

CLINICAL REPORT

Sjogren–Larsson Syndrome: A case series of five members from an extended family with a novel mutation

Kamel T. Abidi¹  | Naglaa M. Kamal²  | Ayman A. Bakkar A.³ | Maram Alotaibi³ | Haifa Asseri³ | Kawthar A. Bokari⁴

¹Faculty of Medicine, Al Manar University, Tunis, Tunisia

²Kasr Alainy Faculty of Medicine, Cairo University, Cairo, Egypt

³Alhada Armed Forces Hospital, Taif, KSA

⁴Taif University, Taif, KSA

Correspondence

Kamel T. Abidi, Faculty of Medicine, Al Manar University, Tunis, Tunisia.
Email: abidikamel952@gmail.com

Abstract

Background: Sjogren–Larsson syndrome (SLS) is a rare autosomal recessive disorder, characterized by a triad of spastic tetraplegia or diplegia, congenital ichthyosis, and intellectual disability.

Methods: We report a seven-years-old female born to consanguineous parents who presented with erythematous dry scaly skin all over the body sparing the face, without collodion membrane which started since birth. There were associated with global developmental delay and seizure disorder. SLS was suspected and hence sequence analysis of the *ALDH3A2* gene by next-generation sequencing was performed for the patient.

Results: A novel nucleotide exchange in homozygous state at position c.1320 in exon 9 of the *ALDH3A2* gene (c.1320T>A), leading to a stop of the protein sequence (p.Tyr440) was detected in the patient. Genetic testing of the patient's extended family revealed another four affected family members with the same mutation.

Conclusions: SLS should be suspected in any patient with a triad of ichthyosis, intellectual disability and spastic di/tetraplegia. Molecular genetic testing of the *ALDH3A2* gene should be performed to confirm the diagnosis. Extended family screening is highly recommended.

KEYWORDS

ALDH3A2 gene mutation, ichthyosis, Sjogren–Larson Syndrome

1 | INTRODUCTION

Sjogren–Larsson syndrome (SLS); Phenotype MIM number 270200 (SLS; MIM#270200) (Rouillet & Rizzo, 2014); is a rare neurocutaneous recessively inherited autosomal disease with spasticity (tetraplegia or diplegia), congenital ichthyosis and intellectual disability (mild to moderate). Less commonly, they are born preterm with retinal perifoveal

crystalline inclusions and in some reports retinal pigmentary degeneration in the macular region, short stature, kyphoscoliosis, seizures, and delayed speech (Rizzo, 2016).

The incriminated genetic mutation in SLS is the *ALDH3A2* gene mutation; Gene/Locus MIM number 609523. *ALDH3A2* gene encodes fatty aldehyde dehydrogenase enzyme (FALDH), an enzyme that catalyzes the oxidation of the fatty aldehyde to fatty acid (Rizzo, 2014).

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. *Molecular Genetics & Genomic Medicine* published by Wiley Periodicals LLC.

The *ALDH3A2* gene is located on chromosome *17p11.2*. More than 70 mutations have been discovered in SLS patients, in form of small deletions or insertions, splicing defects, missense mutations, and complex mutations composed of deletion/insertions and nucleotide substitutions (Engelstad et al., 2011).

Diagnosis of SLS is confirmed by sequence analysis of the *ALDH3A2* gene on the locus *17p11.2*, and/or measurement of FALDH or fatty alcohol: NAD oxidoreductase in cultured skin fibroblasts (Engelstad et al., 2011). Although some other reports of SLS had been released from Saudi Arabia but mostly without genetic confirmation apart from one report from the Jeddah region, which confirmed a novel large deletion in the *ALDH3A2* gene (Gaboon, Jelani, Almramhi, Mohamoud, & Al-Aama, 2015).

2 | METHODS

“Ethical Compliance”: The study was approved by the research and ethics committee of Alhada Armed forces Hospital, Taif, Saudi Arabia.

Here, we report a case series of SLS in a patient and her extended family with a novel genetic mutation. Parents of the patient have provided informed consent for publication of the case.

3 | CASE DESCRIPTION

We herein report, a 7-year-old Saudi female born to consanguineous parents; first degree cousins. She was born full-term but small for gestational age by normal vaginal delivery with a birth weight of 1.5 kg. Her parents claimed that pregnancy and delivery have been uneventful. Since birth, she was noted to have erythematous dry scaly skin all over the body sparing the face, without collodion membrane with progressive course.

Parents sought medical advice many times with different dermatologists with good response to abundant hydration with emollient baths, moisturizing creams, and keratolytic agents. Since very early infancy, the patient started to show motor developmental delay and generalized tonic-clonic

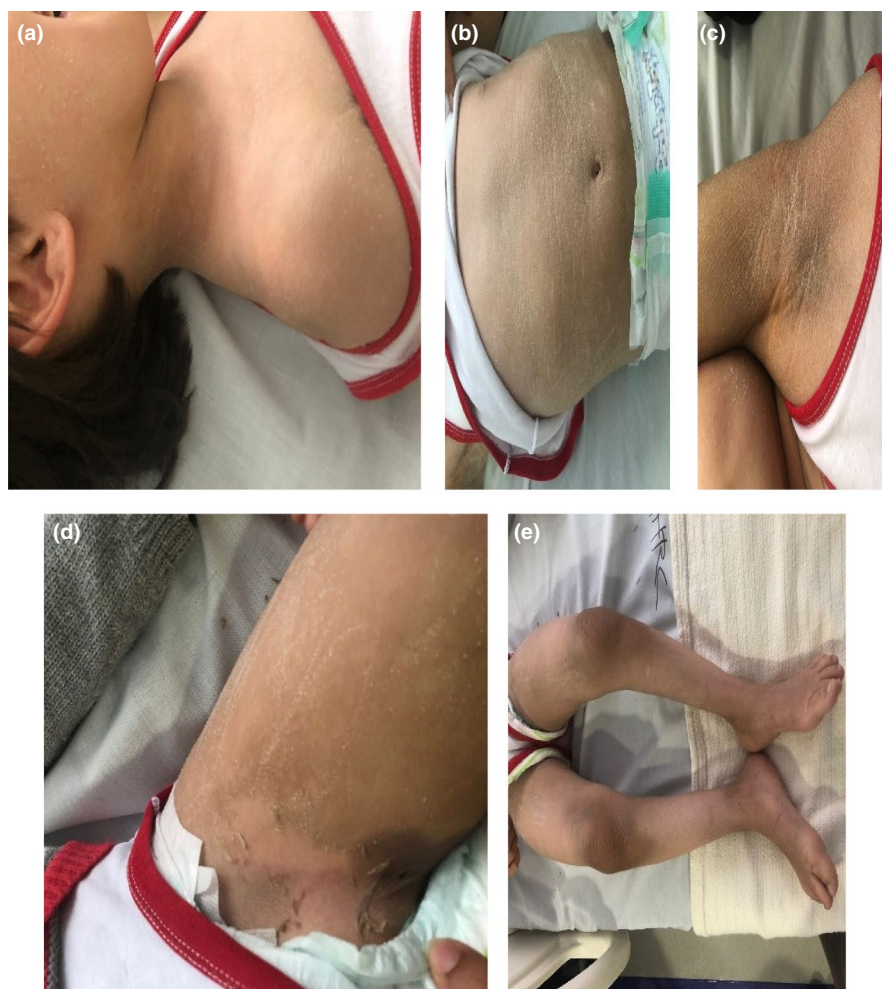


FIGURE 1 (a–e) Generalized ichthyosis, mainly prominent in: (a) the nape, (b) trunk and abdomen, (c and d) flexure areas, (e) extremities, and sparing the face

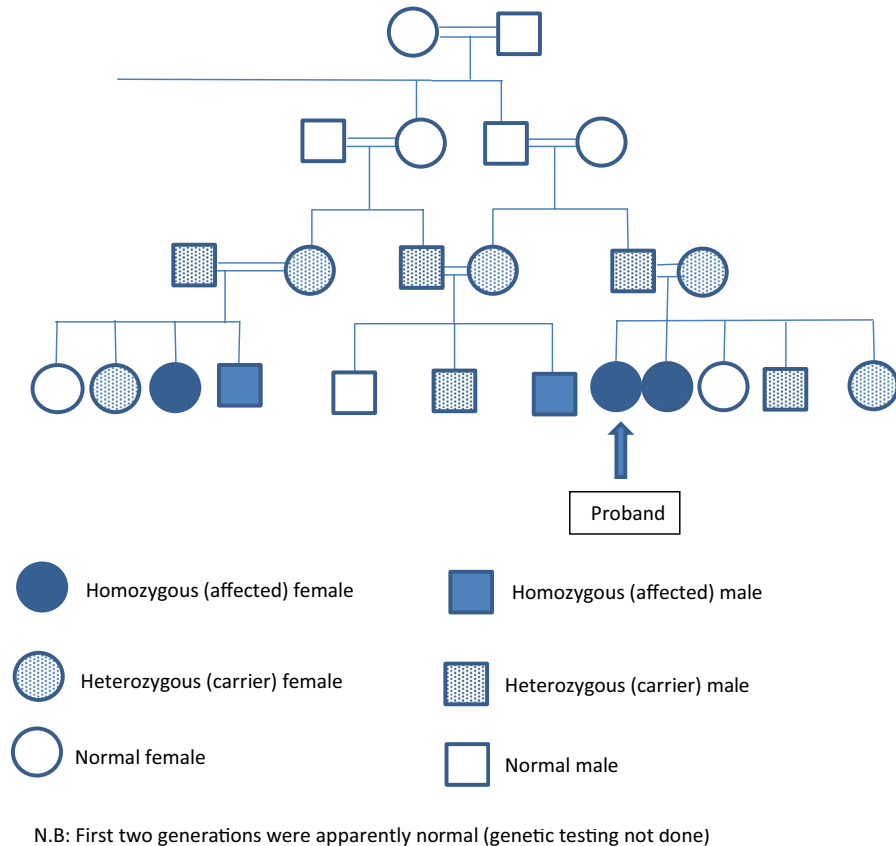


FIGURE 4 Family Pedigree

family revealed the characteristic triad of ichthyosis, spasticity, and developmental delay in one male cousin and two female cousins from maternal aunts.

Constellation of the previous findings suggested the diagnosis of SLS and genetic testing for *ALDH3A2* mutation was requested for the index case.

3.1 | Genetic analysis of the index case

The coding exons of the *ALDH3A2* gene were enriched using Roche/Nimble Gen sequence capture technology and sequenced on an Illumina NextSeq 500 system (next-generation sequencing, NGS) which revealed homozygous pathogenic variant *c.1320T>A* p.(Tyr 440*) in the *ALDH3A2* gene.

Molecular genetic analysis of the *ALDH3A2* gene by NGS showed a nucleotide exchange in homozygous state at position *c.1320* in *exon 9* of the *ALDH3A2* gene (*c.1320T>A*), leading to a stop of the protein sequence (*p.Tyr440*), as shown in Figure 3. To the best of our knowledge, this variant has not been described in the literature so far.

Genetic counseling of the family was provided with a focus on future pregnancies, the expectations of offspring, and the need to perform molecular genetic testing for the

parents, and other siblings along with the extended family for the mutation detected in the *ALDH3A2* gene.

Interestingly, molecular genetic testing revealed that the proband's younger sister and three cousins are homozygous to the same mutation found in the proband establishing the diagnosis of SLS in the five family members. The parents of the affected five children were heterozygous for the same mutation. Four of the other apparently healthy children from the examined extended family were also heterozygous for the same mutation while three of them did not carry any *ALDH3A2* gene mutations (Figure 4).

Patients are currently on regular follow-up with multidisciplinary care plan with dermatologist, pediatrician, neurologist, ophthalmologist, genetic specialist, and physiotherapist.

4 | DISCUSSION AND CONCLUSIONS

In 1957, Sjogren and Larson described a rare syndrome consisting of congenital ichthyosis associated with spastic pyramidal symptoms (di/or tetraplegia) and intellectual disability which was named under their names [(Mittal, Maini, Gupta, & Gupta, 2011), (Sjogren & Larsson, 1957)].

SLS is an inborn error of lipid metabolism caused by a deficiency of the microsomal enzyme FALDH that is a component of fatty-alcohol: NAD-oxidoreductase-enzyme-complex. FALDH deficiency may lead to an accumulation of long-chain-fatty-alcohols within structural consequences for cell membrane integrity which disrupts the function of the skin barrier and the white matter of the brain (Mittal et al., 2011).

SLS patients present cutaneous manifestations due to FALDH deficiency that affects epidermal functioning and leaky water barrier causes ichthyosis (Rizzo, 2014). This kind of ichthyosis in SLS is usually present at birth and is the first symptom that brings the patient to medical attention (Rizzo, 2007) as described in our series.

Most patients with SLS are born without a collodion membrane covering the skin. The ichthyosis is generalized in distribution and is prominent in the nape, trunk, flexure areas, extremities, and sparing the face. The skin is mildly erythematous early in life (Rizzo, 2007), as shown in our series who showed congenital ichthyosis all over the body sparing the face since birth.

Neurological manifestations are variable including non-progressive intellectual disability and delayed or impaired speech which is usually obvious at 1 to 2 years of age and can range from mild to severe [(Carman, Yimenicioglu, Ekici, & Yakut, 2012), (Fuijkschot, Maassen, Gorter, Gerven, & Willemsen, 2009)].

Spasticity may be apparent before the age of 3 years and is more prominent in the lower limbs than in other parts of the body. The majority of SLS patients require a wheelchair for mobility over time and they also develop contractures (Roulet & Rizzo, 2014). That agreed with our case in whom, the developmental delay was noticed at very early infancy evidenced by the sitting at 2 years of age, crawling at 3 years, and not being able to stand and walk. Delayed speech was also observed; however, intelligence was low average with an intellectual co-efficient of 89. Papatthemeli et al reported normal intelligence of 95 in their patient (Papatthemeli et al., 2017).

Cerebral palsy (CP) is the most common cause of motor disability in childhood. CP and SLS share the same features of spasticity and a non-progressive nature in the clinical course (Carman et al., 2012). The reported index case was first misdiagnosed as CP.

MRI of the brain usually shows hypomyelination involving the periventricular white matter may be extended from the frontal to the occipital area and mild ventricular enlargement may be an additional feature. These findings are due to lipid metabolism products accumulation in the central nervous system (Nakayama, Távora, Alvim, Araujo, & Gama, 2006). Similarly, in the reported proband, brain MRI showed a faint rim of high T2 and FLAIR signal intensity in the peritrigonal area and periventricular at both frontal regions most suggestive of delayed myelination.

Ophthalmological manifestations may be caused by the accumulation of long-chain fatty alcohols or fatty aldehydes (Cho, Shim, & Kim, 2018). The main features are crystalline juvenile macular dystrophy, cystoid foveal atrophy, and lack of macular pigment [(Cho et al., 2018), (van der Veen et al., 2010)]. High refractive errors (Papatthemeli et al., 2017) and photophobia may be present (Cho et al., 2018). Those were not detected in our patient who had a normal ophthalmological assessment.

The reported patient seems not to present as a complete form of SLS, being Ocular signs absent. Many articles point attention to incomplete presentation and atypical findings in SLS [(Papatthemeli et al., 2017), (Didona et al., 2007)]. Didona et al, reported two Italian patients with absent ocular manifestations (Didona et al., 2007). Similarly, Papatthemeli et al reported absence of the pathognomonic ophthalmological findings of SLS in their patient (Papatthemeli et al., 2017).

The differential diagnosis of SLS includes congenital ichthyosiform erythroderma with neurological signs such as Conradi–Hunermann–Happle syndrome, and Tay syndrome and neurocutaneous disorders such as multiple sulfatase deficiency and neutral lipid storage disease. However, MRI, proton magnetic resonance spectroscopy findings help to differentiate SLS from these disorders (Bindu, 2020). Also, the clinical presentation including ichthyosis and developmental delay with spastic diplegia made SLS the leading differential. Proton magnetic resonance spectroscopy was not available in our center.

The diagnosis is confirmed by the sequence analysis of the *ALDH3A2* gene (Engelstad et al., 2011). In our case study, molecular genetic analysis of the *ALDH3A2* gene by NGS showed a nucleotide exchange in homozygous state at position c.1320 in exon 9 of the *ALDH3A2* gene (c.1320T>A), leading to a stop of the protein sequence (p.Tyr440). Same mutation was detected in the other four affected family members. To the best of our knowledge, this variant has not been described in the literature so far.

We followed the agreed world-wide symptomatic management plan of SLS (Jagell & Lidén, 2008) in all the five patients. We implemented a multidisciplinary care plan with the involvement of a dermatologist, a pediatrician, a neurologist, an ophthalmologist, a genitologist, and a physiotherapist.

The physiotherapy and frequent soft tissue surgery, for example, hamstring release surgery and braces that will help in controlling the spasticity of limbs and facilitate the patient to move around (Jagell & Lidén, 2008). The symptomatic treatment for ichthyosis is including the topical application of soft paraffin, lanolin, 5% citric acid ointment or mineral oil (Kondremul, Zymenol), also, emollients (Vitamin D-3 analogs), the skin retinoids, and keratolytic (urea) agents are also recommended for SLS patients as they reduce the increased epidermal turnover and soften the epidermis [(Jagell & Lidén, 2008), (Bindu, 2020)].

The sauna baths and frequent showers help in reducing the pruritic condition of SLS patients. Leukotriene synthesis

inhibitors were predicted as curative treatment of the future for the ichthyosis and pruritus of the SLS patients (Bindu, 2020).

There are some prospective potential therapeutic options for SLS including; antioxidants, retinoids and vitamin D analogs, dietary lipid modification, fatty aldehyde scavengers, ALDH activators, modulation of sphingosine signaling pathway, replacement of cutaneous lipids, reduction of fatty alcohol production, inhibition of Leukotriene B4 synthesis, and gene therapy (Bindu, 2020).

In conclusion, SLS should be suspected in any patient presenting by the triad mentioned earlier. Molecular genetic test proves the diagnosis and extended family testing of the detected offending mutation help to identify undiagnosed cases and in the prevention of further cases in the same family by proper genetic counseling to avoid the marriage of relatives.

ACKNOWLEDGEMENTS

Not applicable.

CONFLICT OF INTEREST

All authors declare no competing interests related to the study.

AUTHORS' CONTRIBUTIONS

KA: set the idea of the study and designed the study. KA, NK, AB, MA, HA, KB: reviewed literature, drafted the manuscript, critically analyzed the data. All authors reviewed and approved the manuscript for final publication.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the research and ethical committee of the participating hospitals. All parents of enrolled children signed written informed consent for the participation of their children in the current study.

CONSENT FOR PUBLICATION

All parents of enrolled children signed written informed consent for the publication of the current study.

ORCID

Kamel T. Abidi  <https://orcid.org/0000-0002-9608-2105>

Naglaa M. Kamal  <https://orcid.org/0000-0002-8535-3838>

REFERENCES

- Bindu, P. S. (2020). Sjogren-Larsson Syndrome: Mechanisms and management. *The Application of Clinical Genetics*, 13, 13–24.
- Carman, K. B., Yimenicioglu, S., Ekici, A., & Yakut, A. (2012). Sjogren-larsson syndrome: A rare differential diagnosis of cerebral palsy. *International Journal of Clinical Pediatrics*, 1(4–5), 133–135.
- Cho, K. H., Shim, S. H., & Kim, M. (2018). Clinical, biochemical, and genetic aspects of Sjögren-Larsson syndrome. *Clinical Genetics*, 93(4), 721–730.

- Didona, B., Codispoti, A., Bertini, E., Rizzo, W. B., Carney, G., Zambruno, G., ... Terrinoni, A. (2007). Novel and recurrent ALDH3A2 mutations in Italian patients with Sjogren-Larsson syndrome. *Journal of Human Genetics*, 52, 865–870.
- Engelstad, H., Carney, G., S'Aulis, D., Rise, J., Sanger, W. G., Rudd, M. K., ... Rizzo, W. B. (2011). Large contiguous gene deletions in Sjögren-Larsson syndrome. *Molecular Genetics and Metabolism*, 104(3), 356–361.
- Fuijkschot, J., Maassen, B., Gorter, J. W., Gerven, M. V., & Willemsen, M. (2009). Speech-language performance in Sjögren-Larsson syndrome. *Developmental Neurorehabilitation*, 12(2), 106–112.
- Gaboon, N., Jelani, M., Almramhi, M., Mohamoud, H., & Al-Aama, J. (2015). Case of Sjögren-Larsson Syndrome with a large deletion in the ALDH3A2 gene confirmed by single nucleotide polymorphism array analysis. *Journal of Dermatology*, 42(7), 706–709.
- Jagell, S., & Lidén, S. (2008). Ichthyosis in the Sjogren-Larsson syndrome. *Clinical Genetics*, 21(4), 243–252.
- Mittal, A., Maini, B., Gupta, S., & Gupta, S. (2011). Sjogren-Larsson syndrome: A case report of a rare disease. *Indian Dermatology Online Journal*, 2(1), 31.
- Nakayama, M., Távora, D. G. F., Alvim, T. C. L., Araujo, A. C. B., & Gama, R. L. (2006). MRI and ¹H-MRS findings of three patients with Sjogren-Larsson syndrome. *Arquivos De Neuro-Psiquiatria*, 64(2b), 398–401.
- Papathemeli, D., Mataftsi, A., Patsatsi, A., Sotiriadis, D., Samouilidou, M., Chondromatidou, S., & Evangelidou, A. (2017). Atypical presentation of Sjogren-Larsson syndrome. *Case Reports in Pediatrics*, 2017, 7981750.
- Rizzo, W. B. (2007). Sjögren-Larsson syndrome: Molecular genetics and biochemical pathogenesis of fatty aldehyde dehydrogenase deficiency. *Molecular Genetics and Metabolism*, 90(1), 1–9.
- Rizzo, W. B. (2014). Fatty aldehyde and fatty alcohol metabolism: Review and importance for epidermal structure and function. *Biochimica Et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, 1841(3), 377–389.
- Rizzo, W. B. (2016). Genetics and prospective therapeutic targets for Sjögren-Larsson Syndrome. *Expert Opinion on Orphan Drugs*, 4(4), 395–406.
- Roulet, J.-B., & Rizzo, W. B. (2014). Sjögren-Larsson Syndrome. In R. Daroff & M. Aminoff (Eds.), *Encyclopedia of the neurological sciences* (2nd ed., pp. 179–184). USA: Academic Press.
- Sjogren, T., & Larsson, T. (1957). Oligophrenia in combination with congenital ichthyosis and spastic disorders; a clinical and genetic study. *Acta Psychiatrica Neurologica Scandinavica Supplementum*, 113, 1–112.
- van der Veen, R. L. P., Fuijkschot, J., Willemsen, M. A. A. P., Cruysberg, J. R. M., Berendschot, T. T. J. M., & Theelen, T. (2010). Patients with Sjogren-Larsson syndrome lack macular pigment. *Ophthalmology*, 117(5), 966–971.

How to cite this article: Abidi KT, Kamal NM, Bakkar A. AA, et al. Sjogren–Larsson Syndrome: A case series of five members from an extended family with a novel mutation. *Molecular Genetics & Genomic Medicine*. 2020;8:e1487. <https://doi.org/10.1002/mgg3.1487>