

Barriers to disclosure of diagnoses and diagnostic testing in families affected by X-linked adrenoleukodystrophy

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Abstract

Background

X-linked adrenoleukodystrophy (X-ALD) is a rare hereditary white matter disorder with diverse manifestations, including adrenal insufficiency, myeloneuropathy, and life-threatening cerebral disease. Although treatments can halt severe progression, they require early diagnosis and monitoring. In settings without newborn screening, open communication about diagnosis and carrier risk within families is crucial. This cross-sectional study assessed potentially affected family members (PAFMs) in X-ALD-positive families who were neither informed nor tested and identified barriers to disclosure and family communication.

Methods

The prevalence of uninformed or untested PAFMs was calculated from pedigree charts of 51 adults with X-ALD (30 women [58.8%], mean age = 51.4 ± 12.9 years, range: 30–74). Semi-structured interviews assessed disease understanding and motivations for informing or not informing relatives. Pearson correlations examined relationships between uninformed/untested PAFMs and participant characteristics. Independent *t*-tests and χ^2 tests compared factors between informed and uninformed PAFMs.

Results

Of 639 PAFMs, 40.5% (259) had not been tested for X-ALD. One third of participants (17/51; 33.3%) reported at least one uninformed PAFM. In 80.4% of family trees (41/51), at least one PAFM was informed but untested. Decisions to inform were influenced by knowledge of inheritance, degree of relation, emotional closeness, contact frequency, symptom presence, and (grand-)parental status.

Conclusions

Significant deficiencies exist in family communication and the testing cascade for X-ALD. Healthcare providers can support patients by improving disease understanding and facilitating information sharing with PAFMs, promoting earlier diagnosis and treatment where newborn screening is unavailable.

Plain language summary

X-linked adrenoleukodystrophy (X-ALD) is a rare genetic disorder affecting the brain, nerves, and adrenal glands. Treatments can prevent severe disease progression but require early detection and monitoring. Where newborn screening is absent, open family communication about diagnosis and carrier risk is essential for early genetic testing. In 51 adults with X-ALD in this study, 40.5% of 639 at-risk relatives had

never been tested; one in three participants reported at least one uninformed relative, and in over 80% of families at least one relative was informed but untested. Decisions to inform depended on understanding of inheritance, relationship closeness, emotional ties, contact frequency, presence of symptoms, and parental or grandparental status. These gaps in communication and testing highlight a key challenge for rare X-linked diseases and support the need for clinical strategies to empower patients to disclose diagnoses to at-risk family members in areas where newborn screening is not available for this disease.

Introduction

X-linked adrenoleukodystrophy (X-ALD) is a rare hereditary metabolic disease (birth incidence $\approx$ 1:15,000) that causes progressive demyelination of the central and peripheral nervous system [1, 2]. The genetic defect, located in the *ABCD1* gene, manifests as a spectrum of phenotypes ranging from asymptomatic forms and Addison's disease-only variants to adrenomyeloneuropathy (AMN), a slowly progressive spastic paraparesis and polyneuropathy with adult onset, affecting all men starting from the age of 20 to 30 and 60–80% of women over 40 years of age, and cerebral X-ALD (CALD), a rapidly progressive, fatal degeneration of cerebral white matter that affects approximately 35% of males in childhood (CCALD) and 25% in adulthood (ACALD) [2]. In CALD, inflammatory destruction of cerebral white matter leads to profound cognitive and neurological decline, typically progressing to a vegetative state and death within a few years of symptom onset [3]. Curative treatments for CALD are available with growing experience in hematopoietic stem cell transplantation (HSCT) in boys and men [3–6], and ex vivo gene therapy for boys [7]. In addition, new pharmacological agents such as the oral PPAR- γ agonist leriglitazone are currently undergoing clinical testing and have shown a slowing of cerebral disease progression in phase 3 trials in children [8] and compassionate-use data in adults [9, 10]. However, treatments for CALD are effective only in the presymptomatic and early clinical phase. Beyond the risk of CALD, up to 80% of affected males develop adrenal insufficiency, often beginning in early childhood, which requires lifelong glucocorticoid replacement therapy [11, 12]. In contrast, females with X-ALD rarely develop CALD or adrenal insufficiency and may remain asymptomatic lifelong [2].

Although various X-ALD phenotypes have been described, there is considerable variability within these phenotypes regarding the onset, course, and severity of symptoms. Furthermore, due to the rarity of the disease and the limited available data, no correlation between genotype and phenotype has yet been described, making it impossible to predict the course of the disease for an individual at the time of diagnosis [2, 13, 14]. Recent research points to a biochemical–phenotype correlation by showing that circulating C26:0-lysophosphatidylcholine and related very long chain fatty acids (VLCFA)-containing lipids correlate with disease manifestation and *ABCD1* variant pathogenicity [15, 16]. However, prediction of cerebral conversion or individual disease trajectory on this basis remains unreliable [16]. This prognostic uncertainty challenges patients and clinicians and underscores the need for early diagnosis to enable close monitoring and timely detection of treatable Addison's disease and CALD in males [17–19]. Due to X-linked inheritance, affected women transmit the mutation to 50% of offspring regardless of

sex, whereas affected men transmit it to all daughters but not to sons [2, 20]. Particularly for females affected from X-ALD, carrier-status knowledge supports informed family planning [21].

In countries without X-ALD newborn screening (NBS), such as Germany, it is usually the first person diagnosed – the index patient – who is asked to share information about X-ALD with potentially affected family members (PAFMs). If the index patient refuses disclosure, clinicians cannot share this information with PAFMs due to legal confidentiality obligations [22, 23]. Recent findings from other hereditary conditions suggest that low emotional closeness and bonding, as well as infrequent contact between the index patient and the PAFMs act as barriers to the disclosure of diagnoses and the sharing of information about hereditary diseases within the family [24]. In addition, patients may fear distressing their relatives and triggering family conflicts, guilt, or blame over passing on the genetic condition [25–27]. On the other hand, when the risk is known and families are adequately informed, parents largely favor genetic testing for potentially affected children. Schaller et al. [18], surveying families affected by X-ALD, found that approximately 90% of parents supported genetic testing for at-risk sons and daughters, with a clear preference for testing prenatally or shortly after birth.

To date, no studies have examined the extent to which PAFMs in X-ALD-positive families remain uninformed about their own carrier risk, nor the proportion who, despite being aware of this risk, do not undergo genetic testing. Moreover, the reasons underlying these decisions remain unclear. This cross-sectional study aimed to 1) estimate the prevalence of not informed and not tested PAFMs in X-ALD-positive families, and 2) to identify potential barriers to patients' disclosure of diagnoses and intrafamilial communication and information sharing regarding X-ALD. The findings are clinically relevant in identifying ways to improve genetic counseling for patients and guide strategies to overcome family communication barriers, thereby facilitating early diagnosis and treatment of X-ALD and minimize preventable morbidity and mortality from X-ALD in countries without NBS programs.

Materials and Methods

Study population

Recruitment took place at the Leukodystrophy Outpatient Clinic at Leipzig University Hospital, Germany between January and October 2024. Information about the study was additionally shared via social media and the patient organization European Leukodystrophy Association (ELA) Germany. Inclusion criteria included genetically and/or biochemically confirmed X-ALD, an age of at least 18 years, and sufficient German language skills to communicate with the study team. The study was approved by the Ethics Committee of the Medical Faculty, Leipzig University (365/23-ek) and written informed consent was obtained prior to participation in the study. All participants were assured that their data as well as the data of family members collected by third-party anamnesis, would be pseudonymized. In accordance with the duty of confidentiality, the study team did not contact any of the participants' family members.

Procedure

All participants took part in a one-time survey, either on site ($n=6$) or online ($n=45$) using the open-source video conferencing system BigBlueButton™ [28]. Depending on the complexity of the family, the assessment took between 120 and 180 minutes. It included the systematic creation of a pedigree chart and a semi-structured interview about knowledge of X-ALD, and awareness of and communication about the disease within the family, from the participant's perspective. The interviews were recorded and reviewed on a random sample basis by a second rater to ensure standardized administration and inter-rater reliability. Prior to audio recording, participants provided consent to be recorded. Declining to be recorded did not exclude individuals from participating in the study.

Pedigree chart

The family pedigree was systematically created together with the participant using the open-source program CeGaT Pedigree Chart Designer [29]. In the case of online participation via video call, the examiners shared their screen to allow the participant to see the family chart created, enabling errors to be identified and corrected immediately. By default, family members from two generations before and after the participant surveyed were recorded. For each family member in the pedigree who was potentially affected by X-ALD due to inheritance, parameters relating to demographics, diagnosis, symptoms, and phenotype were recorded. Participants were also asked to provide their genetic test results, if available, to determine the genotype prevalent in their family, as well as their Adult ALD Clinical Scale (AACS, [30]) score and their Expanded Disability Status Scale (EDSS, [31]) score from their most recent neurological examination, in order to evaluate their current symptom burden.

The proportion of PAFMs within each pedigree who were not informed about X-ALD ($\%PAFM_{\text{not informed}}$), and the proportion who were informed but did not undergo X-ALD genetic testing ($\%PAFM_{\text{not tested}}$), were calculated using the total number of PAFMs in the pedigree and the number of informed PAFMs, respectively. These proportions were then expressed as percentages.

Semi-structured interview

The first part of the semi-structured interview involved assessing the participant's knowledge of the disease using a scoring system for the following subscales: *inheritance* (two items, score range: 0-3), *clinical phenotypes* (eight items, score range: 0-12), *diagnosis* (two items, score range: 0-3), and *treatment options and family planning* (five items, score range: 0-8). Items considered to be essential knowledge about the disease were scored with two points, while those considered less essential were scored with one point. A total score of between 0 and 26 points could be achieved, with higher scores indicating greater knowledge of the disease. Furthermore, all participants were asked to rate their

knowledge of the disease subjectively on a scale from 1 (*no knowledge at all*) to 10 (*very good knowledge*).

In the second part of the interview, participants were asked about their possible reasons for informing or not informing PAFMs as well as rating their emotional closeness to the respective family member on a scale from 1 (*not at all close*) to 10 (*extremely close*), providing the geographical proximity (in km), and describing the type and frequency of their contact with the family member.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics (version 29.0). All tests were conducted two-tailed with a significance level of $\alpha=0.05$. Pearson correlation analyses were performed to determine associations between the %PAFM_{not informed} or %PAFM_{not tested} within a pedigree and the participant characteristics (age, time since diagnosis, AACS score, disease knowledge total and sub scores).

Across all recorded pedigrees, differences between the groups of informed and uninformed PAFMs were compared with respect to sociodemographic and relationship characteristics, using independent *t*-tests for continuous variables and χ^2 tests for categorical variables. In terms of violation of normality and homogeneity of variances, non-parametric tests were used and reported if results differed from parametric tests. Effect sizes were estimated for all analyses and interpreted according to Cohen [32].

Results

Sample Description

A total of *N*=51 German-speaking adults with X-ALD (30 women [58.8%], 21 men [41.2%]; mean age=51.4±12.9 years [range: 30-74]; mean years since own diagnosis=18.7±10.4, [range: 1-44]) from 47 different families were included in our study. A detailed description of the characteristics of each participant and the family members included in the pedigree, along with information on genotype and phenotype frequencies, can be found in Table S1 in the supplementary information. Most participants reported clinical symptoms of myeloneuropathy or AMN (women: 24/30, men: 13/21), while six women were asymptomatic, one man had Addison's disease only and seven men showed ACALD (acute: *n*=1; spontaneously arrested: *n*=1, arrested after HSCT in adulthood: *n*=5) with additional AMN symptoms. The degree of relationship of the participants to the index patient is shown in Table 1. Of all family members who had tested positive for X-ALD (*n*=320), the most prevalent phenotypes were AMN in males (*n*=70; 21.9%) and myeloneuropathy in female adults (*n*=75; 23.5%), followed by an asymptomatic course in females (*n*=70; 21.9%), cerebral ALD in boys (*n*=50, 15.6%) and men (*n*=23; 7.2%), and an asymptomatic disease in girls (*n*=14; 4.4%), men (*n*=5, 1.7%) and boys (*n*=4; 1.3%). The symptom status of eight family members (2.5%) was reported as unknown.

Table 1. Participant's relationship to the index patient.

The index patient is the	Participant	Son	Daughter	Father	Sibling	Uncle/Aunt	Distant relative
Man (<i>n</i>)	10	n/a	0	n/a	5	1	5
Women (<i>n</i>)	1	15	1	5	4	1	3

Notes. n/a=not applicable.

Across all pedigree charts, a total of 40.5% (259/639) of PAFMs had not yet been tested for X-ALD. The majority of these individuals were women ($n=132$; 51.0%), followed by men ($n=77$; 29.7%), girls ($n=35$; 13.5%), and boys ($n=15$; 5.8%). One-third of participants (17/51; 33.3%) stated that at least one PAFM in their pedigree chart had not yet been informed about the family risk for X-ALD. There was no significant difference in the percentage of PAFMs who had not been informed between participants who were index person and those who were not ($M_{\text{index}}=22.9\pm33.3$ vs. $M_{\text{non-index}}=10.5\pm19.9$; $t[1, 12.0]=1.18$, $p=.259$, $d=0.54$). In 80.4% of participants' pedigree charts (41/51), there was at least one PAFM who had been informed but not tested for X-ALD.

Associations with participants' characteristics

The Pearson correlations between the percentage of not informed or not tested PAFMs within a pedigree and the participants' characteristics are shown in Figure 1. The percentage of not informed PAFMs was negatively correlated with the participants' knowledge of X-ALD inheritance ($r=-.32$, $p=.021$). Negative correlations were also found between the time period since the participants' diagnosis (in years) and both the percentage of not tested PAFMs within a pedigree ($r=-.27$, $p=.054$) and the participants' knowledge of diagnostic testing for X-ALD ($r=-.25$, $p=.082$). However, these results were below the threshold of statistical significance. Accordingly, the participants' AACs score was negatively linked to knowledge of X-ALD inheritance ($r=-.32$, $p=.041$), and, as expected, positively associated with their age ($r=.40$, $p=.009$). Furthermore, strong positive correlations were found between the total score achieved in the knowledge test on X-ALD and its individual subscales ($rs=.39-.92$, $ps\leq.005$), except for the inheritance subscale ($r=.20$, $p=.168$). Participants' knowledge of different X-ALD phenotypes was positively associated with their knowledge of specific treatment options and family planning ($r=.68$, $p\leq.001$). Additionally, the subjective assessment of the participants' disease knowledge was positively correlated with the total score in the knowledge test and its individual subscales ($rs=.30-.58$, $ps\leq.005$), except for knowledge about the diagnostic testing for X-ALD ($r=.23$, $p=.113$). Participants' phenotype had no significant effect on the mean percentage of not informed ($M_{\text{asymptomatic}}=21.5\pm28.7$ vs.

$M_{\text{myeloneuropathy/AMN}}=9.6\pm19.0$ vs. $M_{\text{CALD}}=25.1\pm37.8$; $F[2, 8.10]=0.91$, $p=.441$, $\eta^2=0.07$) or not tested PAFMs ($M_{\text{asymptomatic}}=23.1\pm18.2$ vs. $M_{\text{myeloneuropathy/AMN}}=30.9\pm29.7$ vs. $M_{\text{CALD}}=34.1\pm33.4$; $F[2, 10.75]=0.44$, $p=.655$, $\eta^2=0.01$) within a pedigree chart as well as on the mean total score achieved in the knowledge test on the disease ($M_{\text{asymptomatic}}=19.0\pm3.0$ vs. $M_{\text{myeloneuropathy/AMN}}=19.4\pm5.1$ vs. $M_{\text{CALD}}=20.7\pm3.8$; $F[2, 11.73]=0.43$, $p=.663$, $\eta^2=0.01$).

Comparison of informed versus not informed PAFMs

Results of the comparison of informed versus uninformed PAFMs with regard to sociodemographic data and characteristics of the relationship to the participant are summarized in Table 2. Significant, large differences were found between the groups in terms of kinship, emotional closeness, the type and frequency of contact between the participant and the PAFM, and the symptomatic and (grand)parental status of the PAFM ($p < .001-.003$). Specifically, participants had closer biological and emotional relationships with informed PAFMs than with those who are not informed, and these relationships were characterized by more frequent and more personal contact. In addition, participants were more likely to be aware of the symptomatic status of informed PAFMs than of those who were not informed. In contrast, not informed PAFMs were more frequently reported as parents or grandparents of children at risk of X-ALD than informed PAFMs. Participants were also more likely to be unaware of whether not informed PAFMs had children or grandchildren ($p = .003$). Not informed PAFMs tended to be older than informed PAFMs ($p = .070$), and participants were more likely to live closer to informed PAFMs than to not informed PAFMs ($p = .182$); however, these results were not statistically significant. No group differences were found with regard to sex ($p = .765$).

Table 2. Comparison of informed versus not informed PAFMs across all pedigree charts examined.

	Informed PAFMs (<i>n</i> =56)	Not informed PAFMs (<i>n</i> =28)				
	<i>M (SD)</i>	<i>M (SD)</i>	<i>t</i>	<i>df</i>	<i>p</i>	<i>d</i>
Age (years)	60.1 (20.7)	66.9 (13.4)	-1.84	1, 76.36	.070	-0.37
Emotional closeness (1-10)	6.6 (2.5)	2.5 (2.1)	7.41	1, 82	<.001	1.72
Geographical proximity (km)	142.1 (324.9)	483.7 (1277.7)	-1.37	1, 27.69	.182	-0.44
	<i>n (%)</i>	<i>n (%)</i>	χ^2	<i>df</i>	<i>p</i>	<i>V</i>
Sex						
female	41 (71.9)	21 (75.0)	0.09	1, 85	.765	0.03
male	16 (28.1)	7 (25.0)				
Symptom status						
symptomatic	12 (21.1)	3 (10.7)	31.25	2, 85	<.001	0.61
asymptomatic	45 (78.9)	12 (42.9)				
unknown	0 (0.0)	13 (46.4)				
Children/grandchildren at risk						
yes	30 (52.6)	20 (71.4)	11.36	2, 85	.003	0.37
no	26 (45.6)	4 (14.3)				
unknown	1 (1.8)	4 (14.3)				
Degree of kinship						
child	8 (14.0)	0 (0.0)	46.32	7, 85	<.001	0.74
parent	17 (29.8)	0 (0.0)				
sibling	19 (33.3)	0 (0.0)				
uncle/ant	3 (5.3)	6 (21.4)				
cousin	7 (12.3)	11 (39.2)				
nephew/niece	0 (0.0)	1 (3.6)				
grandparent	1 (1.8)	2 (7.2)				

distant relative	2 (3.5)	8 (28.6)				
Contact frequency						
daily	12 (21.4)	1 (3.8)	34.05	5, 82	<.001	0.64
weekly	22 (39.3)	1 (3.8)				
monthly	10 (17.8)	5 (19.3)				
yearly	9 (16.1)	4 (15.4)				
every few years	2 (3.6)	6 (23.1)				
no contact	1 (1.8)	9 (34.6)				
Type of contact						
in person	23 (41.1)	14 (53.9)	25.55	3, 82	<.001	0.56
by phone	29 (51.7)	2 (7.7)				
by messenger/SMS	3 (5.4)	1 (3.8)				
No contact	1 (1.8)	9 (34.6)				

Notes. Significant *p* values are printed in bold. Effect sizes *Cohen's d* and *Cramer's V* were interpreted according to Cohen (small effect: $0.20 \leq d < 0.50$, medium: $0.50 \leq d < 0.80$, large: $d \geq 0.80$; small effect: $0.10 \leq V < 0.30$, medium: $0.30 \leq V < 0.50$, large: $V \geq 0.50$ [32]). PAFMs=Potentially affected family members.

Reasons given for disclosure and non-disclosure

When asked about the main reason for informing PAFMs about the disease, 30 participants (53.6%) reported that they wanted to ensure that the family member could receive a diagnosis and proper treatment in the event of symptoms. Six participants (10.7%) indicated that disclosure was motivated by upcoming family planning, and five participants (8.9%) reported informing the PAFM to facilitate testing of their offspring. In contrast, five participants (8.9%) stated that they had communicated the information solely based on a recommendation from a geneticist or neurologist, without a clear understanding of its purpose. Additionally, 10 participants (17.9%) reported disclosing the disease primarily for their own emotional relief, unaware of the relevance of testing for the PAFMs.

Regarding reasons for non-disclosure, 18 participants (64.3%) assumed that another family member had already communicated information about X-ALD and the associated risk to the PAFM. However, 14 of these participants were uncertain whether such communication had actually occurred. Six participants (21.5%) reported that they already had no contact with the PAFM prior to their diagnosis, precluding information sharing. Two participants (7.1%) indicated that their own disease burden prevented them from informing the PAFM, while another two participants (7.1%) reported perceiving no need for

disclosure due to a presumed low risk, based on the PAFM's age, absence of symptoms, and lack of offspring.

Discussion

This study demonstrates that a substantial portion of PAFMs in X-ALD-positive families are either unaware of their genetic risk or choose not to undergo genetic testing, even when informed. This highlights critical gaps in intrafamilial communication and cascade testing. Notably, over 40% of PAFMs had not been tested and one third of participants reported at least one PAFM who was not informed, underscoring missed opportunities for early diagnosis in a condition where the effective treatment in preventing severe disabilities and premature death in males depends on early detection [2–7]. Our results reveal informational and relational factors to be key determinants of disclosure, consistent with previous findings in genetic conditions [24, 33]. Notably, a lack of – or even incorrect – knowledge about the inheritance of X-ALD was associated with a higher prevalence of PAFMs who were not informed within the participants' families. Some participants in our survey mistakenly believed that X-ALD is transmitted “only by women” due to its X-linked inheritance pattern, overlooking the fact that affected men pass the pathogenic variant to all of their daughters. This misconception may help to explain why female carriers often remain unidentified, particularly since they are frequently asymptomatic or only mildly affected during their reproductive years [34–36]. The present study further reflects incomplete testing across subsequent generations in a high proportion of untested at-risk women (51.0%) identified in our pedigrees. These findings suggest that improved education led by clinicians is essential to help diagnosed patients understand which family members should undergo genetic testing. This is particularly important when the primary concern is not their own health but the silent transmission of the variant to future generations, especially through asymptomatic women to their sons, who are at high risk of developing CALD.

Our correlation analyses suggest that a longer period of time since participants' diagnosis is associated with higher uptake of genetic testing among informed PAFMs. However, this was not associated with better overall disease knowledge in participants; instead, it showed a trend towards poorer knowledge of X-ALD diagnostics. Similarly, the participants' disease burden, as measured by the AACCS score, increased with age, but was negatively correlated with participants' knowledge of X-ALD inheritance. These findings have important clinical implications. They suggest that family pedigrees should be reassessed and that patients should receive up-to-date information on the disease at every follow-up visit [37, 38], even in families with a long-standing history of X-ALD. Clinicians should not assume that younger at-risk relatives, such as grandchildren, have already undergone testing, since family members may misjudge their own risk. In line with this concern, 5.8% of at-risk boys in the pedigrees surveyed had not yet been tested for X-ALD.

Consistent with findings from other inherited conditions [24, 27, 39, 40], we observed that closer degrees of kinship, stronger emotional closeness and bonding, more frequent and more personal contact, and knowledge of the PAFM's symptom status and (grand-) parental status facilitated the disclosure of

carrier risk by diagnosed family members. It is noteworthy that 10.7% (3/28) of the not informed PAFMs exhibited X-ALD-typical symptoms, and 71.4% (20/28) had children and/or grandchildren. However, for one-third (34.6%) of the not informed PAFMs (9/28), contact had generally already been lost before the index patient's diagnosis, which precluded any warning or information regarding their own risk of being a carrier. Regarding the reasons for disclosure, a substantial proportion of respondents reported doing so primarily to enable cascade testing, timely treatment, family planning, and risk assessment in offspring. However, disclosure was not always driven by a clear understanding of its purpose: 8.9% of participants acted on a health professional's recommendation without fully grasping the rationale for familial screening, whereas 17.9% disclosed information mainly for personal emotional relief. Among non-disclosers, most participants assumed that another family member had already provided the PAFMs with information about X-ALD and the associated risk, yet three-quarters of them were uncertain whether this information had actually reached the at-risk individual. Additional barriers included lack of contact information, limited capacity due to disease burden, and perceived low risk in the relative. These findings highlight gaps in understanding the purpose of cascade screening and to structural barriers in family communication. They also emphasize the need for repeated, comprehensible genetic counselling and proactive support to reach more distant or less connected relatives [41, 42]. Low-threshold strategies, such as standardized lay-language leaflets that summarize key facts about X-ALD, its implications for relatives, and contact details for genetic counselling services and leukodystrophy centers, may help to reduce communication barriers. Providing such information through the index patient via post, for example, may also facilitate outreach to relatives with limited contact and reduce information loss within families. Finally, the substantial proportion of disrupted or absent contact with PAFMs, even prior to diagnosis, emphasizes the limitations of family-mediated cascade screening. Against this background, our findings support the international expansion of NBS for X-ALD. NBS have already been implemented in most US states as well as in Taiwan, the Netherlands, and Australia, and pilot programs are underway in additional states [43]. Experience in these countries to date shows that NBS enables the early identification of individuals with X-ALD at the presymptomatic stage, thereby facilitating the timely diagnosis and treatment of severe disease manifestations [12, 43]. Future studies should address the remaining challenges of NBS for X-ALD, including managing variants of uncertain significance, screening females, and related ethical considerations.

The strengths of this study include the relatively large sample size for a rare disease and the systematic, multimodal assessment of X-ALD-positive families and patient perspectives, which was conducted using both pedigree charts and semi-structured interviews. However, several limitations should be considered when interpreting our findings. First, pedigree data and information on PAFMs may be affected by recall bias because they are based on participant reports, particularly when participants have not been in contact with the respective family member for an extended period. In such cases, index patients' knowledge may be outdated, especially if contact was lost some time ago. Consequently, information on symptoms, genetic testing, and family structure may be incomplete or inaccurate, and relevant family members may have been omitted. Additionally, some participants in the survey were not the first in their family to be diagnosed with X-ALD, and the proportion of index patients was relatively

low (21.6%, or 11 out of 51). Consequently, the reasons for not disclosing the condition and informing other PAFMs reported by our sample may differ from those reported in surveys that include only index patients. Finally, the uneven gender distribution of the participants in our sample - due to gender-specific genetic factors and phenotypes in X-ALD - may have influenced the reasons cited for withholding or sharing diagnoses and information with PAFMs.

Conclusions

In the absence of NBS programs for X-ALD in most parts of the world, it remains essential to empower index patients and affected individuals to communicate genetic risk effectively within their families. This study revealed that a significant proportion of at-risk family members in X-ALD-positive families who had either not been informed or had been informed but remained untested. The findings have three immediate clinical implications for strategies aimed at improving the disclosure of diagnoses and facilitating diagnostic testing within X-ALD families. First, there should be repeated reassessment of family pedigrees and ongoing education during routine follow-up visits, including for patients with a longstanding history of X-ALD. Second, close collaboration is needed with patient advocacy groups such as ALD Connect [44], the United Leukodystrophy Foundation [45] and ELA International [46]) to disseminate current evidence. Third, the use of standardized information leaflets is recommended that include contact details for specialized leukodystrophy centers and which can be given by index patients to distant relatives with limited contact or emotional closeness. Finally, our findings reveal specific structural barriers, such as missing contact information, that prevent family members from being warned promptly about X-ALD risk. This again underscores the clinical imperative to include X-ALD in NBS programs worldwide.

Declarations

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Ethics declarations

This study was approved by the Ethical Committee at the Medical Faculty, Leipzig University, Germany on November 21, 2023 (365/23-ek). Participants' written informed consent for voluntary participation was obtained prior to enrollment. All participants were informed that their data, as well as family data obtained through third-party medical history, would be analyzed and published in pseudonymized form.

Competing interests

WK received funding for ALD-related research from the Federal Ministry of Health of Germany and the Saxonian State Ministry of Science, Research and Arts; has been principal investigator of clinical trials for Bluebird Bio, Swan Bio Vigil, Viking, Minoryx; received consulting fees from Minoryx, Neuraxpharm, all are unrelated to the present manuscript, and has been an unpaid advisor for the European Leukodystrophy Association, Myelin Project Germany, and the United Leukodystrophy Foundation. CCB has been principal investigator of clinical trials for Minoryx and received funding from Vigil Neuroscience, all unrelated to the present research. LS, LD, JL, and MP report no disclosures relevant to the manuscript.

Authors' contribution

LS, LD, and CCB made significant contributions to the study's design and methodology. LS, LD, JL, MP, WK, and CCB were involved in data acquisition. LS performed the data analysis, interpretation and drafted the manuscript. All authors critically reviewed and revised the manuscript and approved the final version.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

	%PAFM_not informed	%PAFM_not tested	age of respondent	time since diagnosis of respondent	AACS of respondent	Disease knowledge - total score	Disease knowledge - inheritance	Disease knowledge - clinical phenotypes	Disease knowledge - diagnosis	Disease knowledge - treatment options and family planing	Disease knowledge - subjective assessment
%PAFM_not informed	1										
%PAFM_not tested	0,046	1									
age of respondent	0,054	0,053	1								
time since diagnosis of respondent	-0,109	-0,271	0,180	1							
AACS of respondent	0,135	0,014	0,396	0,088	1						
Disease knowledge - total score	-0,038	-0,163	-0,072	-0,063	-0,051	1					
Disease knowledge - inheritance	-0,322	-0,135	-0,145	0,054	-0,317	0,196	1				
Disease knowledge - clinical phenotypes	0,042	-0,077	-0,103	-0,023	0,002	0,923	0,047	1			
Disease knowledge - diagnosis	0,216	-0,061	0,101	-0,246	-0,068	0,388	0,018	0,312	1		
Disease knowledge - treatment options and family planing	-0,163	-0,207	-0,051	-0,021	-0,040	0,867	0,152	0,682	0,074	1	
Disease knowledge - subjective assessment	0,008	-0,012	0,002	0,072	0,100	0,58	0,303	0,458	0,225	0,534	1

Figure 1

Matrix of correlations between the percentage of not informed or not tested PAFMs within a pedigree and the participants' characteristics and disease knowledge.

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