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Novel Mutation in Sjögren-Larsson Syndrome Is Associated With Divergent Neurologic Phenotypes

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Abstract

Sjögren-Larsson syndrome is an inherited disorder of lipid metabolism caused by mutations in the *ALDH3A2* gene that codes for fatty aldehyde dehydrogenase, which results in accumulation of fatty aldehydes and alcohols and is characterized by ichthyosis, intellectual disability, and spastic diplegia/quadruplegia. The authors describe 2 unrelated Honduran patients who carried the same novel homozygous nonsense mutation (c.1309A>T, p.K437X) and *ALDH3A2* DNA haplotype, but widely differed in disease severity. One patient exhibited spastic quadriplegia with unusual neuroregression, whereas the other patient had the usual static form of spastic diplegia with neurodevelopmental disabilities. Biochemical analyses showed a similar profound deficiency of fatty aldehyde dehydrogenase activity and impaired fatty alcohol metabolism in both patients' cultured fibroblasts. These results indicate that variation in the neurologic phenotype of Sjögren-Larsson syndrome is not strictly determined by the *ALDH3A2* mutation or the biochemical defect as expressed in cultured fibroblasts, but by unidentified epigenetic/environmental factors, gene modifiers, or other mechanisms.

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Author Contributions

KD contributed to the case reviews, organization, and writing of the manuscript. KRH examined the patients, obtained specimens, and contributed to the writing of the manuscript. DS performed genetic and biochemical studies on the patients. CA and MGM provided medical care for the patients and obtained medical history. WBR contributed to the organization, laboratory testing, and writing of the manuscript. All authors reviewed and approved the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Informed consent was obtained from the patients' parents to perform this study and publish all the clinical information including photographs of the patients.

Keywords

ichthyosis; spasticity; aldehyde dehydrogenase; mutation; fatty alcohol; Sjögren-Larsson; neurologic; phenotype

Sjögren-Larsson syndrome is a rare autosomal recessive disorder caused by mutations in the *ALDH3A2* gene that codes for fatty aldehyde dehydrogenase.¹ The clinical features of Sjögren-Larsson syndrome include ichthyosis, spastic diplegia or quadriplegia, intellectual disability, epilepsy, photophobia, and a distinctive retinal maculopathy with glistening white dots. Patients are often born premature.² The ichthyosis is usually present at birth and later becomes pruritic. Neurologic symptoms typically emerge during the first year of life. Spastic diplegia is much more common than quadriplegia. Motor and cognitive abilities are impaired, but loss of previously acquired cognitive functions is unusual. Brain MRI typically shows evidence of a dysmyelinating white matter disease that becomes evident by several years of age.³ Although Sjögren-Larsson syndrome is found in all geographic and ethnic groups, most patients have been identified in Europe, particularly northern Sweden, where the disease was originally described.⁴

Fatty aldehyde dehydrogenase deficiency is the primary biochemical defect in Sjögren-Larsson syndrome.⁵ This enzyme catalyzes the oxidation of aliphatic aldehydes to fatty acids and is necessary for the complete metabolism of fatty alcohols to fatty acids.⁶ Sjögren-Larsson syndrome patients accumulate fatty alcohols and aldehydes, which are thought to be responsible for the symptoms of this disease.¹ Many different mutations in the *ALDH3A2* gene have been identified in Sjögren-Larsson syndrome including deletions, insertions, missense mutations, splicing defects, and complex rearrangements.^{7,8} Most mutations are private, although several common mutations have been found in patients from Europe,^{9–12} the Middle East,⁷ and Brazil.¹³ We describe the first genetically confirmed cases of Sjögren-Larsson syndrome in Honduras. These 2 apparently unrelated patients carried the same novel *ALDH3A2* mutation, but exhibited significant differences in neurologic phenotypes.

Case Reports

Patient 1

This 4¾-year-old Honduran female presented with a history of global neurodevelopmental delays and “dry” skin since birth. Family history was only significant for 2 paternal cousins who reportedly had “dry” skin without other abnormalities. The family denied consanguinity. She was born at 31 weeks gestation to a gravida-1 para-0 female. The pregnancy was complicated by malaria and varicella infections at 6 and 7 months gestation, respectively. Birth weight was 1.5 kg (45th percentile). A collodion membrane covered the newborn at birth, which resolved into dry hyperkeratotic skin, and by 1 year of age she showed increasing amounts of cutaneous scales. She had early global neurodevelopmental delays, especially in speech, language, and motor milestones. She first spoke at 2 years of age and did not walk until she was 2½ years old. Her receptive language was reportedly better than expressive language. At 2 years and 2½ years of age, she had brief isolated

generalized tonic-clonic seizures with fever but has had no subsequent recurrences while on no antiepileptic drugs. Cranial tomography at 4 years of age was normal.

On examination at 4¾ years of age, she had diffuse generalized ichthyosis on the neck, trunk, and extremities (Figure 1A, B). Hyperkeratosis was present on her forehead, but the central face was spared. The hyperkeratosis appeared as lamellar-like scales on the legs, and she had excoriations due to pruritus. Hair and nails were normal. Other than her skin findings and severe frontal dental caries, her head, ears, eyes, nose and throat, heart, lungs, and abdominal and genitalia exams were normal. Neurologic exam revealed a right-handed normocephalic female with moderate global neurodevelopmental delays in language, cognition, and gross motor function. Cranial nerves II through XII were normal including fundoscopy, which exhibited mild generalized hypopigmentation but was free of retinal or optic nerve abnormalities. She had generalized hyperreflexia, lower extremities greater than upper extremities, with an unsteady spastic diplegic gait, bilateral ankle clonus, and plantar extensor reflexes bilaterally. At rest, she exhibited mild generalized hypotonia with low normal muscle bulk and no gross cerebellar abnormalities. There were no gross exteroceptive sensory deficits.

At 7¼ years of age, her interval history and re-examination revealed moderate neurodevelopmental delays with no neuroregression. Her neurodevelopmental milestones were now consistent with a 4-year-old, but her speech impediment had worsened. Her spastic diplegic gait had also worsened in the interim, which had prompted treatment with ankle tendonotomies 3 months earlier. Her gait subsequently improved postoperatively, and she was now beginning to run. The generalized ichthyosis had improved with regular use of skin moisturizing creams. On physical examination, her height was 111 cm (< 5th percentile), weight was 18.2 kg (< 5th percentile), and head circumference was 49 cm (3rd percentile). No hair or nail abnormalities were present. Ophthalmologic exam revealed the new appearance of perifoveal glistening white dots, but no other abnormalities. No new dental caries were present. Her heart, lungs, abdomen, and genitalia exams were normal. Neurologic exam was significant for a happy cooperative child with nonprogressive moderate global neuro-developmental delays and spastic diplegia with an improved gait. The remainder of her neurologic examination was unchanged.

Patient 2

This 3½-year-old Honduran male was born after an uncomplicated 40-week gestation to a gravida-1 para-0 female. Birth weight was 2.6 kg (5th percentile), birth length was 50 cm (50th percentile), and head circumference was 34 cm (10th percentile). Apgar scores were 8 at 1 minute and 9 at 5 minutes. He had no collodion membrane, but exhibited ichthyosis initially on his hands, and the entire body by 2 to 3 months of age. He had global neurodevelopmental delays beginning at 3 to 6 months of age. He sat at 12 months of age, rolled over at 16 months, but never crawled or stood independently. He used a spoon at 13 months and transferred objects at 14 months. After initially babbling, he first spoke at 15 months of age, but his vocabulary did not progress beyond “papa” and “mama.” At 18 months of age, he developed nocturnal myoclonus thought to be epilepsy and was treated and well-controlled with valproic acid. At about 3 years of age, he was hospitalized for

idiopathic thrombocytopenic purpura, which was thought to be secondary to valproic acid. His valproic acid was replaced by diphenylhydantoin at that time. He subsequently developed necrolytic epidermolysis bullosa, and his anticonvulsant was discontinued for 3 months. He was eventually placed back on oxcarbazepine, levetiracetam, and clonazepam with good seizure control. The review of systems was significant for a history of corneal ulcerations during his hospitalization. Additional problems included persistent drooling, chronic constipation, and gradual neurodevelopmental regression from a prior age equivalent level of 9 to 12 months to a level of 6 months at 3½ years of age. The family history was positive for consanguinity. A paternal great uncle had ichthyosis, a maternal aunt and 2 paternal cousins had neurodevelopmental disabilities with intellectual delays, a paternal uncle and cousin had spasticity, and a maternal cousin had epilepsy.

Physical examination at 3½ years of age showed a weight of 16.4 kg (55th percentile), height was 110 cm (90th percentile), and head circumference was 51.5 cm (60th percentile). He exhibited bilateral corneal scarring which prevented a thorough fundoscopic examination, but he could follow bright objects. He had generalized facial hypotonia, multiple dental caries and gingival hypertrophy, and an undescended right testicle. The skin showed ichthyosis with a dark patchy distribution on his trunk (Figure 2C), whereas it was more lamellar-like on his lower legs. He had onychomycosis affecting the nails of his hands. Neurologic exam revealed global neurodevelopmental disabilities including profound intellectual delays and severe spastic quadriplegia with partial contractures in all extremities (Figure 2C, D). He had lack of bilateral pincer grasps with sustained clonus at the knees and ankles and extensor plantar responses. He was unable to stand or crawl.

Follow-up evaluation at 6½ years of age revealed the patient had further neuroregression in gross and fine motor skills as well as cognition. He was no longer able to sit if placed, roll over, transfer objects, or use a pincer grasp. His speech of 2 words (“papa” and “mama”) had become much less distinct, and his language skills/sounds were in the profoundly delayed range of function. His generalized myoclonic and clonic seizures were well controlled on levetiracetam and clonazepam. On physical examination, his weight was 15.9 kg (8th percentile), height was 113.5 cm (20th percentile), and head circumference was 51.75 cm (50th percentile). He had corneal opacities (left > right) with severe photophobia. Fundi could not be visualized. He exhibited dental caries, an open mouth with persistent drooling, and little facial expression. His chest showed clear lung sounds and back had a developing kyphosis. Abdominal exam showed no organomegaly and a high-riding right testicle. Neurologic exam showed profound global neurodevelopmental disabilities with poor head control, grossly intact vision and hearing, and an equivocal gag reflex. He had spastic quadriparesis with limb contractures, spontaneous scissoring of his lower extremities, and bilateral upper and lower clonus in the extremities accompanied by bilateral plantar extensor responses. No gross cerebellar or sensory deficits were found.

Laboratory Results

Patient 2's brain magnetic resonance imaging at 4¾ years of age revealed increased T2-weighted signal intensities in the periventricular region, particularly in the regions of the trigones (Figure 3). There also was poorly defined myelination in the periphery of the

subcortical white matter, where many of the U-fibers were underdeveloped. A nonictal electroencephalogram at age 6 years of age exhibited generalized slowing with no focal or generalized spikes or spike-wave discharges. High-resolution chromosomes, free T3 and T4, plasma amino acids, and plasma total and free carnitines were normal.

Patient 1's cranial tomography at 4 years of age was normal, which discouraged the need for ordering additional brain magnetic resonance imaging studies.

As shown in Table 1, fatty aldehyde dehydrogenase activity in cultured skin fibroblasts from patient 1 and patient 2 was measured⁵ and found to be less than 1% of normal activity. Oxidation of radioactive octadecanol (30 nM) to octadecanoic acid by intact fibroblasts⁵ was comparably deficient in both patients (mean 27% to 33% of normal). DNA sequencing of the *ALDH3A2* gene⁸ in both patients revealed a homozygous c.1309A>T mutation in exon 9, which converts lysine 437 to a termination codon (p.K437X) (Figure 3A). The mother of patient 1 and both parents of patient 2 were found to be heterozygous carriers for this mutation; patient 1's father was unavailable for testing. Haplotype analysis of the *ALDH3A2* gene⁸ using 4 intragenic single nucleotide polymorphisms indicated that the c.1309A>T mutation carried by both patients was associated with haplotype 2.

Discussion

Our patients are the first genetically confirmed Sjögren-Larsson syndrome patients from Honduras. Both are homozygous for the identical novel nonsense mutation and have the same *ALDH3A2* haplotype. Although their family names differ and pedigree studies do not otherwise link them together, DNA haplotype analysis suggests that they share a common distant ancestor. It is likely that the disease in these patients is associated with a genetic founder effect among the native Honduras population. This type of finding has been reported in several other geographic regions around the world, including Sweden,^{14,15} Northern Europe,^{9–12} the Middle East,⁷ and Brazil.¹³ In most cases, DNA haplotype analyses using intragenic single nucleotide polymorphisms or microsatellite markers indicate that these common mutant alleles are identical, that is, they have the same DNA haplotype, which is consistent with a founder effect. Identification of additional patients will be necessary to determine whether the c.1309A>T mutation is a common cause of Sjögren-Larsson syndrome in the Honduran population.

The c.1309A>T mutation causes a premature stop codon (AAA→TAA; K437X) that is predicted to result in a truncated fatty aldehyde dehydrogenase protein. Alternative splicing of the *ALDH3A2* gene generates 2 protein isoforms of fatty aldehyde dehydrogenase, 485 amino acids and 508 amino acids long, that are targeted to the endoplasmic reticulum and peroxisomes, respectively, by their carboxy-terminal domains.^{16,17} The K437X mutation in our patients is predicted to result in truncated protein isoforms that lack the carboxy-terminal 49 or 72 amino acids from the endoplasmic reticulum or peroxisome-targeted proteins, respectively, and is expected to cause mislocalization of fatty aldehyde dehydrogenase and its enhanced degradation. Fatty aldehyde dehydrogenase is necessary for the oxidation of aliphatic aldehydes and alcohols derived from metabolism of several precursor lipids (Figure

3B). In Sjögren-Larsson syndrome, deficiency of this enzyme results in accumulation of long-chain alcohols and aldehydes, which are thought to be responsible for the symptoms.¹

Despite having identical genotypes and similar deficiencies in fibroblast enzyme activity and fibroblast fatty alcohol oxidation, our 2 patients exhibited striking differences in neurologic severity. Patient 1 had the more typical spastic diplegia seen in Sjögren-Larsson syndrome, whereas patient 2 showed severe spastic quadriplegia. Usually either spastic diplegia or quadriplegia is generally consistent within families or patients with the same genotype.^{12,18,19} However, rare patients have been reported with divergent neurologic symptoms unrelated to the extent of ichthyosis. Willemsen et al¹² described 2 adult siblings with Sjögren-Larsson syndrome; one had a mild spastic gait with hyperreflexia, whereas the other sibling had no neurologic signs or symptoms. Nigro et al²⁰ reported a family with 3 affected siblings who varied widely in severity of spastic diplegia. Variation in the severity of neurologic disease and brain magnetic resonance imaging has been previously reported in a large Arab family with 6 affected siblings carrying the homozygous c.682C>T mutation, but all of the patients exhibited spastic diplegia.²¹ Brain magnetic resonance imaging was only done in our most severely affected patient (patient 2), done with Patient 1.

The mental and motor neuroregression, exhibited by our patient 2, is distinctly unusual for Sjögren-Larsson syndrome. Most patients show a gradual premature plateau in neurologic and developmental advancement but do not lose most of their attained fine motor or cognitive skills. Although brain magnetic resonance imaging reveals an apparent dysmyelinating white matter disease, as seen in patient 2, with accumulation of lipid on MR spectroscopy, no active demyelinating process occurs.³ However, rare patients have been reported to exhibit a progressive phenotype with some deterioration in neurologic function similar to patient 2. Engelstad et al²² reported a Sjögren-Larsson syndrome patient with a homozygous contiguous gene deletion of *ALDH3A2* and 4 flanking genes, who showed loss of motor and oral motor function during adolescence. Even though our patients share the same *ALDH3A2* mutation, it is possible that they differ with respect to fatty aldehyde metabolism in brain, which could influence their clinical course. Aldehyde dehydrogenases comprise a family of enzymes that vary with respect to substrate specificity, subcellular distribution, and tissue expression.²³ *ALDH3A2* knockout mice completely lack fatty aldehyde dehydrogenase activity but exhibit about 30% of the aldehyde dehydrogenase enzyme activity seen in wild-type mice, indicating the presence of other aldehyde dehydrogenase isozymes that are also capable of oxidizing long-chain aldehydes (Rizzo, unpublished observations). Although profoundly deficient in fatty aldehyde dehydrogenase activity, the intact fibroblasts from our patients were able to oxidize some fatty alcohol, indicating the ability to partially bypass the metabolic block. Even though the basis for the neuroregression in Sjögren-Larsson syndrome remains unknown, we can speculate that individual variation in the activity of these other aldehyde dehydrogenase isozymes could contribute to the variation in neurologic phenotype seen in patients.

In summary, we demonstrate markedly unusual phenotypic variability in the neurologic disease of 2 Honduran Sjögren-Larsson syndrome patients carrying an identical novel *ALDH3A2* mutation. Our findings indicate that the differing neurologic symptoms in these Sjögren-Larsson patients are not from their *ALDH3A2* mutation, which they share, but

likely a consequence of other unidentified isozymes, biochemical pathways, modifier genes, or environmental/epigenetic factors still to be discovered.

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Figure 1.

Clinical appearance of the patients. (A) Patient 1 at 4 $\frac{3}{4}$ years of age shows generalized ichthyosis on the trunk, neck, and extremities. The pruritic nature of the ichthyosis is evident from excoriations on the left upper arm and neck. Note the hyperkeratotic skin on the forehead but sparing of the central face. (B) Ichthyotic lamellar-like scales can be seen on the legs of patient 1. (C) Clinically apparent spastic quadriplegia seen in patient 2 at 3 $\frac{1}{2}$ years of age. (D) Dark hyperkeratotic skin is evident on the trunk of patient 2. The nails have onychomycosis.

Figure 2.

Brain magnetic resonance imaging at 4 $\frac{3}{4}$ years of age showing an axial T2-weighted image of patient 2. Note periventricular white matter bright signal, particularly in the regions of the trigones, as well as poorly defined myelination in the peripheral subcortical white matter. Underdeveloped U-fibers (arrows) in the bilateral frontal and left parietal regions contrast are in contrast with the more well defined U-fibers (arrowheads) in the mesial posterior brain.

Figure 3.

Genetic analysis and metabolic defect in both patients. (A) DNA sequencing chromatogram showing the homozygous mutation (c.1309A>T; K437X) converting Lys437 to a termination codon (arrow). (B) Biochemical pathway for fatty alcohol and fatty aldehyde metabolism in Sjögren-Larsson syndrome.

Table 1

Biochemical and Genetic Studies in the Patients.

Laboratory test	Patient 1	Patient 2
Fibroblast fatty aldehyde dehydrogenase activity (% of control)	< 1	< 1
Oxidation of octadecanol in intact fibroblasts (% of control)	27 ± 2	33 ± 7
<i>ALDH3A2</i> genotype	c.1309A>T/c.1309A>T	c.1309A>T/c.1309A>T
<i>ALDH3A2</i> DNA haplotype	2	2

Fatty aldehyde dehydrogenase activity was measured using octadecanal as substrate.⁵ Oxidation of ³H-octadecanol (30 nM) to fatty acid was measured in intact fibroblasts after 18 hours incubation.⁵ Mutation analyses and *ALDH3A2* haplotype determinations (haplotypes 1–4) were done as described.⁸