Archives of Dermatological Research (2019) 311:721–730
https://doi.org/10.1007/s00403-019-01953-6

ORIGINAL PAPER

Genetic assessment of ten Egyptian patients with Sjögren–Larsson syndrome: expanding the clinical spectrum and reporting a novel ALDH3A2 mutation

Khalda Amr[1] · Hala T. El-Bassyouni[2] · Samira Ismail[2] · Eman Youness[3] · Sherien M. El-Daly[3] · Abeer Y. Ebrahim[4] · Ghada El-Kamah[2]

Received: 25 February 2019 / Revised: 23 May 2019 / Accepted: 13 July 2019 / Published online: 6 August 2019

Abstract

Assessment of ten Egyptian patients with Sjögren–Larsson syndrome (SLS) detected; unusual clinical manifestations, a first report of brain atrophy in SLS, some patients exhibited neither retinal dots nor white matter changes previously reported as essential manifestations. We identified five mutations in ALDH3A2 gene including a novel one and suggest a founder effect. Sjögren–Larsson syndrome is a rare autosomal recessive inborn error of lipid metabolism caused by mutations in the ALDH3A2 gene that codes for fatty aldehyde dehydrogenase and result in a triad of ichthyosis, spasticity, and mental retardation. Clinical, radiological, biochemical, and neurophysiological evaluation in ten SLS patients descending from seven unrelated Egyptian pedigrees was followed by Sanger sequencing of *ALDH3A2* performed by ABI 3500. All patients presented with SLS triad; ichthyosis, spasticity of four limbs and hyperreflexia with an intelligent quotient (IQ) ranging from (39 to 69). Other manifestations were dysmorphic features, seizures, and skeletal and ophthalmological affection. Mutational analysis of ALDH3A2 gene revealed three missense, one splice site, and one novel stop codon mutation; c.991G>T (p.E331X). Biochemical studies showed decrease of fatty aldehyde dehydrogenase activity. Our results reinforce the distinct clinical, radiological, and biochemical features of *ALDH3A2*-related SLS which are the clue for targeted molecular testing. Moreover, we present additional unreported clinical findings and a novel mutation thus expanding the phenotypic and mutational spectrum of this rare disorder.

Keywords ALDH3A2 gene · ALDH activity · Novel mutation · Sjögren–Larsson syndrome

Introduction

Sjögren–Larsson syndrome (SLS) (MIM 270200) [1] is a rare inborn error of lipid metabolism caused by mutation of ALDH3A2 at 17p11.2 encoding fatty aldehyde dehydrogenase (FALDH). Dysfunctional FALDH affects proper oxidation of long-chain aliphatic alcohols to fatty acid, resulting in buildup of fatty alcohols in the brain and skin, which debilitates the cell membrane integrity that disturbs the barrier function of both skin and white matter of the brain [2–4]. FALDH enzyme activity in leukocytes is a specific marker and reliable biochemical diagnostic test for SLS [5]. Sjögren and Larsson first described the autosomal recessive syndrome in 1957, as the clinical triad of ichthyosis, intellectual disability, and spastic diplegia or tetraplegia [3, 6]. Ichthyosis being the earliest manifestation of the disease, which is associated with prominent pruritus when generalized [7]. There is no accurate prevalence estimate for SLS worldwide and the prevalence probably differs throughout the world, in Sweden, and the estimated prevalence of Sjögren–Larsson syndrome is 0.4 per 100,000 individuals [8]. However, it is estimated that SLS is to be observed in 1 in every 1000 patients with mental retardation and in 1 in every 2500 pediatric dermatologic patients [6]. Patients also

✉ Ghada El-Kamah
gg.kamah@nrc.sci.eg

1 Molecular Genetics Department, National Research Centre, Cairo, Egypt

2 Clinical Genetics Department, National Research Centre, Cairo, Egypt

3 Medical Biochemistry Department, National Research Centre, Cairo, Egypt

4 Medicinal and Aromatic Plant Researches, National Research Centre, Cairo, Egypt

present with short stature, white matter demyelination, and unusual lipid peak in myelin, speech disorders, epilepsy, and retinal abnormalities [9, 10].

Clinical heterogeneity makes clinical phenotype not usually sufficient for SLS diagnosis without molecular confirmation [10]. FLADH has three transcripts with different lengths due to differences in polyadenylation sites. The gene consists of 11 exons, numbered 1–10 with an additional exon (exon 9′ to be distinguished from exon 9) situated between exons 9 and 10, spanning about 30.5 kb, and the coding region encompasses 1458 bp and encodes a protein of 485 amino acids [11, 12]. Splicing of the gene at alternative sites results in two transcripts that encode proteins differing in the C-terminal region and results in a minor transcript that includes an additional sequence of (exon 9) which leads to a larger protein of 508 amino acids [12].

Several mutations were identified in patients from different ethnic backgrounds [13–17], and haplotype studies suggested a possible founder effects and inbreeding. However, several mutations were frequently detected in SLS patients such as c.1297_1298delGA in European patients [18] and c.943C>T, particularly in Swedish patients [19].

Herein, we highlight the molecular and biochemical findings and impact on clinical phenotype in ten Egyptian patients diagnosed as Sjögren–Larsson syndrome.

Patients and methods

The study included ten patients descending from seven unrelated Egyptian families. Patients were referred to the Clinical Genetics and Genodermatoses Clinics, National Research Centre (NRC), Cairo, Egypt, for diagnosis and counseling. All patients were first diagnosed clinically, and then, biochemical and mutational analyses were performed. Written informed consents were obtained from parents after explaining the aim of the study. All patients' data were confidential, neither the data nor the collected samples were used in any other research. Ten healthy children of matching age and sex served as controls for the estimation of the aldehyde dehydrogenase.

Clinical assessment

Each patient was subjected to complete medical history taking, three-generation pedigree construction, clinical examination, and anthropometric measurements in addition to intelligent quotient (IQ) assessment using Wechsler intelligence scales [20].

Electroencephalogram (EEG), complete eye evaluation including electroretinogram (ERG), and magnetic resonance imaging (MRI) of the brain were also assessed in all patients. Patients were followed regularly for growth parameters and musculoskeletal symptoms.

Biochemical assessment

The Aldehyde Dehydrogenase Activity Colorimetric Assay kit (Sigma-Aldrich Catalog Number MAK 082, UDA) was used to determine the ALDH activity in serum by a coupled enzyme assay in which acetaldehyde is oxidized by ALDH generating NADH and reacts with a probe generating a colorimetric (450 nm) product proportional to the ALDH activity present. One unit of ALDH is the amount of enzyme that will generate 1.0 nmole of NADH per minute at pH 8.0 at room temperature. ALDH activity was estimated as nmole/min/ml and expressed as percentage of normal mean enzyme activity [21].

Mutation analysis

The whole FALDH gene was amplified in all patients and their available parents using primer pairs according to Rizzo et al. [13]. Purified PCR products were sequenced in both direction and analyzed on an ABI 3500 sequencer. Human Genome Variation Society (HGVS) nomenclature was used throughout for cDNA and protein numbering. For nucleotide numbering, the A nucleotide of the ATG start codon was designated + 1 and is based on an FALDH splice form (cDNA FLADH GenBank accession numbers NM_000382.2). Amino acid numbering corresponds to the initiating Met with signal peptide included http://www.ncbi.nlm.nih.gov/OmimGenBank-EMBL:

http://www.ncbi.nlm.nih.gov/Genbank/index.html HUGO-Gene Nomenclature.

Committee: http://www.gene.ucl.ac.uk/nomenclature/. Functional prediction of the identified mutation was performed using the Mutation Taster algorithm, SIFT, and Polyphen2.

Haplotype analysis was defined in all families carried either private or recurrent mutation.

Results

The clinical, radiological, and biochemical findings of our patients are summarized in Table 1.

Clinical and biochemical analysis

The ten studied patients were descending from seven unrelated families referred from different governorates in Egypt. Parental consanguinity was positive in 80% of studied families (Fig. 1). The patients were five females and five males whose ages at presentation ranged from 2 to 14 years (mean

Table 1 The clinical and biochemical data of patients with Sjögren–Larsen syndrome

	Family 1 (Case III.1) patient 1	Family 2 (case III.2) patient 2	Family 3 (Case III.2) patient 3	Family 4 (case II.1) patient 4	Family 4 (case III.3) patient 5	Family 5 (case III.2) patient 6	Family 5 (case III.5) patient 7	Family 6 (case III.1) patient 8	Family 7 (case III.1) patient 9	Family 7 (case III.2) patient 10
Age in years	4	3	14	8	7	10	14	3	2	5
Gender	F	F	M	M	F	M	F	M	F	M
Consanguinity	−	+	+	+	+	+	+	−	+	+
Similar family cases	−	−	−	+	+	+	+	−	+	+
Developmental delay	+	+	+	+	+	+	+	+	+	+
Dysmorphic features	+	+	+	_	_	_	+	+	+	+
Dermatological manifestations										
Ichthyosis	+	+	+	+	+	+	+	+	+	+
Pruritis	−	−	−	+	+	−	+	−	−	+
Hyper-pigmentation	+	−	−	−	−	+	−	−	+	−
Nail dstr.	−	−	−	+	−	−	−	−	−	−
Eye manifest.	Squint abnormal VEP	−	−	Squint, nystagmus	−	_	−	−	−	−
Spasticity	+	+	+	+	+	+	+	+	+	+
Weight	Mean	Mean	Mean	Mean	Mean	Mean	Mean	−3.2 SD	Mean	Mean
Height	Mean	−3.2 SD	Mean	−2.5 SD	Mean	Mean	−4 SD	4.2 SD	Mean	Mean
Head circumference	−5.7 SD	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Brain MRI changes										
WM demyelination	+	+	−	+	−	+	−	−	−	+
Brain Atrophy	−	−	+	−	−	−	+	+	+	_
CC hypogen	−	−	−	−	−	−	−	−	+	−
Seizures/EEG changes	−	−	+	−	+	+	−	−	−	−
IQ	60	39	48	65	69	65	50	66	70	55
FALDH%	5	9	8	12	12	4.6	4	4	14	11.5

Mean* = anthropometric evaluation falls within the mean normal values for age and sex

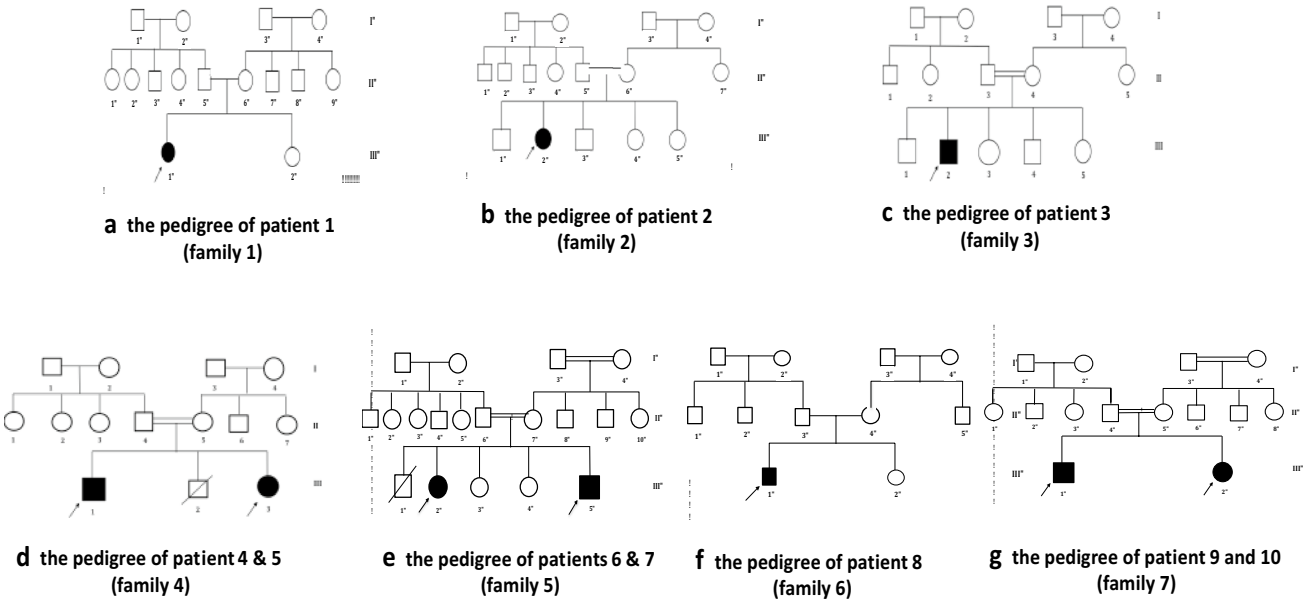

Fig. 1 Pedigrees of studied patients

6.4 ± 2.2). Similarly, affected sibs were detected in three families (families 4, 5, and 7) [Fig. 1]. All patients exhibited global developmental delay. Phenotypic manifestations are shown in Table 1, and Figs. 2 and 3. All ten patients had ichthyosis with scaly lesions mostly on upper and lower limbs and abdomen, and four of them (40%) suffered marked pruritis. All patients presented also with spasticity of four limbs and hyperreflexia. Seven patients had dysmorphic features in the form of recession of anterior hairline, long lashes, synophrys, long philtrum, and large low set ears. Skeletal affection was detected in the form of short stature in 4 (40%) patients and microcephaly in one patient.

The intelligent quotient (IQ) evaluation in the studied patients ranged from (39 to 69) indicating intellectual

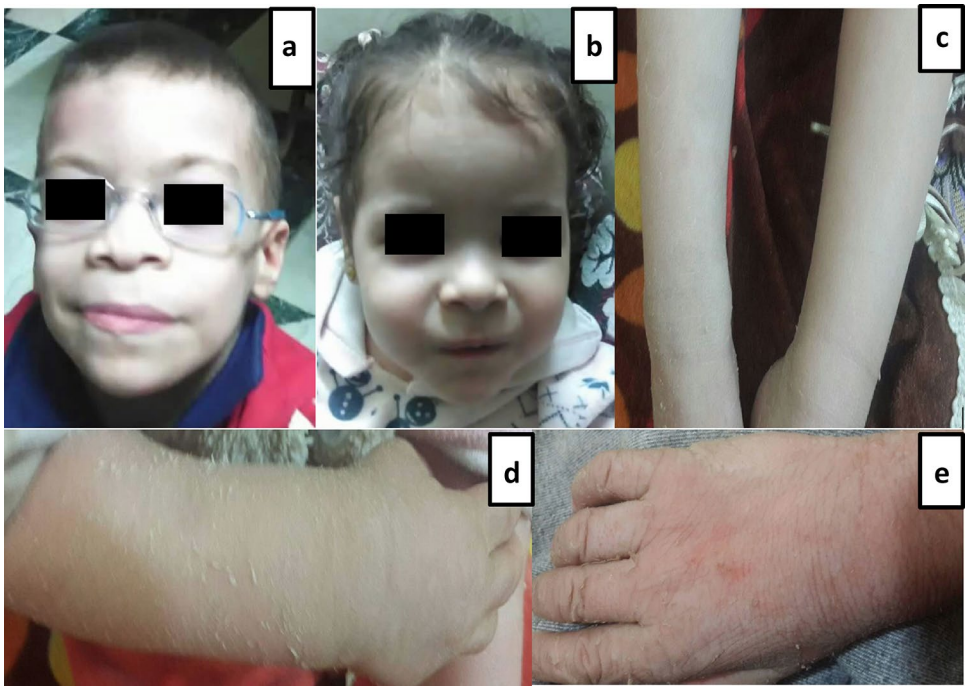

Fig. 2 Clinical phenotype of patients: **a** and **b** Faces of patient 3 and 4 (brother and sister); the brother **a** showed high anterior hair line, squint, depressed nasal bridge, pear shaped nose, long flat philtrum and low set ears, whereas the sister, **b** displayed less features. **c**, **d**, **e** Legs, upper limb, and hands showing ichthyosis and scales

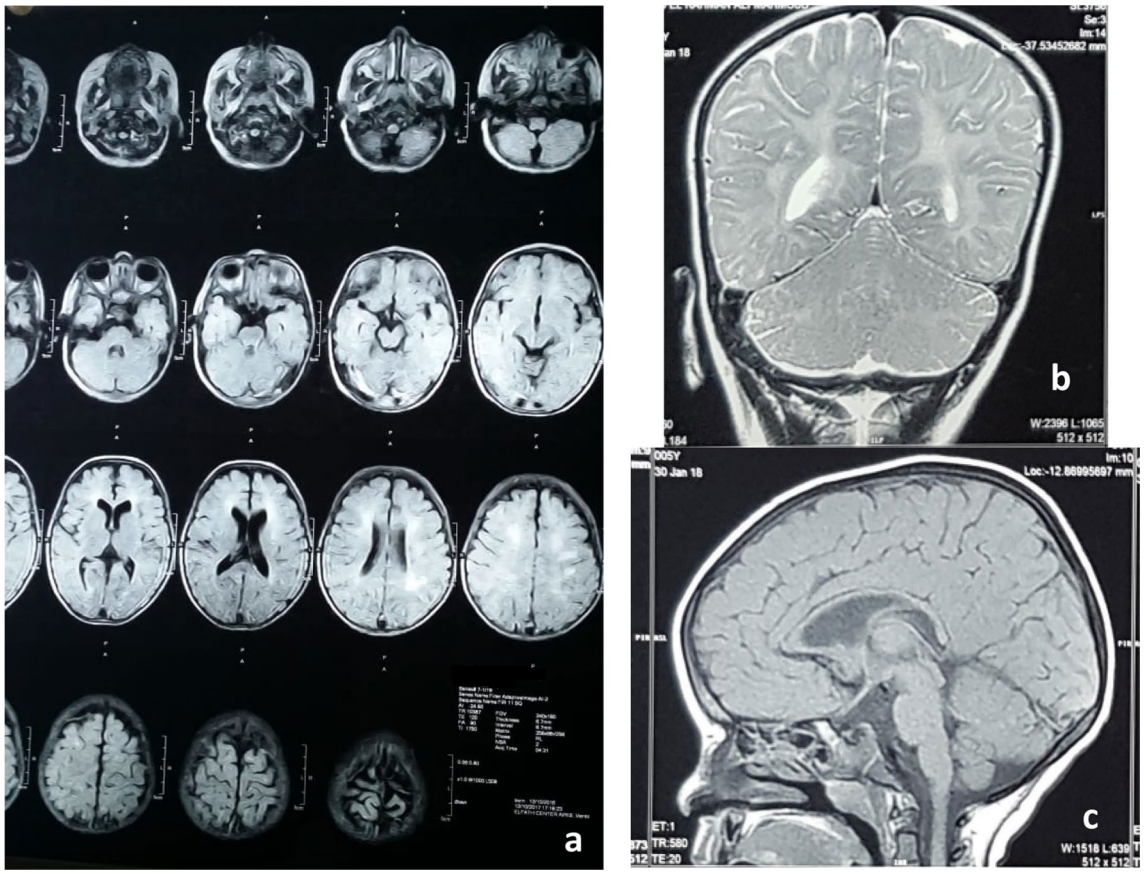

Fig. 3 Brain MRI showing; **a** white matter demyelination in patient 2, and **b** and **c** coronal and sagittal sections showing increased signal of white matter and hypogenesis of corpus callosum in patient 9

disability. Seizures with multifocal epileptogenic dysfunction in the EEG were detected in 3 (30%) patients. Ophthalmological examination revealed squint and nystagmus in 2 (20%) patients; however, glistening spots could not be detected during fundus examination. Brain magnetic resonance imaging in the studied patients revealed white matter demyelination, brain atrophy, and hypogenesis of corpus callosum in five (50%) patients (Fig. 3).

All patients were deficient in FALDH activity, which ranged from 4 to 14% of mean control (Table 1).

Molecular results

Mutational analysis of the ALDH3A2 gene revealed five mutations in intron 2, exon 4, and exon 7 (Fig. 4 and Table 2). The mutations identified were splice site c386-6A>G, missense mutations; c551C>G (p.T184R), c.563C>T (p.A188V), c.1094C>T (p.S365L), and nonsense c.991G>T (p.E331X). Of them, the c.991G>T stop codon novel pathogenic mutation was detected in both heterozygous and homozygous alleles in three families (families 4, 5, and 6) representing 8/20 (40%) alleles.

Mutations were found in homozygous (eight patients) or compound heterozygous (two patients). Patients' respective parents were heterozygous confirming the recessive mode of inheritance of the disorder. The novel mutation was not found in the dbSNP, 1000G, and ExAC and its pathogenicity was predicted by Polyphen2, Mutation Taster, and SIFT. Both c.386-6A>G and 563C>T mutations were described in ExAC database in few heterozygous alleles and were predicted as being possibly damaging or disease causing using either Polyphene2 prediction or Mutation Taster tools. All families harboring c.991G>T mutation shared the haplotype pattern of having 3 polymorphisms (rs4646793, rs1800869, and rs7216). Neither the novel c.991G>T nor the rare c.386-6A>G and 563C>T mutations were detected in 100 normal chromosomes of Egyptian origin.

Discussion

Reviewing the literature to date, patients from about 160 unrelated families with SLS have been described. The majority of reported patients were from Europe and Asia

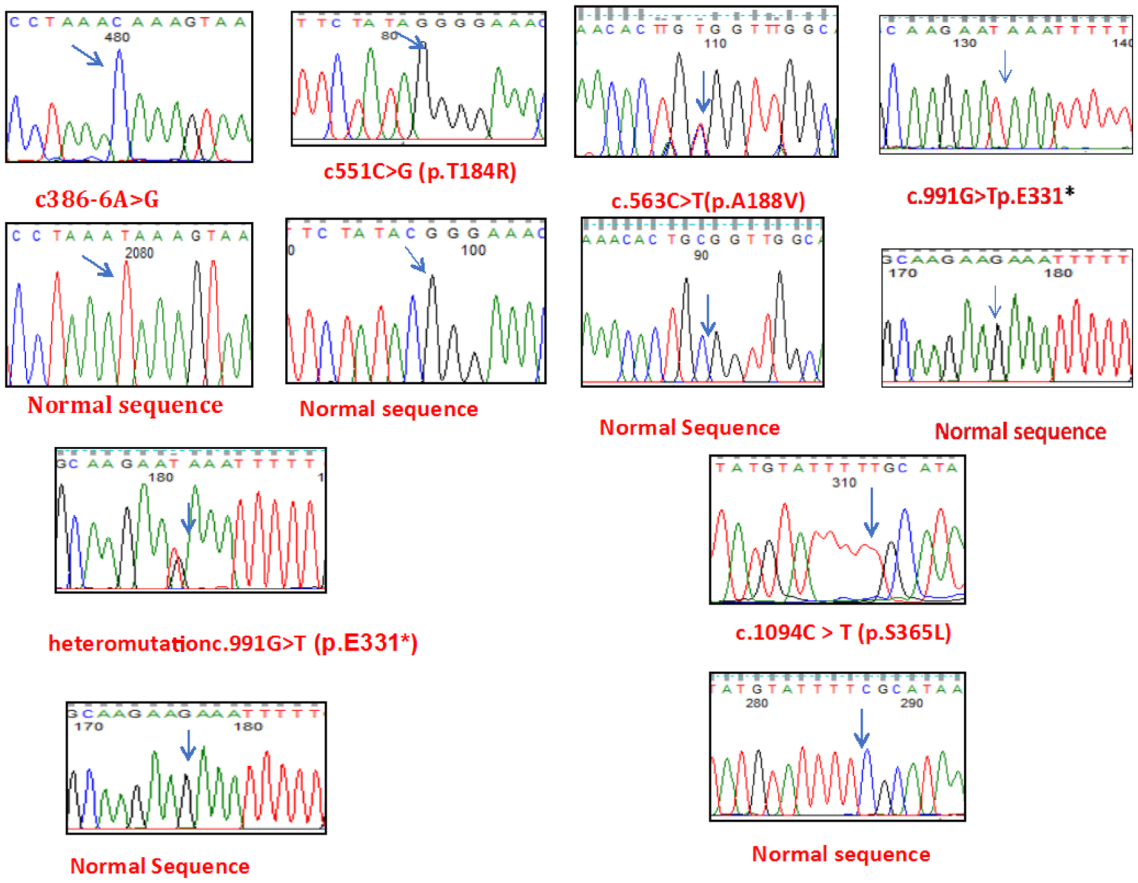

Fig. 4 Part of the sequencing electropherograms showing the five ALDH3A2 mutations identified in the studied patients

with few sporadic cases from Turkey and North Africa [13, 22]. Herein, we report on the clinical, biochemical, and first molecular study of Egyptian patients with SLS. More than 105 mutations of the ALDH3A2 gene have been reported for SLS [23]. The commonest reported mutations were missense comprising approximately 38.1% followed by splice mutation 11.4% and then nonsense mutations representing 5.7% of reported mutations [23].

In the current study, we detected five different variants in the ALDH3A2 gene. Of them, c.991G>T stop codon novel pathogenic mutation was recurrent in five out of ten unrelated patients who also shared a similar haplotype consisting of some intronic and coding variants [rs4646793, rs1004491, rs1800869, and rs7216], suggesting a founder effect.

Few nonsense mutations were reported in SLS patients, a total of six nonsense homozygous mutations were previously reported according to Davis et al. [17] and HGMD [23]. Our novel nonsense mutation was identified in two forms; heterozygous state in patients 4 and 5 (Family 4) and in homozygous state in patients 6 (Family 5), and 7 and 8 (Family 6). The mutation resulted in severely truncated protein including domain essential for catalytic enzyme activity.

The other four variants identified in the current study are; splice site c386-6A>G and missense mutations; c551C>G (p.T184R), c.563C>T (p.A188V), and c.1094C>T (p.S365L). Mutations detected in the ALDH3A2 gene appeared to be randomly distributed; in our patients, mutations were located in intron 2, exon 4, and exon 7 of ALDH3A2 gene.

Approximately 55% of SLS patients are homozygous for their ALDH3A2 allele [24]; however, only two of our cohort patients (20%) belonging to family 4 harbored compound heterozygous alleles.

The c386-6A>G mutation involving splice-acceptor site, was identified in patient 1 (family 1) and predicted to be disease causing although it was found in ExAC with rs117330764 as likely benign allele by Illumina laboratory service in SLS patients. It is worth noting that all 12 detected splice mutations in SLS patients were predicted to result in multiple ALDH3A2 transcript abnormalities as reported in SLS patients of different ethnic populations [13, 25–28].

In the literature, the c551C>G variant detected in patients 2 and 3 (family 2) has been previously associated with classic SLS phenotype. The mutation gives rise to two different base changes (551C>G and 551C>T) leading to substitution

Table 2 Mutations detected in the *FALDH* gene in the studied patients and associated haplotypes

Patient number	Location	Mutation	Amino acid change	Mutation type	Status		c.153 + 39 C>T rs4646793	c.471 + 39 C>T rs1004491	c.940 + 53 G>C rs1800869	1446 A>T rs7216
Patient 1 [family 1 case III.1]	Intron 2	c386-6A>G	–	Splice	Homozygous	Reported mutation	C/T	C	C	A
Patient 2 [family 2 case III.2]	Exon 4	c551C>G	p.T184R	Missense	Homozygous	Reported mutation	C	T	G	A
Patient 3 [family 3 case III.2]	Exon 4	c551C>G	p.T184R	Missense	Homozygous	Reported mutation	C	C	G	A
Patient 4 [family 4 case III.1]	Exon 4/Exon 7	c.563C>T c.991G>T	p.A188 V/p.E331X	Missense/stop codon	Heterozygous	Reported mutation/novel mutation	T	C/T	G	T
Patient 5 [family 4 case III.3]	Exon 4/Exon 7	c.563C>T c.991G>T	p.A188 V/p.E331X	Missense/stop codon	Heterozygous	Reported mutation/novel mutation	T	C/T	G	T
Patient 6 [Family 5 Case III.2]	Exon 7	c.991G>T	p.E331X	Stop codon	Homozygous	Novel mutation	T	C	G	T
Patient 7 [family 5 case III.5]	Exon 7	c.991G>T	p.E331X	Stop codon	Homozygous	Novel mutation	T	C	G	T
Patient 8 [family 6 case III.1]	Exon 7	c.991G>T	p.E331X	Stop codon	Homozygous	Novel mutation	T	C	G	T
Patient 9 [family 7 case III.1]	Exon 7	c.1094C>T	p.S365L	Missense	Homozygous	Reported mutation	T	C/T	C	A
Patient 10 [family 7 case III.2]	Exon 7	c.1094C>T	p.S365L	Missense	Homozygous	Reported mutation	T	C/T	C/G	A

of Thr184 by Arg or Met, respectively. The conversion Thr184 to Methionine was reported in one German and two other European SLS patients [13]. However, the missense mutation Thr184Arg identified in our SLS patients was previously reported in one Tunisian patient, which might raise speculations about being a Mediterranean or North African mutation or probably has arisen from common ancestors; as was the case in previous reports [29]. It is worth noting that c.551C>G was detected in two SLS families descending from different governorates of Egypt who were associated with two different haplotypes while sharing three homozygous polymorphisms (Table 2). The c551C>G variant results in reduction to 1–9% of normal catalytic activity of FALDH protein [14]. In our studied cases, the mutation resulted in 8–9% reduction in enzyme activity.

There is a confliction about the variant c.563C>T co-inherited in patients (4 and 5) belonging to family 4 which is registered as possibly causative variant in polyphene2, still due to the controversy among prediction tools in few heterozygous alleles, using the ExAC database prediction tool, the c.563C>T was found to be predicted as a damaging variant. The FALDH is considered a safeguarding enzyme expressed in almost all cells and tissues. The SJL heterozygotes patient 4 and 5 revealed partial deficiency in FALDH activity (12% of the mean normal activity) consistent with this enzyme being the primary genetic defect in SLS. Rizzo and Craft declared that the mean FALDH activity in the heterozygous SJL patients was 8% of mean normal activity [30].

Also of note is, sequence analysis could identify about 95% of mutations in each allele of ALDH3A2 [31]. Hence following the ExAC prediction, there might be another mutation possibly located in an intronic region far from the splicing sites or in a regulatory element located far from the transcription unit. Another explanation might be a large genomic deletion, which could not be detected due to selective amplification of the other allele only. The state of the presence of one allele carrying only one pathogenic variant was also reported previously where it was suggested that clinical phenotype may originate from the deleted contiguous genes [32].

The missense mutation c.1094C>T (p.S365L) identified in patients 9 and 10 (family 7) was previously reported in several SLS patients of German ancestry [13, 19] and Italian ancestry, and found to be associated with different haplotype owing to the difference in genetic background [13, 15, 19]. Interestingly, this mutation has never been reported in non-Caucasians, such as the Japanese population [15, 33].

Expression studies have shown that the S365L mutant FALDH results in reduction of enzyme activity to only 3% residual activity [13]. However, in our patients, the S365L mutation resulted in reduction of FALDH enzyme activity to 12–14%; possibly due to different evaluation methodologies as the enzyme level was estimated in plasma instead of fibroblasts. Moreover, all detected private variants in this study were associated with different haplotypes supporting the suggestion that the mutation arose independently on different genetic backgrounds.

Interestingly, it was found that most of these nucleotide changes involve CpG dinucleotides and might represent mutational hotspots in the gene [15]. The three-dimensional structure of the crystallized FALDH has been analyzed allowing the structural location of most of the reported missense mutations mapped in the functional domains of the protein, and in turn help detailed predictions of their effects on protein catalysis, dimerization, and folding [34]. The reported mutations located in exon 9 are related to the C-terminal alpha helix thereon, a coding locus and protein misfolding is observed for most exons except for exon 8, which has only been found to cause an altered dimer interface [6, 13].

Patients with Sjögren–Larsson Syndrome (SLS), an inborn error of lipid metabolism, usually suffer from the triad of ichthyosis, mild to profound intellectual disability, and spastic diplegia or tetraplegia [3, 6, 35]. All patients in our study presented with early developmental delay, ichthyosis, spasticity, and mental disability (IQ ranging from 39 to 70).

Biochemical analyses of the ten studied patients showed deficiency of fatty aldehyde dehydrogenase enzyme activity in serum, which is considered a housekeeping enzyme expressed in almost all cells and tissues [36] and the resulting excessive fatty aldehydes in SLS patients is thought to be the cause of the cutaneous and neurologic symptoms [14, 37].

Willemsen et al. [22] reported FALDH enzyme activity in cultured fibroblasts and leukocytes as specific marker and reliable biochemical diagnostic test for SLS. Furthermore, they suggested that there is no phenotype biochemical correlation in the SJL patients. FALDH enzyme is required to oxidize fatty alcohol to fatty acid [26, 34, 38], and lipid profile disturbances, accumulation of long-chain fatty alcohols, and modification of macromolecules by the excess fatty aldehydes are thought to be the pathophysiologic mechanisms underlying the clinical manifestations where fatty acids are incorporated into brain lipid fractions, including phospholipids, proteolipids, and myelin [27].

Among our studied patients, fatty aldehyde dehydrogenase activity was decreased which is in agreement with the aforementioned studies. However, our study confirmed the correlation between the degree of reduction in FALDH enzyme activity and underlying molecular pathology; severe mutations such as the novel detected mutation c.991G>T resulted in marked reduction in enzyme activity to around 4% in the homozygous patients who almost all manifested with the same degree of clinical severity.

Accumulation of long-chain fatty alcohols and modification of macromolecules by an excess of fatty aldehydes may lead to alteration of the epidermal water barrier and increased trans-epidermal water loss, subsequently leading to ichthyosis [17]. Pruritus, a prominent feature that is not found in other types of ichthyosis [39], was present only in 3/10 (30%) studied patients. Seizures were present in 2/10 (20%) studied patients, while Rizzo [39] reported seizures in about 30–50% of SLS patients.

Ophthalmologic findings previously reported comprise shining white dots in the retina, however; our patients did not display this finding instead of 2/10 (20%) patients presented with squint; this might be attributed to the young age of studied patients [22]. Anthropometric studies revealed short stature, which coincides with the finding of El-Bassyouni et al. [40].

Brain MRI studies revealed demyelination in 3/10 (30%) patients, which again can be due to the accretion of fatty aldehydes and fatty alcohols in the brain [41].

Brain atrophy was also detected in patients 3, 7, 8, and 9, and hypogenesis of corpus callosum was detected in patient 9; to our knowledge, this was not previously reported. This might be due to the variability of the disease; moreover, some of these changes could be due to physiological and different genetic causes not related with the specific mutation.

Although the biochemical mechanisms for SLS are delineated, more approaches concerning the biochemical pathogenesis are being investigated [10]. It is of importance to evaluate the impact of the biomarkers on the end phenotypic aspects of SLS this might lead to novel effective therapies.

In conclusion, our patients shared the distinguishing clinical and radiological features of the syndrome with additional unreported MRI findings. However, unusual to SLS, some patients exhibited neither retinal dots nor white matter changes, previously reported as essential manifestations. Molecular studies revealed a novel pathogenic variant in the ALDH3A2 gene including one novel mutation and suggested a founder effect. A clear phenotype–genotype correlation was noted regarding enzyme activity. Genetic testing helps in providing proper counseling to families with Sjögren–Larsen syndrome including prenatal diagnosis.

References

1. https://www.omim.org/2019
2. Rizzo WB, Heinz E, Simon M et al (2000) Microsomal fatty aldehyde dehydrogenase catalyzes the oxidation of aliphatic aldehyde derived from ether glycerolipid catabolism: implications for Sjögren–Larsson syndrome. Biochem Biophys Acta 1535:1–9
3. Roy U, Das U, Pandit A, Debnath A (2016) Sjögren–Larsson syndrome: a rare disease of the skin and central nervous system. BMJ Case Rep 5:6. https://doi.org/10.1136/bcr-2016-215110
4. Nagappa M, Bindu PS, Chiplunkar S, Gupta N, Sinha S, Mathuranath PS, Bharath RD, Taly AB (2017) Child neurology: Sjögren–Larsson syndrome. Neurology 88(1):e1–e4
5. Rizzo WB, Dammann AL, Craft DA (1988) Sjögren–Larsson syndrome Impaired fatty alcohol oxidation in cultured fibroblasts due to deficient fatty alcohol:nicotinamide adenine dinucleotide oxidoreductase activity. J Clin Invest 81(3):738–744
6. Schwartz RA (2018) Dermatologic manifestations of Sjögren–Larsson Syndrome. https://emedicine.medscape.com/article/1114823-overview#a6
7. Vural S, Vural A, Akçimen F, Bağci IS, Tunca C, Gündoğdu Eken A, Ruzicka T, Başak AN (2018) Clinical and molecular characterization and response to acitretin in three families with Sjögren–Larsson syndrome. Int J Dermatol 57:843–848
8. Tavasoli A, Sayyahfar S, Behnam B (2016) A rare case of Sjögren–Larsson syndrome with recurrent pneumonia and asthma. Korean J Pediatr 59(6):276–279
9. Gaboon NE, Jelani M, Almramhi MM, Mohamoud HS, Al-Aama JY (2015) Case of Sjögren–Larsson syndrome with a large deletion in the ALDH3A2 gene confirmed by single nucleotide polymorphism array analysis. J Dermatol 42(7):706–709
10. Rizzo WB (2016) Genetics and prospective therapeutic targets for Sjögren–Larsson Syndrome. Expert Opin Orphan Drugs 4(4):395–406
11. Chang C, Yoshida A (1997) Human fatty aldehyde dehydrogenase gene (ALDH10): organization and tissue-dependent expression. Genomics 40:80–85
12. Rogers GR, Markova NG, De Laurenzi V, Rizzo WB, Compton JG (1997) Genomic organization and expression of the human fatty aldehyde dehydrogenase gene (FALDH). Genomics 39:127–135
13. Rizzo WB, Carney G, Lin Z (1999) The molecular basis of Sjögren–Larsson syndrome: mutation analysis of the fatty aldehyde dehydrogenase gene. Am J Hum Genet 65:1547–1560
14. Rizzo WB, Carney G (2005) Sjögren–Larsson syndrome: diversity of mutations and polymorphisms in the fatty aldehyde dehydrogenase gene (ALDH3A2). Hum Mutat 26:1–10
15. Didona B, Codispoti A, Bertini E et al (2007) Novel and recurrent ALDH3A2 mutations in Italian patients with Sjögren–Larsson syndrome. J Hum Genet 52:865–870
16. Auada MP, Puzzi MB, Cintra ML et al (2006) Sjögren–Larsson syndrome in Brazil is caused by a common c.1108-1G>C splice-site mutation in the ALDH3A2 gene. Br J Dermatol 154:770–773
17. Davis K, Holden KR, S'Aulis D et al (2013) Novel mutation in Sjögren–Larsson syndrome is associated with divergent neurologic phenotypes. J Child Neurol 28:1259–1265
18. Rizzo WB, Carney G, DeLaurenzi V (1997) A common deletion mutation in European patients with Sjögren–Larsson syndrome. Biochem Mol Med 62:178–181
19. Sillen A, Anton-Lambrecht I, Braun-Quentin C et al (1998) Spectrum of mutations and sequence variants in the FALDH gene in patients with Sjögren–Larsson syndrome. Hum Mut 12:377–384
20. Watkins MW, Beaujean AA (2014) Bifactor structure of the Wechsler Preschool and Primary Scale of Intelligence–Fourth Edition. Sch Psychol Q 29(1):52–63
21. Rizzo WB, Craft DA (2000) Sjögren–Larsson syndrome: accumulation of free fatty alcohols in cultured fibroblasts and plasma. J Lipid Res 41(7):1077–1081
22. Willemsen MA, IJlst L, Steijlen PM, Rotteveel JJ, de Jong JG, van Domburg PH, Mayatepek E, Gabreëls FJ, Wanders RJ (2001) Clinical, biochemical and molecular genetic characteristics of 19 patients with the Sjögren–Larsson syndrome. Brain 124(Pt 7):1426–1437
23. Human Genome Mutation Database (HGMD) (2018). www.hgmd.org

24. Lin Z, Carney G, Rizzo WB (2000) Genomic organization, expression, and alternate splicing of the mouse fatty aldehyde dehydrogenase gene. Mol Genet Metab 71:496–505
25. Kraus C, Braun-Quentin C, Ballhausen WG, Pfeiffer RA (2000) RNA-based mutation screening in German families with Sjögren–Larsson syndrome. Eur J Hum Genet 8:299–306
26. Carney G, Wei S, Rizzo WB (2004) Sjögren–Larsson syndrome: seven novel mutations in the fatty aldehyde dehydrogenase gene ALDH3A2. Hum Mutat 24(2):186
27. Sarret C, Rigal M, Vaurs-Barriere C et al (2012) Sjögren–Larsson syndrome: novel mutations in the ALDH3A2 gene in a French cohort. J Neurol Sci 312:123–126
28. Burgueño-Montañés C, García-Fernández M, Colunga-Cueva M, García-López A (2014) Sjögren–Larsson syndrome: optical coherence tomography and a novel mutation. Arch Soc Esp Oftalmol 89:504–507
29. Amr K, Messaoud O, El Darouti M, Abdelhak S, El-Kamah G (2014) Mutational spectrum of Xeroderma pigmentosum group A in Egyptian patients. Gene 533(1):52–56 **(Epub 2013 Oct 14)**
30. Rizzo WB, Craft DA (1991) Sjögren–Larsson syndrome: deficient activity of the fatty aldehyde dehydrogenase component of fatty alcohol NAD^+ oxidoreductase in cultured fibroblasts. J Clin Invest 88:1643–1648
31. Cho KH, Shim SH, Kim M (2018) Clinical, biochemical, and genetic aspects of Sjögren–Larsson syndrome. Clin Genet 93(4):721–730
32. Engelstad H, Carney G, S'Aulis D, Rise J, Sanger WG, Rudd MK, Richard G, Carr CW, Abdul-Rahman OA, Rizzo WB (2011) Large contiguous gene deletions in Sjögren–Larsson syndrome. Mol Genet Metab 104(3):356–361
33. Didona B, Codispoti A, Bertini E, Rizzo WB, Carney G, Zambruno G, Dionisi-Vici C, Paradisi M, Pedicelli C, Melino G, Terrinoni A (2007) Novel and recurrent ALDH3A2 mutations in Italian patients with Sjögren–Larsson syndrome. J Hum Genet 52(10):865–870
34. Keller MA, Zander U, Je F et al (2014) A gatekeeper helix determines the substrate specificity of Sjögren–Larsson syndrome enzyme fatty aldehyde dehydrogenase. Nat Commun 5:4439
35. Rizzo WB (2001) Sjögren–Larsson syndrome: fatty aldehyde dehydrogenase deficiency. The metabolic and molecular bases of inherited disease, vol 2, 8th edn. McGraw Hill, New York, pp 2239–2258
36. Kim JY, Kim SH, Park MJ, Kim SH, Cho WH, Choi J, Ki CS, You SJ (2018) Identification of homozygous likely pathogenic variant of ALDH3A2 in a Korean Boy with Sjögren–Larsson Syndrome. Ann Lab Med. 38:80–82
37. Zribi H, Souissi A, Azzouz H, Drissi C, Ben Hamouda M, Tabib N, Mokni M, Ben Osman A (2014) Sjögren–Larsson syndrome: a rare neurocutaneous disease. Rev Neurol (Paris) 170(4):297–298
38. Hargrove JL, Greenspan P, Hartle DK (2004) Nutritional significance and metabolism of very long chain fatty alcohols and acids from dietary waxes. Exp Biol Med (Maywood) 229(3):215–226
39. Rizzo WB (2014) Fatty aldehyde and fatty alcohol metabolism: review and importance for epidermal structure and function. Biochim Biophys Acta 1841:377–389
40. El-Bassyouni HT, Said OA, Abdel Maksoud S (2005) Clinical and biochemical changes in Egyptian patients with Sjögren–Larsson syndrome. Egypt J Med Hum Genet 6:135–144
41. Kariminejad A, Barzgar M, Bozorgmehr B, Keshavarz E, Kariminejad MH, S'Aulis D, Rizzo WB (2017) Novel mutations and a severe neurological phenotype in Sjögren–Larsson syndrome patients from Iran. Eur J Med Genet 61(3):139–144