figure 5 T2 Fluid-attenuated inversion recovery (FLAIR) brain MRI of two subjects with P/LP GFAP variants in UK Biobank. Sagittal (A) and axial (B, C) slices of a man in his 50s, carrying p.Asp128Asn variant previously reported as pathogenic. This subject self-reported as having a 'demyelinating disease (not multiple sclerosis)' as well as having 'urological problems'. There is atrophy of the medulla and cervical cord (arrows in A), with associated hyperintensity (arrow in B). There are also bilateral high signal intensities in both cerebellar dentate nuclei (arrows in C). The supratentorial white matter is spared. Sagittal (D,E) and axial (F) slices of another man in his 50s, carrying a p.Arg376Gln variant previously described as likely pathogenic. There are multifocal supratentorial and pontine white matter abnormalities (arrows in D, (E), with a microvascular appearance as well as changes in signal intensity in the medulla oblongata (arrow in F). There is less atrophy than seen in the first patient. GFAP, glial fibrillar acidic protein; P/LP, pathogenic and likely pathogenic variants.

had variants at one of four residues—R239 (20.3% of cases), R79 (16.6%), R88 (7.9%) and R416 (5.6%).[3] Certain genotypes appear to be associated with particular phenotypes, for example, R239 and R79 variants are associated with early onset and a severe phenotype in keeping with type 1 Alexander disease (and may be responsible for up to 70% of this phenotype).[92] On the other hand, the phenotype–genotype correlation is less clear with other variants—for example, with the R88 and R416 variants—and indeed patients with identical *GFAP* variants can differ in the age of onset, type of disease, severity of clinical presentation and progression rate.

This is the first study providing insights into the frequency of pathogenic *GFAP* variants in a large population-scale dataset. In total, 36 such variants were identified in 106 individuals. Variants were spread across all nine exons of the GFAP gene. Given the frequency of these variants in the Biobank dataset, we predict 6.85 carriers of P/LP *GFAP* variants per 100 000 individuals, at least 1.42 per 100 000 of which to be carrying variants previously reported as disease-causing, substantially higher than would be expected given literature published to date. This is in fact likely to be an underestimate. The selection bias of the UK Biobank, with enrolment only of those aged between 40 and 69 years old, means it will not have included those already severely clinically affected by Alexander disease. For example, while in our cohort, we identified 10 patients (9.4%) with R88 variants, we could not find any patients with the common R239 or R79 variants, which are associated with younger disease onset and more severe phenotype.

Though penetrance appears to be nearly 100% in individuals with the infantile and juvenile forms, in adult-onset forms penetrance of *GFAP* variants is less clear and harder to study given the range in age of onset and phenotypic presentation. In a review of 293 individuals, 10 (3%) of those with an identifiable *GFAP* pathogenic variant were reported to be asymptomatic during the period of observation.[11 31 65 93 94] Our study suggests that the penetrance of *GFAP* variants is incomplete, that there is under recognition or misdiagnosis of milder phenotypes of late-onset Alexander disease, or both. In previous work using UK Biobank data, we have shown that the carrier frequency of disease causing mutations in *CSF1R*, which lead to adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), is also substantially higher than previous estimates.[95] In that study, *CSF1R* variants were associated with significantly increased rates of neuropsychiatric, cognitive and movement disorders, which are common manifestations of ALSP.

Interestingly, recent data from multiple groups working across different genetic disorders have found similar results. A recent study found that the carrier frequency of pathogenic repeat expansions in multiple genes, including *c9orf72* and *HTT*, was approximately 10-fold higher than expected in the general population.[18] Similar work on disease prevalence of Fabry disease and cardiac transthyretin amyloidosis in UK Biobank have also found similar results.[96 97] Taken together, these results all suggest that the penetrance of late-onset autosomal dominant diseases may be lower than previously thought, or that the phenotypic expression of these disorders may include very mild phenotypes that go unrecognised.

Interestingly, we found that individuals carrying P/LP *GFAP* variants are significantly more likely to have an ICD10 diagnoses of bladder dysfunction, upper airway respiratory symptoms and psychiatric disease, which are common symptoms in adult-onset Alexander disease. We also found they were significantly more likely to have a family (specifically paternal) history of dementia. As these symptoms (among others not seen here) are very common in Alexander disease and given high rates of misdiagnosis especially in early phases of the disease, this may suggest that individuals in the *GFAP* variant cohort were in an early symptomatic or prodromal stage of the disease. Phenotypic representation of Alexander disease may also be underestimated here. In a cohort study of 85 adult patients with Alexander disease, symptom onset occurred after age 65 years in 11% of cases—meaning they may have aged of UK Biobank inclusion criteria prior to presentation.[90]

From a limited sample, we found evidence that P/LP *GFAP* variants were associated with significant atrophy of the brainstem (total volume) and pons, with reduced (but not significantly so) midbrain and medulla volume also. These may again represent phenotypic presentations of later-onset or type II Alexander disease, which not only typically shows marked atrophy of the infratentorial structures on brain MRI, most notably involving the medulla, but also involving the remainder of the brainstem, cerebellum and cervical spinal cord.[9] We show the MRIs of two subjects in particular in figure 5. These subjects have P/LP *GFAP* variants and imaging appearances in keeping with Alexander disease. We found no significant difference in medullary volumes—the area typically affected most in Alexander disease—between the two groups, nor any difference in Medulla: Midbrain ratio or Medulla: Pons ratio, which have previously been reported as sensitive for the disease.[98] This may be due to the use of FreeSurfer segmentation—which while accurate to larger region atrophy (eg, the brainstem as a whole), has limitations in accurately subsegmenting brainstem structures.[99–101]

The limitations of our study include the use of exome data (which precludes detection of variants that are outside of GFAP exons as well as potentially disease causing structural variants), the extent of phenotypic data accessible in the UK Biobank and the relatively small number of individuals with P/LP vairants. Diagnostic data (including self-reported and ICD-10 coded) may be too crude to detect subtle signs or symptoms of Alexander disease, misclassified or under-represented. Moreover, MRI was only available in a small subset of participants and presented without longitudinal follow-up. Furthermore, most subjects are of white British ancestry, which may restrict applicability of the findings to other population groups.

In conclusion, our research shows that P/LP *GFAP* variants are more common than expected in the general population, and that these variants are associated with clinical and radiological signs of Alexander disease. Although there are currently no approved treatments for the disease, a phase 1–3 trial of Zilganersen (ION373), an antisense oligonucleotide targeting GFAP mRNA, is currently underway (ClinicalTrials.gov ID NCT04849741). Early consideration and recognition of Alexander disease, with referral to appropriate specialist support, is therefore increasingly important.

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