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Adult-onset cerebello-brainstem dominant form of X-linked adrenoleukodystrophy presenting as multiple system atrophy: Case report and literature review

Kotaro Ogaki, MD, Ph.D.[1], **Shunsuke Koga, M.D., Ph.D.**[1], **Naoya Aoki, M.D.**[1], **Wenlang Lin, Ph.D.**[1], **Kinuko Suzuki, M.D.**[2], **Owen A. Ross, Ph.D.**[1], and **Dennis W. Dickson, M.D.**[1]

[1]Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA

[2]Department of Neuropathology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan, and Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, NC USA

Abstract

X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disorder and is caused by *ABCD1* mutations. A cerebello-brainstem dominant form that mainly involves the cerebellum and brainstem is summarized in a review of the literature, with autopsy confirmed cases exceedingly rare. We report a 69-year-old white man who was diagnosed with this rare disorder and describe neuropathologic, ultrastructural and genetic analyses. He did not have adrenal insufficiency or a family history of X-ALD or Addison's disease. His initial symptom was temporary loss of eyesight at age 34 years. His major symptoms were chronic and progressive gait disorder, weakness in his lower extremities, and spasticity, as well as autonomic failure and cerebellar ataxia suggesting possible multiple system atrophy (MSA). He also had seizures, hearing loss, and sensory disturbances. His brain MRI showed no obvious atrophy or significant white matter pathology in cerebrum, brainstem or cerebellum. He died at age 69 years with a diagnosis of multiple system atrophy. Microscopic analysis showed mild, patchy myelin rarefaction with perivascular clusters of PAS-positive, CD68-positive macrophages in the white matter most prominent in the cerebellum and occipital lobe, but also affecting optic tract and internal capsule. Electron microscopy of cerebellar white matter showed cleft-like trilamellar cytoplasmic inclusions in macrophages typical of X-ALD, which prompted genetic analysis that revealed a novel *ABCD1* mutation, p.R163G. Given the relatively mild pathological findings and long disease duration, it is likely that the observed pathology was the result of a slow and indolent disease process. We described a patient who had sporadic cerebello-brainstem dominant form of X-ALD with long clinical course, mild pathological findings, and an *ABCD1* p.R163G substitution. We also review a total of 34 cases of adult-onset cerebello-brainstem dominant form of X-ALD. Although rare, X-ALD should be considered in the differential diagnosis of MSA.

Address correspondence and reprint requests to: Dennis W. Dickson, MD, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, dickson.dennis@mayo.edu, Phone: 904-953-7137, Fax: 904-953-7117.

Keywords

adrenoleukodystrophy; cerebello-brainstem dominant form; multiple system atrophy; olivopontocerebellar atrophy; *ABCD1*

INTRODUCTION

X-linked adrenoleukodystrophy (X-ALD; OMIM #300100) is the most common peroxisomal disorder and is caused by *ATP-binding cassette, sub-family D (ALD), member 1* gene (*ABCD1*; OMIM #300371). Peroxisomal dysfunction elevates plasma and tissue levels of very long-chain fatty acids (VLCFA), which affects various tissues, including the adrenal cortex, testes, and the nervous system.[1] The disease phenotype ranges from the severe childhood cerebral form to a mild adrenomyeloneuropathy (AMN) form.

The most common phenotype is AMN (40–46%), where disease onset typically occurs during the second and third decades of life.[2] The clinical presentation includes a progressive, spastic gait, erectile dysfunction, abnormal sphincter control, and sensory disturbances due to the involvement of peripheral nerves.[1, 3–5] The main lesions occur in the spinal cord and peripheral nerve.[6] The second most frequent phenotype is a cerebral form (31–35%), which presents in childhood with visual disturbances, hearing loss, mental retardation, spastic gait, and seizures.[2, 7] Onset of symptoms in boys is usually around 10 years of age, and the vast majority have a poor prognosis.[1] Typically, the most severe lesions are found in the white matter of the cerebrum, especially the occipital white matter, but the cerebellum and brainstem are largely spared.[2, 8] A rare phenotype of X-ALD, the “cerebello-brainstem dominant form,”[9] in which the cerebellum and brainstem are mainly involved, has been estimated to account for 1–2% of ALD.[2] Neuropathological reports of this rare form are exceedingly rare. This phenotype was firstly reported as “adrenoleukomyeloneuropathy presenting as spinocerebellar degeneration” by Marsden et al. in 1982,[10] and it has been referred to by other names, such as “olivo-ponto-cerebellar form,”[2] “cerebellar involvement, ”[8] “ataxic variant,”[11] or “spinocerebellar variant,”[12] In this study we refer to this form as “cerebello-brainstem dominant form” because this term is all-inclusive.

We report a patient with adult-onset cerebello-brainstem dominant form of X-ALD with long disease duration, mild pathological findings, and a novel *ABCD1* mutation. We review the literature of 34 patients with adult-onset cerebello-brainstem dominant form of X-ALD.

CLINICAL SUMMARY

The patient was a 69-year-old white man who had chronic neurological complaints. His family history was negative for neurologic disease. He had no children or living first degree relatives. At age 34 years, he had temporary loss of vision that lasted about three weeks, which was thought to be caused by optic neuritis due to multiple sclerosis (MS). When he presented at his initial evaluation at age 36 years, he had an unsteady gait, poor coordination, and foot dragging. He had urinary and bowel urgency with incontinence and sexual impotence. His symptoms were considered to be consistent with MS, and his differential diagnoses were spastic paraparesis and spinocerebellar degeneration. By age 49

years, he required a wheel chair because he could not ambulate. He developed reactive depression. He was treated with amitriptyline. He had excessive drowsiness and a dry mouth. Other problems included restless legs syndrome and obstructive sleep apnea, the latter treated with continuous positive airway pressure. An MRI scan of his brain when he was 56-years-old was unremarkable. His medical history was notable for complex partial seizures, glaucoma, strabismus, sensorineural hearing loss, and hyperlipidemia.

At age 60 years his mental state was normal. His speech and language were clear and coherent, except for mild hypophonia. There was weakness in lower extremity muscles. Reflexes were hyperactive in both upper and lower extremities, and he had bilateral extensor plantar responses. He had cerebellar ataxia on finger-to-nose testing. He was unable to perform heel-to-shin testing, which was possibly due to severe weakness. He had decreased sensation to light touch, vibration, joint position, temperature, and pinprick in his lower extremities. An MRI of his brain showed stable areas of T2 hyperintensity in the white matter of the right centrum semiovale, which was thought to be non-specific because the size of T2 hyperintensities had not changed in 2 years. There was no evidence of a widespread demyelinating process involving the periventricular white matter. The brainstem, cerebellum, and cervical spinal cord were unremarkable. He was diagnosed as having multiple system atrophy (MSA). The patient died at age 69. An autopsy limited to examination of the brain was performed.

METHODS

Neuropathologic methods

Macroscopic and microscopic assessments were performed at the brain bank for neurodegenerative disorders at the Mayo Clinic in Jacksonville, Florida. The brain bank operates under procedures approved by the Mayo Clinic IRB. The autopsy on this patient was performed after informed consent from his caregiver who had legal power-of-attorney for this patient. The left hemi-brain was fixed in formalin and embedded in paraffin; the right was frozen for research studies. The areas sampled for histology were middle frontal gyrus, superior temporal gyrus, inferior parietal gyrus, pre-and post-central gyri, visual cortex, cingulate gyrus, anterior and posterior hippocampus, amygdala, basal nucleus of Meynert, caudate nucleus, putamen, thalamus, midbrain, pons, medulla, cerebellum, and optic nerve. Paraffin-embedded 5-μm thick sections mounted on glass slides were stained with hematoxylin and eosin (H&E) and thioflavin S stains. Select sections were processed for Luxol fast blue (LFB) or periodic acid-Schiff (PAS) stain with and without diastase. Immunohistochemistry was performed using antibodies against α-synuclein (NACP, 1:3000 rabbit polyclonal, Mayo Clinic antibody), TDP-43 (MC2085,[13] 1:2500 rabbit polyclonal, from Leonard Petrucelli, Mayo Clinic), CD68 (M0814, 1:1000 mouse monoclonal, DAKO), and neurofilament (SMI-31, 1:80000 mouse monoclonal, Covance). After immunostaining, the sections were briefly counterstained with hematoxylin.

Electron microscopy

Small pieces of cerebellum were fixed in 2.5% glutaraldehyde-0.1 M cacodylate buffer, post-fixed in 1% aqueous osmium tetroxide, stained in 2% uranyl acetate in 50% ethanol,

dehydrated in ethanol and propylene oxide, infiltrated and embedded in Epon 812. Thin sections were stained with uranyl acetate and lead citrate, and examined with a Philips 208S electron microscope fitted with a Gatan 831 digital camera. Images were processed with Adobe Photoshop CS5 software.

Genetic methods

Genomic DNA and cDNA were extracted from brain tissue using a standard protocol. The entire cDNA of *ABCD1* was sequenced, and the consensus RefSeq accession NM_000033.3 was used to assign all variants within the *ABCD1* gene and protein. Subsequently, genomic DNA was sequenced to confirm the mutation found in the cDNA. (Primers are available on request.) For prediction of the functional consequences of the mutation in *ABCD1*, we used publically available software programs: PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/),[14] SIFT (http://sift.jcvi.org/),[15] and Mutation Taster (http://www.mutationtaster.org/).[16]

RESULTS

Neuropathological findings

The calculated whole brain weight was 1240 grams. Macroscopically, the cerebral hemisphere had a normal configuration. No obvious atrophy was evident in midbrain, pons, medulla, or cerebellum. On sections of the cerebellum cut in a transverse plane perpendicular to the long axis of the brainstem there was mild atrophy of the white matter and dentate nucleus (Fig. 1a). The cerebral cortex, hippocampus, basal ganglia, and thalamus were unremarkable. The superior cerebellar peduncle showed mild atrophy. The substantia nigra and locus ceruleus had decreased pigmentation.

Histologically, the cerebellar white matter had mild myelin loss with clusters of mostly perivascular macrophages that had granular, amphophilic-to-slightly basophilic cytoplasmic material (Fig. 1b–c). The material was PAS-positive and diastase-resistant (Fig. 1d), and cells were consistent with macrophages in that they were positive on CD68 immunohistochemistry (Fig. 1e). The white matter lesions were more conspicuous in the folia than in the central white matter, but the axons were relatively preserved in the both regions. There was patchy Purkinje cell loss with Bergmann gliosis and scattered Purkinje cell axonal torpedoes, especially in the vermis. The dentate nucleus was relatively preserved, but the hilus had myelin loss.

The cerebral white matter had patchy and poorly circumscribed areas of myelin rarefaction with PAS-positive macrophages that were most frequent in the occipital lobe (Fig. 1b and f). Vessels in the white matter had mild arteriosclerotic medial and adventitial hyalinosis and mild dilation of perivascular spaces, some containing PAS-positive macrophages. In contrast, the neocortex was well preserved. There was no obvious neuronal loss or gliosis in the neocortex, hippocampus, amygdala, basal nucleus of Meynert, basal ganglia or thalamus. The substantia nigra had mild neuronal loss with extraneuronal neuromelanin, while other brainstem nuclei, including the pontine nuclei and inferior olivary nucleus, were preserved.

The optic nerve had mild myelin rarefaction with expansion of the fibrovascular connective tissue septae. There were scattered clusters of PAS-positive macrophages. The optic tract had less obvious changes (Fig. 1g). The internal capsule, especially the posterior limb, had patchy myelin rarefaction and clusters of PAS-positive macrophages (Fig. 1h). The fiber tracts in the brainstem were also affected, especially the decussation of the superior cerebellar peduncle and the longitudinal fibers in the pontine base. The pyramidal tract in the medulla was minimally affected.

Immunohistochemistry for α-synuclein did not reveal glial cytoplasmic inclusions, which are the hallmark lesions of MSA. There were sparse Lewy bodies predominantly in the brainstem that were consistent with a coincidental age-related finding (so-called “incidental Lewy bodies”), since they were not associated with neuronal loss in affected nuclei. There was also other age-related pathology, most notably cortical amyloid plaques, with minimal medial temporal neurofibrillary tangles. There were no TDP-43-positive inclusions.

Electron microscopy

Electron microscopy showed that the macrophages contained membrane-bound cytoplasmic inclusions that had a cleft-like trilamellar membrane structure consistent with those seen in lipidoses (Fig. 2). Given the similarity of the macrophage inclusions to those found in X-ALD,[17, 18] we conducted genetic studies on the gene responsible for X-ALD, *ABCD1*.

Genetic findings

A novel *ABCD1* mutation was discovered in exon 1 – p.R163G (c.487 C>G) (Fig. 3a). R163 is a conserved residue (Fig. 3b), supporting the notion that this site is of functional importance and that the R-G variant is pathogenic. No other family member was available to show segregation of the mutation with disease phenotype, but all three prediction tools (PolyPhen-2, SIFT and Mutation Taster) indicated that the p.R163G mutation should be a damaging mutation.

DISCUSSION

We report a patient who was clinically diagnosed as having MSA in his later disease stage due to cerebellar and long tract signs with autonomic dysfunction. Neuropathological studies, especially electron microscopy, confirmed that he had cerebello-brainstem form of X-ALD. No blood samples were available to test for accumulation of VLCFA and given that the autopsy was limited to the brain, histologic studies of the adrenal were not possible. A diagnosis of X-ALD was never entertained during his life. He had long disease duration (35 years) and lacked characteristic MRI findings of X-ALD (and of MSA). The major pathologic findings were widespread, but patchy, white matter lesions characterized by myelin rarefaction and perivascular clusters of PAS-positive macrophages. Electron microscopic analyses in the cerebellum showed trilamellar membrane structures in cytoplasmic inclusions typical of X-ALD. The characteristic ultrastructural findings led to targeted genetic studies since there was no clear family history of disease. This case demonstrates the continuing value of ultrastructural characterization of atypical neuropathological conditions.

A review of the literature showed that most reports of cerebello-brainstem dominant form of X-ALD have (1) a family history of X-ALD or Addison's disease (51.7% = 15/29, data of 5 patients were not available), (2) adrenal insufficiency (75.0% = 24/32, data of 2 patients were not available), or (3) T2-weighted hyperintensities in the internal capsule, brainstem, and/or cerebellum (77.8% = 14/18, the data of 16 patients were not available) on MRI. The patient reported here did not have these characteristic features, and T2 signal abnormalities were interpreted as being due to microvascular pathology common in aging.

For many years, this patient carried a clinical diagnosis of and was treated for chronic progressive MS, but antemortem imaging studies never showed findings typical of MS. The pathology in our patient did not bear any resemblance to that of chronic progressive MS. In the later years of his 35-year disease course, his clinical diagnosis was MSA. Although he fulfilled criteria of probable MSA given the presence of a cerebellar syndrome, pyramidal symptoms and autonomic failure,[19] his relatively young age of onset and long disease duration, as well as seizures, temporary loss of eyesight, hearing loss and sensory disturbance are not typical of MSA, and more compatible with X-ALD.

Based on a review of the literature of cases with adult-onset cerebello-brainstem dominant X-ALD (Table 1 and Fig. 4), consideration of age at onset as well as a positive family history may be helpful in arriving at the diagnosis. The mean age at onset of the adult-onset cerebello-brainstem dominant form (33 ± 11, range 20 – 71 years) is earlier than that of MSA (60 ± 9, range 34 – 83 years),[20] although more than 10% of cases have onset after the age of 50 years, which is similar to MSA (Fig. 4b). Previous reports of this variant showed earlier ages at death (28 years, 37 years, and 46 years),[9, 21, 22] and the disease duration for each was 6 years, 3 years, and 25 years respectively.[9, 21, 22] Our patient died at an older age (69 years), which highlights the atypical clinical course of our patient. His other symptoms were common to cerebello-brainstem dominant X-ALD, including cerebellar ataxia, gait disturbance, speech disturbance, pyramidal signs, and autonomic failure (Fig. 4c). VLCFA levels were reported to be increased in 100% (30/30, data of 4 patients were not available), and VLCFA was the diagnostic tool used for those 30 patients. The four patients in which VLCFA data was not available, including our patient, (12%, 4/34) were diagnosed at autopsy.[9, 21, 22] The antemortem clinical diagnoses of these 4 patients were olivopontocerebellar atrophy (OPCA),[9, 21] MS or MSA [our study], or schizophrenia with neurological problems.[22] *ABCD1* mutations were identified in 8 of the 34 patients (Fig. 3c).

Our case had no hyperintensities or atrophy in the brainstem or cerebellum on MRI. In our review, T2-weighed hyperintensity on MRI was reported in the cerebrum in 28% (5/18, the data of 16 patients were not available) of cases, and it was reported in internal capsule, brainstem and/or cerebellum in 78% of the reported cases. Brainstem and/or cerebellar atrophy was found in 62% of the reported cases (20/32, the data of 2 patients were not available). These data seem to indicate that T2 hyperintensity (demyelination or gliosis) can occur before atrophy develops. These data also highlight the importance of MRI findings in diagnosis of this rare disorder. On the other hand, a patient has been reported with atrophy, but without T2 hyperintensities mimicking MSA,[23] which indicates that clinicians also should recognize that MRI findings may not always predict disease. As some previous studies have reported, patients that have cerebello-brainstem dominant form have symptoms

that mimic MSA or OPCA,[9, 21, 24–28] thus, we recommend considering X-ALD in the differential diagnosis of MSA, especially younger patients with atypical clinical features.

Although the mechanism of the cerebellar and brainstem dominant lesion formation is still unknown in these disorders, it is speculated that lipid dysfunction in myelin synthesis and maintenance underlies the neuropathology of MSA[29] as well as X-ALD. In comparison to previous pathologic reports of adult-onset cerebello-brainstem dominant form of X-ALD,[9, 21, 22] the white matter lesions in our patient were mild, even in the most severely affected regions, namely the cerebellar white matter. There was no significant atrophy in the brainstem or cerebellum in our patient, while previous reports have highlighted macroscopic atrophy in brainstem and cerebellum. Two reported cases[21, 22] had remarkable neuronal loss in the subcortical and brainstem nuclei, including the pontine nucleus and inferior olivary nucleus, similar to OPCA. In contrast, no significant neuronal loss was detected in subcortical or brainstem nuclei in our patient. The exception was very mild neuronal loss in the substantia nigra associated with incidental Lewy bodies. For reasons that are not clear, our patient had a relatively benign disease course that played out over several decades and was associated with relatively mild multifocal white matter pathology, affecting optic nerves, cerebral white matter, long tracts and cerebellum. The subtle perivascular lesions might easily have been missed and their significance attributed to age-related changes, had ultrastructural studies clearly indicated another possibility.

The *ABCD1* mutation detected in our patient, p.R163G, has not been reported previously. It is located in the transmembrane domain of ATP-binding cassette transporter D1, which is involved in peroxisomal import of fatty acids. Other diseases causing mutations have been reported at the same position, including p.R163H in a symptomatic female carrier[30] and p.R163P in two AMN patients.[31, 32] These observations supports the pathogenicity of the mutation in our patient. Only 8 mutations have been reported to cause adult-onset cerebello-brainstem dominant form of X-ALD (Fig. 3c).[23, 28, 33–36] All of the mutations are in the transmembrane domain or ATP-binding cassette domain (Fig. 3c), and both domains are “hot spots” for mutations in *ABCD1*.[2] The adult-onset cerebello-brainstem dominant form and AMN display similar features (*e.g.*, age at onset, autonomic failure, pyramidal symptoms and sensory disturbance), but most cases can be distinguished by cerebellar dominant symptoms (Table 1 and Fig. 4b). In line with other nomenclature, we suggest that this disorder be named ALD-C (cerebellar variant of ALD).

This rare phenotype is observed relatively frequently in Asian countries, especially in Japan and South Korea (Table 1 and Fig. 4a). Previous studies estimated that the frequencies of the cerebello-brainstem dominant form are 1–2% globally,[2] but 9% (13/145) in Japanese patients with X-ALD.[37] Therefore, factors modulating X-ALD in Asian patients may be present. Intriguingly, there are some cerebellar variants in other diseases, such as the cerebellar variant of MSA (MSA-C)[38–40] and progressive supranuclear palsy (PSP-C),[41–43] which are also more frequent in Japan than in Europe or the United States. This suggests that there may be environmental, epigenetic or genetic factors that may contribute to or protect from cerebellar predominant pathology in these disorders.

Recently, it has been recognized that a proportion of patients with acyl-CoA oxidase deficiency (ACOX1; OMIM 609751) may exhibit similar clinical, radiological, and histopathological features to those of X-ALD, especially in the cerebello-brainstem form.[44, 45] Inherited deficiencies of peroxisomal straight chain VLCFA β-oxidation include only X-ALD and straight-chain acyl-CoA oxidase deficiency. Although rare, adult-onset cerebello-brainstem dominant ACOX1 was reported and it should be one of differential diagnoses of atypical MSA as well as cerebello-brainstem dominant form of X-ALD.[45]

Conclusion

We described a patient who had the adult-onset sporadic cerebello-brainstem dominant form of X-ALD with the longest clinical course, unexpectedly mild pathological findings, and a new *ABCD1* p.R163G substitution. We also review a total of 34 cases of adult-onset cerebello-brainstem dominant form of X-ALD. Currently, there is no effective treatment for adult-onset X-ALD, but early recognition of this rare disorder would be useful for genetic counselling and future therapy.[46]

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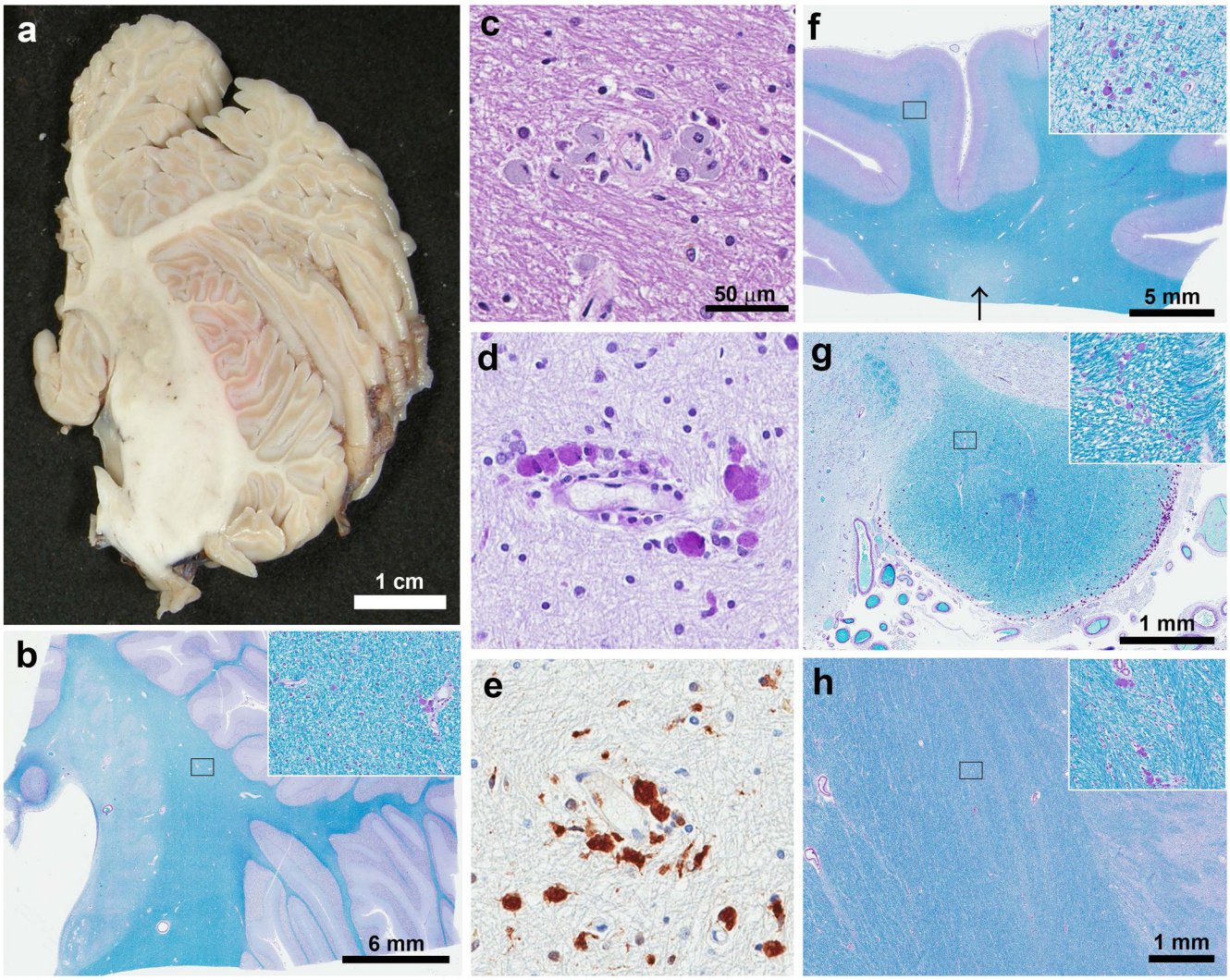

Fig. 1.

(a) Macroscopic finding of cerebellum. (b) LFB staining demonstrates mild myelin pallor in cerebellar white matter (inset shows higher magnification of area in box). (c) Perivascular macrophages in the cerebellar white matter have a granular amphophilic-to-slightly basophilic cytoplasmic material (H&E). (d) The material was PAS-positive and diastase resistant. (e) The cells with storage material were macrophages since they were immunoreactive for CD68. (f) LFB staining demonstrates myelin pallor in occipital lobe (inset shows higher magnification of area in box). Arrow indicates a region of myelin pallor in perivascular region near occipital horn of lateral ventricle. LFB staining shows patchy mild myelin pallor in optic tract (inset shows higher magnification of area in box) (g), and posterior limb of internal capsule (inset shows higher magnification of area in box) (h).

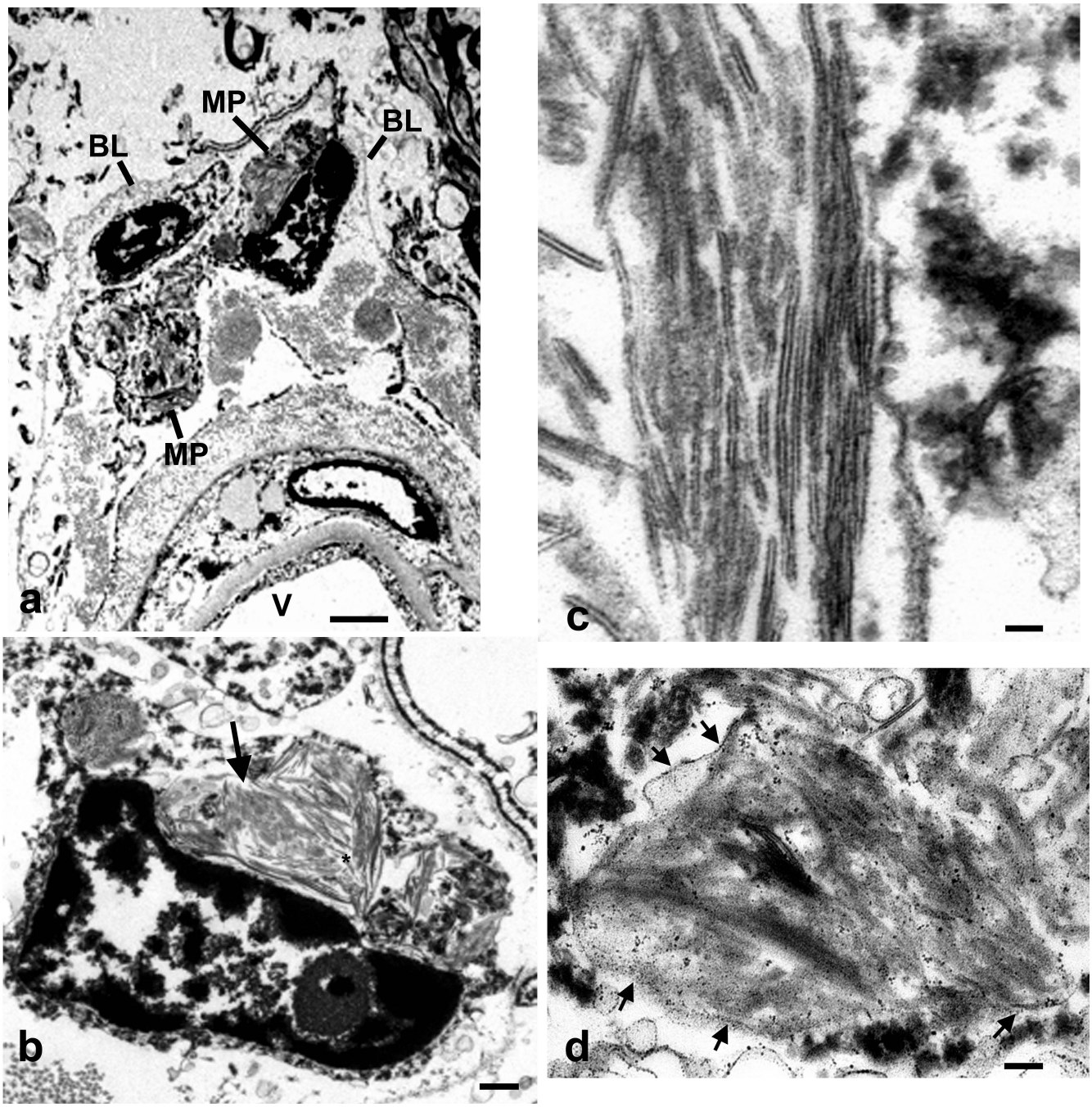

Fig. 2.

(a) Electron micrograph of macrophages (MP) within Virchow Robin space between glia limitans and basal lamina (BL) of a blood vessel (V). Bar, 3 μm. (b) Higher magnification of MP in (a) showing cytoplasmic inclusion (arrow). * indicates the area enlarged in (c). Bar, 0.5 μm. (c) Cleft-like tri-lamellar structures can be observed in the inclusion. Bar, 50 nm. (d) An inclusion is bound by membrane (outlined by arrows). Bar, 0.1 μm.

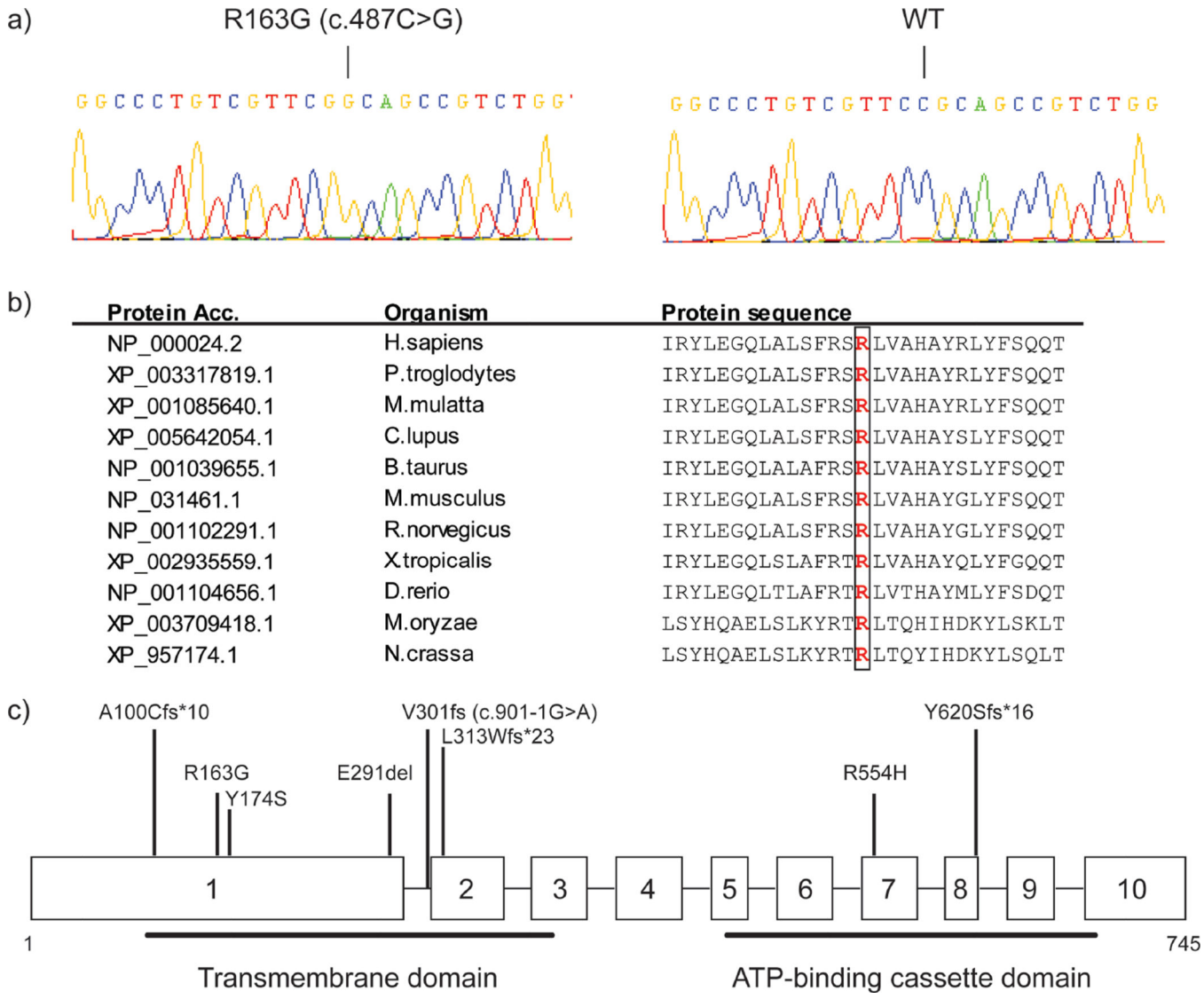

Fig. 3.

Genetic analysis. (a) Electrochromatograph shows a novel mutation in *ABCD1* gene, p.R163G (c.487C>G). (b) Protein sequence of R163 is highly conserved in other species. (c) Localization of *ABCD1* mutations in cerebello-brainstem dominant form of X-ALD.

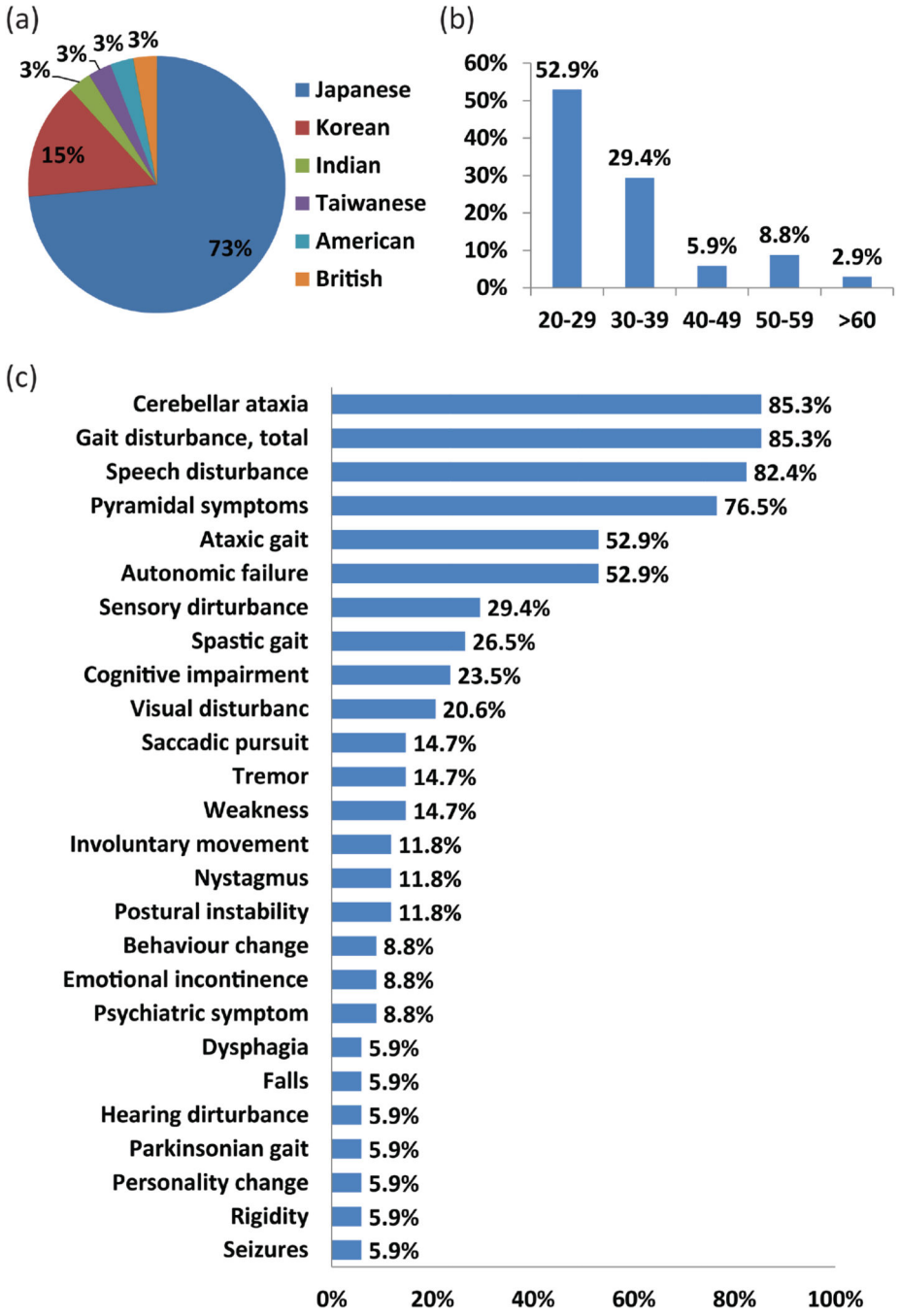

Fig. 4.

Summary of reported cases of cerebello-brainstem dominant form of X-ALD. (a) Proportion of cases by ethnic group (in percent). (b) Proportion of cases by age of onset. (c) Proportion of cases by symptoms (in percent).

Table 1

Reported cases with adult-onset cerebello-brainstem dominant form of X-ALD

							Neuroimaging findings				
							MRI T2WI high signal		Atrophy		
First author	**Ethnicity**	**AAO**	**FH**	**Neurologic findings**	**AI**	**VLCFA**	**Cerebrum**	**IC, Bs and/or cerebellum**	**Bs and/or cerebellum**	**DDx**	**Brain pathology/ *ABCD1* mutation**
Kuroda[9]	Japanese	22	−	BC, CA, EI, GD, PBP, PyS, VD	−	NA	NA	NA	NA	NA	Brain pathology+
Suzuki[27]	Japanese	22	−	AG, CA, EI, falls, PyS, SaP, SG, SpD (ataxic dysarthria)	−	high	NA (CT)	NA (CT)	+	SCD, OPCA	NA
Tsuchida[24]	Japanese	52	−	AF, CA, CI, GD, SpD, IVM, SaP, SeD	+	high	NA (CT)	NA (CT)	+	OPCA	NA
Ohno[25]	Japanese	52	NA	AF, CA, AG, IVM, SaP, SeD, SpD (scanning)	+	high	NA (CT)	NA (CT)	+	OPCA	NA
Kumamoto[47]	Japanese	38	−	CA, CI, GD, Hemiparesis, PN, PyS, SpD, Sz, Tr, We	−	high	NA (CT)	NA (CT)	+	NA	NA
Kobayashi[48]	Japanese	22	+	AG, CA, SG, SpD	−	high	NA (CT)	NA (CT)	+	NA	
Kobayashi[48]	Japanese	27	+	AG, CA, PyS, SaP, SG, SpD (ataxic dysarthria)	+	high	NA (CT)	NA (CT)	+	NA	NA
Nakahara[49]	Japanese	24	−	AF, BC, CA, Dp, EI, falls, GD, HD, PyS, SpD	+	high	NA (CT)	NA (CT)	+	NA	NA
Tateishi[22]	Japanese	21	NA	AF, IVM, PsS	NA	NA	NA	NA	NA	Schizophrenia	Brain pathology+

First author	Ethnicity	AAO	FH	Neurologic findings	AI	VLC FA	Neuroimaging findings: MRI T2WI high signal: Cerebrum	Neuroimaging findings: MRI T2WI high signal: IC, Bs and/or cerebellum	Neuroimaging findings: Atrophy: Bs and/or cerebellum	DDx	Brain pathology/ *ABCD1* mutation
Okamoto[50]	Japanese	28	+	AF, CA, GD, PyS, SeD, SpD, We	−	high	NA (CT)	NA (CT)	+	SCD	NA
Takada[21]	Japanese	34	+	AF, AG, CA, PyS, SeD, SpD, VD	+	NA	NA (CT)	NA (CT)	+	OPCA	Brain pathology+
Sano[51]	Japanese	41	+	AF, AG, Dp, Parkinsonian gait, PyS, rigidity, SpD, SaP, Tr (action)	+	high	T2-low (lateral putamen)	−	−	Striatonigral degeneration	NA
Sano[51]	Japanese	71	−	AF, AG, CI, Parkinsonian gait, PyS, rigidity, SpD, Tr (resting),	+	high	NA (CT)	NA (CT)	−	Striatonigral degeneration	NA
Nakazato[52]	Japanese	33	+	AF, AG, CA, CI, PC, PyS, SG, SpD, VD	+	high	NA (CT)	NA (CT)	−	SCD	NA
Nakazato[52]	Japanese	34	+	AF, AG, CA, PyS, Ny, SG, SpD, VD	+	high	NA (CT)	NA (CT)	+	NA	NA
Nakazato[52]	Japanese	54	+	AG, CA, PyS, SG	+	high	NA (CT)	NA (CT)	+	NA	NA
Miyai[53]	Japanese	26	+	AF, AG, CA, euphoria, PyS, SG, SpD	+	high	+	+	+	NA	NA
Kusaka[11]	Japanese	21	−	CA, GD, PI, PyS, SpD	+	high	−	+	+	NA	NA
Kawai[54]	Japanese	27	−	AF, AG, CA, PyS, SeD, SG	+	high	−	+	+	NA	NA
Ochi[55]	Japanese	29	+	SpD (ataxic dysarthria)	+	high	+	+	−	MS	NA
Waragai[26]	Japanese	29	−	GD, PI, SpD (ataxic dysarthria)	+	high	−	+	+	OPCA	NA

First author	Ethnicity	AAO	FH	Neurologic findings	AI	VLC FA	Neuroimaging findings: MRI T2WI high signal: Cerebrum	Neuroimaging findings: MRI T2WI high signal: IC, Bs and/or cerebellum	Neuroimaging findings: Atrophy: Bs and/or cerebellum	DDx	Brain pathology/ *ABCD1* mutation
Kano[35]	Japanese	47	+	AF, CA, CI, Ny, PC, PsS, PyS, SpD	−	high	−	+	+	NA	p.E291del, c.871_873delGAG
Ochi[56]	Japanese	20	NA	AG, CA, IVM, Ny, PyS, SpD (scanning), Tr	+	high	−	+	−	NA	NA
Dunne[23]	Caucasian	37	+	AF, AG, CA, PI, PyS, SeD, SpD	+	high	−	−	+	familial cerebellar ataxia	p.L313Wfs*23, c.1321delC
Kumagai[57]	Japanese	29	−	AG, CA, PyS, SpD (scanning)	+	high	−	+	+	SCD	NA
Mishra[58]	Indian	26	NA	AF, AG, CA, SpD (ataxic dysarthria), Tr	+	high	+	+	−	NA	NA
Suda[59]	Japanese	28.5	NA	CA, GD, PyS, SpD	+	high	−	+	−	NA	NA
Jung[60]	Korean	37	+	AG, CA, dizziness, Ny, SpD	+	high	−	+	+	SCA, Friedrich ataxia, Fragile X syndrome	NA
Li[36]	Taiwanese	28	−	CA, GD, PyS, SpD, We	−	high	−	+	+	NA	p.Y620Sfs*16, c.1859delA
Kim[34]	Korean	36	−	BC, CA, frontal dysfunction, PyS, SG	+	high	−	+	−	NA	p.Y174S, c.521A>T
Kang[28], Park[33]	Korean	35	+	AF, AG, CA, CI, PI, PyS, SeD, SpD, VD (diplopia), We	−	high	−	+	−	unknown brainstem encephalopathy	p.A100Cfs*10, c.277_296dup20
Park[33]	Korean	23	−	CA, PyS, SeD	+	high	cortico-spinal tract	cortico-spinal tract	−	NA	p.R554H, c.1661G>A
Park[33]	Korean	36	+	AF, CA, PyS, SeD, SpD	+	high	+	−	−	SCA	p.V301fs c.901-1G>A

First author	Ethnicity	AAO	FH	Neurologic findings	AI	VLCFA	Neuroimaging findings: MRI T2WI high signal: Cerebrum	Neuroimaging findings: MRI T2WI high signal: IC, Bs and/or cerebellum	Neuroimaging findings: Atrophy: Bs and/or cerebellum	DDx	Brain pathology/ *ABCD1* mutation
This study	Caucasian	34	−	AF, CA, GD, HD, PyS, PsS, SeD, SpD, Sz, VD, We	NA	NA	+	−	−	MSA, MS, Spastic paraparesis	Brain pathology+ p.R163G, c.487C>G

We found 34 patients of cerebello-brainstem form of X-ALD who fulfilled inclusion criteria – (1) predominant involvement of cerebellum and/or brainstem and diagnosed of X-ALD with VLCFA, pathology or genetics; (2) adequate clinical information (e.g, age at onset, clinical presentation, neuroimaging and neuropathology) ;and (3) adult age of onset (age ≥20). We excluded patients with mental retardation or childhood developmental disorders. Adrenal impairment includes Addison's disease, hyperpigmentation, serum ACTH level, serum cortisol level, abnormal result for rapid ACTH test, urinary 17-ketosteroids and urinary or 17-hydroxycorticosteroids. "-" indicates information is not available.

Abbreviations: AAO, age at onset; AF, autonomic failure; AG, ataxic gait; AI, adrenal impairment; BC, behaviour change; Bs, Brainstem; CA, cerebellar ataxia; CI, cognitive impairment; CT, computed tomography; DDx, differential diagnosis; Dp, dysphagia; EI, emotional incontinence; FH, family history of adrenoleukodystrophy and/or Addison's disease; GD, gait disturbance; HD, hearing disturbance; IC, internal capsule; IVM, involuntary movement; MRI T2WI, magnetic resonance imaging T2 weighted image; MS, multiple sclerosis; MSA, multiple system atrophy; Ny, nystagmus; OPCA, Olivopontocerebellar atrophy; PC, personality change; PI, postural instability, PBP, pseudobulbar palsy; PsS, psychiatric symptoms (including Schizophrenia, depression); PyS, pyramidal symptoms (including hyperreflexia, Babinski sign, spastic paraplegia and/or spasticity); PN, polyneuropathy; SaP, saccadic pursuit; SCA, spinocerebellar ataxia; SCD, spinocerebellar degeneration; SeD, sensory disturbance; SpD, Speech disturbance; SG, spastic gait; Sz, seizures; Tr, Tremor; VD, visual disturbance; VLCFA, Very long-chain fatty acid; We, weakness.