

## DATABASES

# Genotype and phenotype variability in Sjögren-Larsson syndrome

Maximilian Weustenfeld<sup>1</sup> | Reiner Eidelpes<sup>2</sup> | Matthias Schmuth<sup>3</sup> | William B. Rizzo<sup>4</sup> | Johannes Zschocke<sup>1</sup> | Markus A. Keller<sup>1</sup> 

<sup>1</sup>Division of Human Genetics, Medical University of Innsbruck, Innsbruck, Austria

<sup>2</sup>Center for Molecular Biosciences Innsbruck (CMBI), Institute of Organic Chemistry, University of Innsbruck, Innsbruck, Austria

<sup>3</sup>Department of Dermatology, Venereology and Allergology, Medical University of Innsbruck, Innsbruck, Austria

<sup>4</sup>Department of Pediatrics, UNMC Child Health Research Institute, University of Nebraska Medical Center, Omaha, NE, USA

### Correspondence

Markus A. Keller, Division of Human Genetics, Medical University of Innsbruck, Innsbruck, Austria.

Email: markus.keller@i-med.ac.at

Communicated by Johan T. den Dunnen

### Abstract

The Sjögren–Larsson syndrome (SLS) is a rare autosomal recessive disorder caused by pathogenic variants in the *ALDH3A2* gene, which codes for fatty aldehyde dehydrogenase (FALDH). FALDH prevents the accumulation of toxic fatty aldehydes by converting them into fatty acids. Pathogenic *ALDH3A2* variants cause symptoms such as ichthyosis, spasticity, intellectual disability, and a wide range of less common clinical features.

Interpreting patient-to-patient variability is often complicated by inconsistent reporting and negatively impacts on establishing robust criteria to measure the success of SLS treatments. Thus, with this study, patient-centered literature data was merged into a concise genotype-based, open-access database ([www.LOVD.nl/ALDH3A2](http://www.LOVD.nl/ALDH3A2)). One hundred and seventy eight individuals with 90 unique SLS-causing variants were included with phenotypic data being available for more than 90%. While the three lead symptoms did occur in almost all cases, more heterogeneity was observed for other frequent clinical manifestations of SLS.

However, a stringent genotype–phenotype correlation analysis was hampered by the considerable variability in reporting phenotypic features. Consequently, we compiled a set of recommendations of how to generate comprehensive SLS patient descriptions in the future. This will be of benefit on multiple levels, for example, in clinical diagnosis, basic research, and the development of novel treatment options for SLS.

### KEYWORDS

*ALDH3A2*, database, FALDH, fatty aldehyde dehydrogenase, Sjögren–Larsson syndrome, SLS

## 1 | INTRODUCTION

Sjögren–Larsson syndrome (SLS; MIM# 270200) is an autosomal recessive disorder caused by pathogenic loss-of-function variants (denoted “SLS variants”) in the *ALDH3A2* gene, which codes for the enzyme fatty aldehyde dehydrogenase (FALDH) (De Laurenzi et al., 1996; Rizzo & Carney, 2005). One of the main functions of this enzyme is the removal of long-chain aliphatic aldehydes through oxidation into fatty acids (Rizzo, 2001). FALDH deficiency causes a severe disturbance of fatty aldehyde metabolism leading to a variety of clinical features. The primary symptoms are ichthyosis, spasticity, and intellectual disability (Sjogren & Larsson, 1957). Furthermore, ocular problems (retinopathy, photophobia, reduced visual acuity) and

other neurological abnormalities are frequently reported (Fuijkschot et al., 2012; Van der Veen et al., 2010; Willemsen et al., 2000). Clinical manifestations are usually static although neurological symptoms can progress over time (Fuijkschot et al., 2012).

FALDH is a membrane-bound homodimeric NAD<sup>+</sup>-dependent enzyme (E.C.1.2.1.48). Two splice variants determine its subcellular location. A major transcript encodes a 485 amino acid protein integrated into the endoplasmic reticulum, whereas the minor (<10%) transcript encodes a 508 amino acid variant with an elongated carboxy-terminus that guides the enzyme to the peroxisomal membrane (Rogers, Markova, De Laurenzi, Rizzo, & Compton, 1997). Homodimer formation of FALDH is a requirement for the enzyme to be enzymatically active, and for correct alignment along membrane

lipid bilayers (Keller et al., 2010, 2014). Correct orientation and membrane interaction of FALDH is mediated by a large dimerization interface and is supported by a carboxy-terminal hydrophobic alpha helix which likely constrains conformational space for substrates and facilitates traffic of long-chain fatty aldehydes toward the catalytic site (Keller et al., 2014). Each subunit of FALDH has a cofactor binding site which is oriented toward the cytosol, and a substrate binding funnel reaching toward the membranes.

Impaired FALDH function leads to disruption of the cell's ability to detoxify fatty aldehydes (Rizzo, 2014), which have a high capacity of undesired nonenzymatic reactivity (Keller, Piedrafita, & Ralser, 2015). Fatty aldehydes originate from diverse metabolic processes (Keller et al., 2014) such as the catabolism of ether lipids and plasmalogens (Keller, Watschinger, Golderer, Werner-Felmayer, & Werner, 2013; Rizzo, Heinz, Simon, & Craft, 2000). Accumulation of fatty aldehydes leads to the formation of Schiff base adducts with free amino groups of macromolecules such as proteins and lipids, disrupting their biochemical functions (James & Zoeller, 1997). It has also been shown that fatty aldehydes in SLS patient cells are converted into fatty alcohols rather than fatty acids, which represents an additional source for cytotoxic effects (Keller et al., 2012; Rizzo et al., 2008).

Therapeutic options for SLS are currently limited to symptomatic treatment of cutaneous and neurologic manifestations (Rizzo, 2016). Oral retinoids and various topical treatments (e.g., urea containing creams) are used for skin manifestations (Gånemo, Jagell, & Vahlquist, 2009). Spasticity is treated with surgical procedures, botulinum toxin injections, and oral or intrathecal baclofen (Hidalgo et al., 2017). Seizures are controlled with antiepileptics (Gånemo et al., 2009). Novel innovative and prospective therapeutic approaches for SLS are currently under consideration and will potentially help to ease the burden of the severe symptoms of affected patients (Rizzo, 2016).

Disease severity varies between affected persons, symptoms may fluctuate over time, and limited information is available about possible genotype–phenotype correlations. Because of the highly variable quality of published phenotypic information, it is difficult to compare individual cases, rendering a global analysis of the phenotypic spectrum of SLS a challenging task. To address this issue, we have developed a comprehensive, case-centered SLS database which structures the available SLS patient information in a systematic and extendable manner. On the basis of the collected data, it was possible to analyse the relative frequency of individual variants and genotypes, their geographic distribution, as well as the phenotypic spectrum of SLS. Furthermore, frequent deficiencies in the case descriptions could be identified, allowing us to propose a basic framework to be used for reporting SLS cases. This will help to improve quality and scientific value of future publications and should also assist in the assessment of novel treatment strategies in the future.

## 2 | METHODS

Using the Leiden Open-source Variation Database (LOVD) version 3.0 build 20b, we have established a locus-specific database for SLS caus-

ing DNA sequence variation in *ALDH3A2*, available with open access at [www.LOVD.nl/ALDH3A2](http://www.LOVD.nl/ALDH3A2). All data were extracted from the existing *ALDH3A2*- and SLS-related literature through the following steps: (i) collection of all suitable publications containing patient data, (ii) categorization, summarization, and selection of all relevant publications, followed by (iii) extraction of patient-specific data. Patient clinical data have been obtained in a manner conforming to the ethical guidelines of the institutional review board (Medical University of Innsbruck).

1. **Collection of existing literature:** Three hundred and eighty five publications were retrieved from the medical database PubMed in response to the search term “Sjögren–Larsson syndrome” (as of September 2018). All studies were listed in chronological order and full text documents were electronically collected whenever possible.
2. **Categorization, summarization, and selection of publications:** In a next step, all studies were manually inspected for whether they contained patient information relevant for the *ALDH3A2*-variant database. The primary inclusion criterion was the availability of genetic data. Publications prior to the gene identification report in 1996 (De Laurenzi et al., 1996) were excluded because they could not contain genetic data (138 studies published before January 1st, 1996). Of the 247 remaining studies, 114 did not state genetic patient data. For 52 further studies, full text versions were not available and in the majority of these cases, the abstracts did not contain any indication of data usable in the context of this study. Twenty three studies proved to be not relevant because of ambiguous search results (e.g., “Sjögren syndrome”). Finally, eight publications were excluded because of probable patient double counts or other specific reasons (prenatally diagnosed patients, etc.). In total, 50 publications contained relevant genetic data and qualified for inclusion in this study (Alió, Bird, McClellan, & Cunningham, 2006; Aoki, Suzuki, Ito, & Ito, 2000; Auada et al., 2006; Botelho Gomes et al., 2011; Burgueño-Montañés, García-Fernández, Colunga-Cueva, & García-López, 2014; Carney et al., 2004; Cubo & Goetz, 2000; Davis et al., 2013; De Laurenzi et al., 1996; Didona et al., 2007; Engelstad et al., 2011; Gaboon, Jelani, Almrhami, Mohamoud, & Al-Aama, 2015; Gånemo et al., 2009; Garcia-Peris, Latour-Álvarez, Pestana-Eliche, & Sánchez, 2017; Hidalgo et al., 2017; Incecik, Herguner, Rizzo, & Altunbasak, 2013, 2018; Jain et al., 2015; Jean-François, Low, Gonzales, & Sarraf, 2007; Kariminejad et al., 2017; Kim et al., 2018; Kraus et al., 2000; Lossos et al., 2006; Möhrenschrager, Braun-Falco, & Ring, 2005; Nagappa et al., 2017; Nakajima et al., 2011; Nakano et al., 2008; Paiva et al., 2018; Papatthemeli et al., 2017; Rafai et al., 2008; Rizzo et al., 2008, 2010; Sakai et al., 2006, 2010; Sanabria & Coco, 2011; Sarret et al., 2012; Shah et al., 2017; Shamriz, Molho-Pessach, Haag, Daum, & Stepensky, 2016; Shibaki, Akiyama, & Shimizu, 2004; Sijens et al., 2009; Sillén et al., 1998; Tachibana, Aida, Enomoto, Iai, & Kurosawa, 2012; Taghdiri, Kashef, Fardaei, & Miryounesi, 2018; Takeichi et al., 2013; Tanteles et al., 2015; Tavasoli et al., 2016; Tsukamoto, Chang, & Yoshida, 1997; Vural et al., 2018; Willemsen et al., 2001; Yiş and Terrinoni, 2012). One further yet unpublished case has been included into the database.

**TABLE 1** HPO term annotation scheme

General term	Specific terms
HP:0001257 (spasticity)	HP:0001257 (spasticity)
	HP:0001264 (spastic diplegia)
	HP:0002510 (spastic quadriplegia/tetraplegia)
	HP:0001258 (spastic paraplegia)
HP:0002385 (paraparesis)	HP:0002385 (paraparesis)
	HP:0002313 (spastic paraparesis)
	HP:0001249 (intellectual disability)
HP:0001249 (intellectual disability)	HP:0001249 (intellectual disability)
	HP:0012758 (neurodevelopmental delay)
	HP:0001263 (global developmental delay)
HP:0030506 (yellow/white lesions of the retina)	HP:0030506 (yellow/white lesions of the retina)
	HP:0007702 (pigmentary retinal deposits)
	HP:0030507 (retinal crystals)
HP:0011400 (abnormal CNS myelination)	HP:0011400 (abnormal CNS myelination)
	HP:0007266 (cerebral dysmyelination)
	HP:0002188 (delayed CNS myelination)
	HP:0007305 (CNS demyelination)

**3. Data extraction:** Most of the selected publications contained both, genetic and phenotypic/other information, which was categorized into three groups:

- a. Patient-related metadata such as sex, origin, age, consanguinity status, treatment history.
- b. Genetic data.
- c. Phenotypic data.

While extraction of patient-related metadata was generally straightforward, systematic extraction of genetic and phenotypic information was hampered by inconsistent/variable reporting and required diligent analysis. For the genetic data, all reported variants were converted into HGVS nomenclature (den Dunnen et al., 2016) which serves as an international standard for denotation of DNA, RNA, and protein variants. For phenotypic data, the Human Phenotype Ontology (HPO) was used as a standardized vocabulary (Köhler et al., 2014). HPO terms are hierarchically structured in a tree-like manner. Due to a strong variability of the terms used to describe individual SLS phenotypes, some generalizations and simplifications were introduced, as described in Table 1.

## 2.1 | Database structure

Finally, all information was collected in the web-based Leiden Open Variation Database (LOVD) which allows gene-centered open access to the data in an expandable format ([www.LOVD.nl/ALDH3A2](http://www.LOVD.nl/ALDH3A2)). The *ALDH3A2* LOVD database contains the collected information about genetic variants on DNA, RNA, and protein level (whenever possible)

and about individual patients, including for example the respective genotype, zygosity, germline/somatic/*de novo*, and segregation.

## 3 | RESULTS AND DISCUSSION

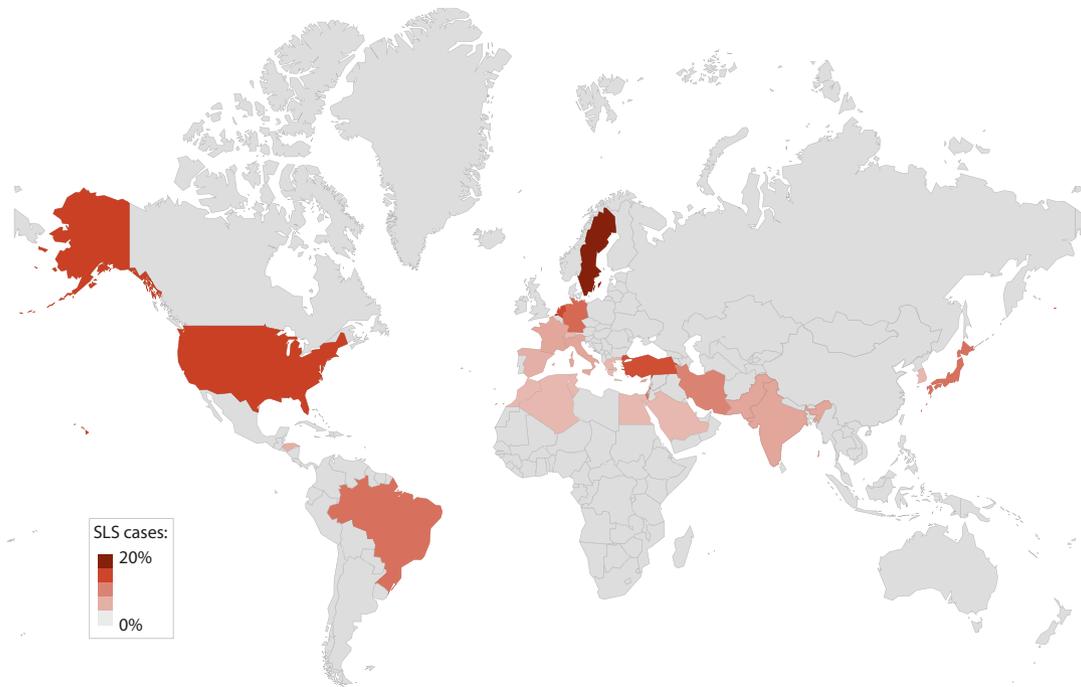
### 3.1 | Individuals

In total, 178 individuals with 90 unique pathogenic SLS variants in *ALDH3A2* were recorded. One hundred and thirty three of these patients (74.7%) carried homozygous SLS variants while 45 (25.3%) were compound heterozygous. In one individual with typical clinical SLS features, only one heterozygous SLS variant was identified; this individual is expected to carry an as yet unidentified second pathogenic variant (Sillén et al., 1998). Information on the biological sex was available for 147 SLS patients published, with a balanced male ( $n = 74$ , 50.3%) to female ( $n = 73$ , 49.7%) ratio (Chi-square: 0.001;  $p$ -value = 0.974). Information on the geographic country of origin was available for 141 patients; patients came from 25 different countries with hotspots in Sweden and the Netherlands indicating increased incidence rates and/or centers active in SLS research (see Figure 1, Supp. Table S1). For the remaining cases, only the location of the respective publishing institution is known and was not included into this analysis. Beside the country of origin, also the ethnic origin of patients would be of interest, which is however only rarely reported.

### 3.2 | Pathogenic variants in the *ALDH3A2* gene

The *ALDH3A2* database (as of September 2018) includes 90 unique variants regarded as pathogenic. All variants are annotated to the transcript variant 2 (NM\_000382.2). Pathogenic variants are scattered throughout the *ALDH3A2* gene with at least one variant in every exon, with the exception of exon 9' which is the alternatively spliced exon responsible for generating the peroxisomal splice form of FALDH, and exon 10 which encodes the four c-terminal amino acids of the ER localizing variant (see Figure 2A). Thus, all pathogenic *ALDH3A2* variants described so far affect both splice transcripts of FALDH, with no pathogenic variant reported for the (extended) peroxisomal transcript variant 1 (NM\_001031806.1). Compared to other autosomal recessive metabolic conditions, the proportion of SLS frame shift variants predicted to completely remove enzyme function is relatively high ( $n = 29$ ; 32.2%). Missense variants ( $n = 30$ , 33.3%) also account for approximately one-third of pathogenic variants, followed by intronic ( $n = 14$ , 15.6%), nonsense ( $n = 9$ ; 10.0%), in-frame insertions/deletions ( $n = 5$ ; 5.6%), and large rearrangements ( $n = 3$ ; 3.3%) (see Figure 2B).

The FALDH structure consists of three large domains (catalytic, cofactor binding, and dimerization), and additional functional units such as the gatekeeper helix and the membrane anchor. As illustrated in Figure 2C, most of the SLS-causing variants affect the catalytic and cofactor domains (45.8% and 41.0%, respectively) while 10.8% of the SLS variants found in the oligomerization domain, compatible with the notion that the formation of the FALDH homodimer is essential for its function. Two variants have been described to affect the gatekeeper helix.



**FIGURE 1** Geographic distribution of published Sjögren–Larsson syndrome cases. Saturation corresponds to the fraction of cases reported for each country. Light grey color indicates that no patients have been reported so far. Numeric values can be found in Supp. Table S1. Please note that this does not reflect the incidence rate but the number of reported cases

### 3.3 | Genotypes

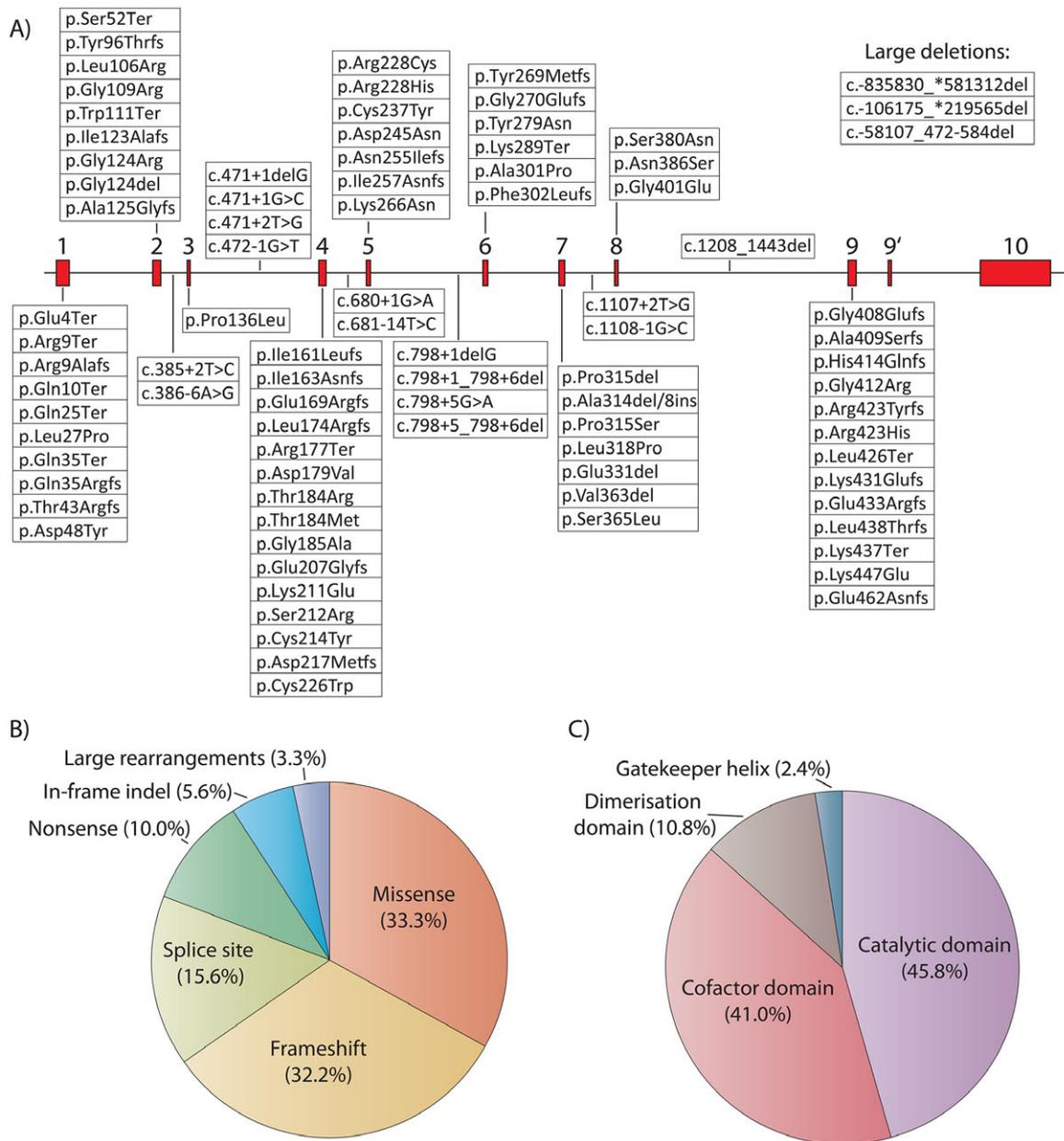
The most prevalent SLS variant c.943C>T (p.Pro315Ser) was present in 33 patients, corresponding to about 20% of all published cases. Twenty six of these individuals were of Swedish origin and all but one were homozygous for this variant ( $n = 25$ ). Six further patients with c.943C>T were from the Netherlands (1 homozygous). The frame shift deletion c.1297\_1298delGA (p.Glu433Argfs\*3) was reported in 19 patients, 9 of which were from the Netherlands (4 homozygous), 3 from Germany (1 homozygous), and 1 from Switzerland (homozygous). Sixteen patients were reported to carry the c.1108-1G>C splice site variant; 9 of them came from Brazil (all homozygous) and 4 of them were from Turkey (all homozygous). The variant c.682C>T (p.Arg228Cys) was found in 10 patients, 8 of which were homozygous from Israel. One further patient, currently under medical treatment at the Department of Dermatology, Venereology and Allergology (Medical University of Innsbruck) also carries this mutation in a homozygous fashion. Six patients with the SLS variant c.733G>A (p.Asp245Asn) were from Germany (3), France (1), Spain (1), and Turkey (1). A total of 54 variants were each found to occur in only one patient. An especially high diversity of genotypes can be found in the population of the United States of America, mirroring this country's history of diverse ethnic immigration. On the population level, the c.943C>T variant can be found with an allele frequency of 1:4,690 in non-Finnish Europeans, while all other SLS variants do exhibit allele frequencies of below 1:10,000 (Genome Aggregation Database, <http://gnomad.broadinstitute.org>, accessed May 21st, 2018).

Seventy three SLS patients were homozygous or compound heterozygous for null (nonsense, frame shift, and splice) variants pre-

dicted to result in complete absence of FALDH protein in the cell. Eight further patients were reported with homozygous in frame indels. SLS missense variants with possible residual function were found in 97 patients. Of these, 68 patients were homozygous, and 29 patients carried a missense variant in combination with a putative null mutation on the other allele, potentially allowing the characterization of residual enzyme function. Only two genotypes in three different patients were compound heterozygous for two missense variants; in both cases, the frequent Swedish c.943C>T variant was combined with a rare variant (c.551C>T, p.Thr184Met and c.798G>C, p.Lys266Asn, respectively). In the FALDH structure, the amino acid residues Lys-266 and Pro-315 are more than 10 Å apart from each other, and the flexibility of the lysine side chain length could reduce this distance to 5 Å. However, there is no indication of a compound heterozygous-specific interaction between these two variants, as the clinical phenotype does not differ from other genotypes involving these variants.

### 3.4 | Phenotypic spectrum of the Sjögren–Larsson syndrome

Phenotypic information in addition to the genetic information was reported for 165 of the 178 patients included in the database, but the representative quality of the data is uncertain. Several reports focus on specific aspects of the disease (e.g., eye manifestation in ophthalmologic publications) while other symptoms might be unreported. Few papers report a comprehensive analysis of the phenotypic spectrum of SLS, specifically stating which disease features were absent in a particular patient. Most publications provide a cross-sectional snapshot of the SLS patient and do not take into account age-dependent clinical features that have not yet appeared in younger patients. Finally,



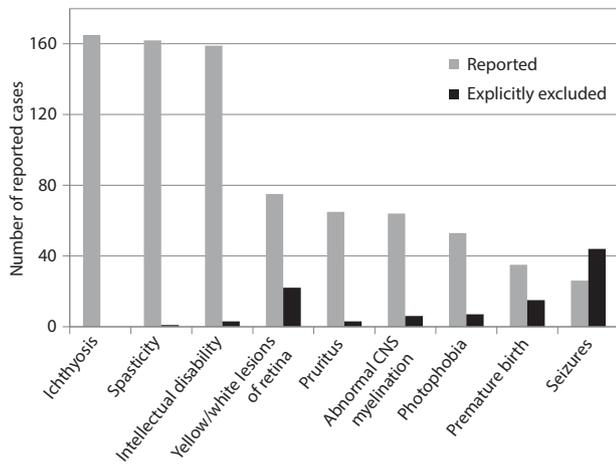
**FIGURE 2** SLS-causing variants in ALDH3A2: (A) Distribution of variants along the genome. Exon/intron structure is drawn to scale. Parenthesis removed from variant nomenclature for better readability. (B) Frequency of variant types. (C) Structural FALDH domains affected by variants (structural elements: catalytic-, cofactor binding-, dimerization domain, gatekeeper helix, membrane anchor)

many patients were diagnosed because of well-known typical disease features, with attenuated or unusual phenotypes less likely to be ascertained.

After merging of redundant features, in total, 65 different symptoms were described in at least one patient, 9 of which can be considered as main symptoms because they mostly are independent from each other and were reported in at least 15% of cases (see Figure 3). The three symptoms generalized ichthyosis, spasticity, and intellectual disability (sometimes termed slightly differently) are regarded as the characteristic symptoms for SLS in the literature and were also present in nearly every patient of the present study. Other symptoms or signs such as “Yellow/white lesions of the retina,” “Pruritus,” “Photophobia,” “Abnormal CNS myelination,” “Preterm birth,” and “Seizures”

were reported with declining frequency. Some disease features were more likely to be explicitly excluded (see Figure 3, Supp. Table S2). Especially for “Yellow/white lesions of the retina” and “Seizures,” a noticeable number of cases were reported in which these symptoms were reported as absent ( $n = 22$  and  $44$ , respectively). Conversely, “Pruritus,” “Premature birth,” “Abnormal CNS myelination,” “Photophobia,” and “Seizures” were neither reported nor excluded in more than 50% of cases (Supp. Table S2).

For the three main symptoms of SLS, many of the publications state degrees of severity or more detailed information. A comprehensive comparison of these gradations proved to be difficult as the specifications used in different papers are heterogeneous, indicating the need of standardized guidelines for future reporting of clinical features (see



**FIGURE 3** Main clinical features of SLS. Phenotypic data was reported for a total of 165 patients. For the nine most common features, all reported cases (grey) as well as explicitly excluded cases (black) were included. Numeric values can be found in Supp. Table S2

below). However, converting the classification information into three broad categories “mild,” “moderate,” and “severe” allowed for a rough assessment of their actual diversity.

For 97 patients, more detailed clinical information regarding “**generalized ichthyosis**” was available, which was described as mild in 17 patients (17.5%), moderate in 21 patients (21.6%), and severe in 59 patients (60.8%). Ichthyosis often goes hand in hand with “**Pruritus**,” defining the abnormalities of the integument in SLS. However, pruritus was only reported in about 40% of patients, and its occurrence was not correlated with the severity of the *Ichthyosis* phenotype. In 17 cases also, “hypohidrosis” (HP:0000966) was mentioned as a rare symptom connected to *ichthyosis*. The severity of “**spasticity**” was specified in detail in 107 cases and described as mild in 3 cases (2.8%) moderate in 32 cases (29.9%), and severe in 72 (67.3%) cases. “**Intellectual disability**” was denoted in detail in 84 patients, divided into mild in 26 (31.0%), moderate in 30 (35.7%), and severe in 28 (33.3%) patients. Only four publications (Lossos et al., 2006; Nakajima et al., 2011; Papatthemeli et al., 2017; Willemsen et al., 2001) provide detailed information about the cognitive status including IQ measurements of some of the reported patients. The median IQ of a total of 12 patients included in three of these studies was 54.5 (range: 39–65). Three patients without intellectual disability (IQ: 95, 83, 84) according to the former DSM-IV definition were excluded from this calculation (Papatthemeli et al., 2017; Willemsen et al., 2001). According to other publications (Alió et al., 2006; Aoki et al., 2000) about 70% of the patients have an IQ lower than 50, which represented the border between mild and moderate mental retardation according to the American DSM classification at that time. Newer versions of the DSM classification system have removed IQ test scores from the diagnostic criteria. In summary, based on limited available data, severe ichthyosis and spasticity is frequent in SLS patients while only about a third of affected individuals have severe forms of intellectual disability, with the limitation that no uniform clinical scoring systems were used.

Although it has been reported that the majority of patients with SLS is born preterm (Staps, Hogeveen, Fuijkschot, Van Drongelen, &

Willemsen, 2018; van Domburg et al., 1999), the phenotype “**premature birth**” was only reported for 35 patients. Duration of gestation was stated for 32 of these patients, with an average duration of 34 weeks. Normal length of pregnancy was stated in 15 cases. In light of the results of an earlier analysis (Staps et al., 2018), it is likely that premature birth represents a SLS phenotype that is strongly under-reported.

For 64 patients, “**abnormal CNS myelination**” was reported. The precise location of the deficit was indicated for 34 patients ( $n = 34$ ). In 30 of these cases (88.2%), the periventricular region of the brain was affected. Together with abnormalities in magnetic resonance imaging (MRI), this phenotype might be under-reported because of lack of technical or financial possibilities (see below). Furthermore, dysmyelination develops with time and may not yet be present in infants; conversely, myelination may mature with age leading to normal MRI findings after an earlier pathological scan (van Domburg et al., 1999).

In earlier studies, it has been reported that about 40% of SLS patients are affected by one or more “**seizures**” (Rizzo, 2001). This is in good agreement with the stated percentage of affected and unaffected individuals (37.1% had seizures) in the database. Seizures in SLS patients are typically grand mal and represent a manifestation that is not easily missed, indicating that the frequency of 35–40% is close to the true incidence at least for classical SLS patients.

Apart from the main clinical features shown in Figure 3 (values in Supp. Table S2) and discussed above, there are also symptoms that were reported less frequently (a full list can be found in Supp. Table S3). Sometimes these symptoms may occur due to other comorbidities but others are likely also associated with SLS. Several main features of SLS fall within the HPO category of “abnormalities of the nervous system,” of which “intellectual disability” is for example sometimes accompanied by the less frequently reported “poor speech” or “dysarthria” (HP:0002465, HP:0001260,  $n = 34$ ) phenotype. Additionally to the main symptoms “seizures” and “spasticity” there is a range of roughly associated features reported, including different abnormalities of muscle tone (HP:0001276, HP:0001252, HP:0008936, HP:0000297,  $n = 17$ ), “hyperreflexia” (HP:0006801, HP:0001347,  $n = 38$ ), “contractures of the joints of the lower limbs” (HP:0005750,  $n = 9$ ), “ankle clonus”/“myoclonus” (HP:0011448, HP:0001336,  $n = 3$ ), and “dysphagia” (HP:0002015,  $n = 1$ ). The nature of these symptoms generates a large intrinsic overlap with the HPO category of “abnormalities of the musculature.” Abnormalities of the eye in SLS patients are mainly reported as “yellow/white lesions of the retina” and “photophobia” but include terms such as “reduced visual acuity” (HP:0007663,  $n = 14$ ), “abnormal colour vision” (HP:0000551,  $n = 4$ ), “hypopigmentation of the fundus” (HP:0007894,  $n = 1$ ), or “corneal opacity” (HP:0007957,  $n = 1$ ). In few patients, “hypertelorism” (HP:0000316,  $n = 2$ ), and “strabismus” (HP:0000486,  $n = 2$ ), “proptosis” (HP:0000520,  $n = 1$ ), and “ptosis” (HP:0000508,  $n = 1$ ) were stated.

Abnormalities of the skeletal system, head, and limbs have been reported in a considerable number of cases. Partly these could be related to chronically increased muscle tone due to spasticity, but also other pathomechanisms (e.g., defects in developmental signaling pathways) are possible. A variety of different rare features that fall within this category have been reported, including “foot deformities” (HP:0001760, HP:0001763,  $n = 26$ ), abnormalities of the spine

(HP:0002751, HP:0002808, HP:0002650,  $n = 10$ ), chest deformities (HP:0000767, HP:0000768,  $n = 3$ ), abnormalities of the skull (HP:0000256, HP:0000252, HP:0000268,  $n = 3$ ), and “facial dysmorphism” (HP:0001999,  $n = 2$ ). In contrast, other symptoms have merely been described in single cases including “dislocated radial head” (HP:0003083), “short 5th finger” (HP:0009237), “short metatarsal bones” (HP:0010743), and “congenital hip dislocation” (HP:0001374).

In summary, the spectrum of rare clinical features described in SLS patients in the literature is broad but their reporting is sometimes spurious and depends on the clinical interests, testing capabilities, and the precise use of established terminology. Thus, although some characteristics may appear to co-occur with specific genetic variants they may be more likely the result of a testing and reporting bias, rather than an actual genotype–phenotype relationship.

### 3.5 | Does residual FALDH activity correlate with the phenotypic spectrum?

Several publications provided information about the residual enzymatic activity associated with the respective SLS variant (Carney, Wei, & Rizzo, 2004; Davis et al., 2013; De Laurenzi et al., 1996; Didona et al., 2007; Kariminejad et al., 2017; Köhler et al., 2017; Rizzo et al., 2010; Sarret et al., 2012; Tsukamoto et al., 1997; Willemsen et al., 2001). In essence, two approaches were used to determine enzymatic activity of FALDH: either quantification in cultured cells from patients (predominantly fibroblasts), or over-expression of mutant FALDH in mammalian, insect, or bacterial cells.

Data on residual enzymatic activity was available for 46 out of the 85 variants (54%), with activity values ranging from 0% up to 23% compared to wild-type. Using activity data for subgrouping patients, no significant phenotype differences were apparent in patients with genotypes predicting different levels of enzyme function. In general, there appears to be only limited quantitative comparability between the residual activity results obtained in different studies. One reason for this could lie within the relatively broad range of enzyme activities measured in cells, potentially resulting from different methodologies as well as natural variability. Furthermore, in cell homogenates there can be as much as 8% of residual long-chain aldehyde oxidizing activity due to other non-FALDH aldehyde dehydrogenases (Engelstad et al., 2011). Thus, residual FALDH activity might be more precisely determined by measuring over-expressed FALDH. Therefore, it cannot be excluded that the lack of genotype–phenotype correlation is at least partly caused by the variable quantitative scales used for describing phenotypes and enzyme activities. Systematic and comprehensive reporting of SLS cases in the future is required to obtain more reliable data.

### 3.6 | Suggestions for a comprehensive documentation of SLS patient data

In the course of this study, one of the strongest limitations was the inconsistent phenotype reporting of published cases. While some articles include detailed and careful descriptions of genetic and phenotype data, other publications only contain superficial reports, missing data, and/or cryptic information. Whereas the three main symptoms

ichthyosis, intellectual disability, and spasticity are stated for most patients, this is not the case for other main phenotypes which should be systematically reported as confirmed or—importantly—explicitly excluded, taking patient age into consideration. Care must also be taken to provide full and correct description of reported genetic variants.

With Supp. Document S1, we provide a checklist that could assist in the process of assembling a comprehensive description of SLS cases. We propose that the patient metadata should include information about geographic and ethnic origin, sex, as well as the ages at first diagnosis and during ascertainment of symptoms. Whenever available, the family history (e.g., consanguinity status of parents) should be reported, for example by supplying a pedigree. Importantly, any relation to already published cases has to be clarified as well. The patient description should also include a statement about other clinical abnormalities not directly related to SLS. On the genetic level, sequencing of both alleles and provision of the identified variants in HGVS format (<http://varnomen.hgvs.org/>) is essential. In order to reliably differentiate between hereditary and *de novo* mutations, variant information for parents or relatives should be included as well.

For phenotype data, we recommend using the HPO nomenclature (Köhler et al., 2017). At a minimum, the 9 most common symptoms (see Figure 3) should be checked, and their occurrence should be confirmed or explicitly excluded along with the respective ages of onset. The respective severity of ichthyosis, intellectual disability, and spasticity should be stated together with the criteria used for this assessment. Different scales are available for ichthyosis (Ezzedine et al., 2012; Kamalpour, Rice, Pavlis, Veledar, & Chen, 2010; Marukian et al., 2017; Paller et al., 2017) and spasticity (Ashworth, 1964; Bohannon & Smith, 1987; Boyd & Kerr Graham, 1999). For classifying intellectual disability, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Regier, Kuhl, & Kupfer, 2013) can serve as a well-established guideline.

## 4 | CONCLUSION

We have established a patient-centered database for pathogenic variants in the *ALDH3A2* gene, which contains both, genotype information for individual patients as well as clinical data. By including all published SLS cases that fulfil the required selection and quality criteria, this study paves the way for the SLS research community to further feed into a homogeneous open-access database. The collected information highlights the insular occurrence of certain (mostly homozygous) genotypes in Sweden, Western Europe, Brazil, and Israel caused by independent founder SLS variants, but also, for example, the mixing of the Swedish with the Western European variants in cases centered around the Netherlands. The low minor allele frequency of “common” SLS variants emphasized the rarity of this disorder. By only including genetically well described cases into this database, we were able to ensure highest data quality, with the limitation that cases with incomplete data in regard to the here applied inclusion criteria could not be considered.

We find that the three major symptoms, i.e. ichthyosis, intellectual disability, and spasticity are readily documented. However, their

detailed classifications, as well as the occurrence of other phenotypic features, are highly variable due to biological heterogeneity and inconsistency in reporting. The resulting broad phenotypic spectrum does not allow identifying genotype–phenotype correlations, which may be at least partially due to incomplete clinical data and difficulties in measuring residual enzyme function. Based on the here assembled data, we established a “SLS case report checklist” (Supp. Document S1) aimed to assist with generating comprehensive patient descriptions in the future. Moreover, with increasing application of whole exome and whole genome sequencing, it is possible that patients with *ALDH3A2*-related variant forms of SLS lacking the typical clinical features will be identified in the future.

## ACKNOWLEDGMENT

This work was supported by a MUI Start grant of the Medical University of Innsbruck to M.A.K.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ORCID

Markus A. Keller  <https://orcid.org/0000-0002-8654-9920>

## REFERENCES

- Alió, A. B., Bird, L. M., McClellan, S. D., & Cunningham, B. B. (2006). Sjögren–Larsson syndrome: A case report and literature review. *Cutis: Cutaneous Medicine for the Practitioner*, *78*, 61–65.
- Aoki, N., Suzuki, H., Ito, K., & Ito, M. (2000). A novel point mutation of the *FALDH* gene in a Japanese family with Sjögren–Larsson syndrome. *Journal of Investigative Dermatology*, *114*, 1065–1066.
- Ashworth, B. (1964). Preliminary trial of carisoprodol in multiplo sclerosis. *Practitioner*, *192*, 540–542.
- Auada, M. P., Puzzi, M. B., Cintra, M. L., Steiner, C. E., Alexandrino, F., Sartorato, E. L., ... Rizzo, W. B. (2006). Sjögren–Larsson syndrome in Brazil is caused by a common 1108-1 G→C splice-site mutation in the *ALDH3A2* gene. *British Journal of Dermatology*, *154*, 770–773.
- Bohannon, R. W., & Smith, M. B. (1987). Interrater reliability of a modified Ashworth scale of muscle spasticity. *Physical Therapy*, *67*, 206–207.
- Botelho Gomes, J. M., Vieira, A. P., Navarro, J., Maré, R., Tavares, P., & Brito, C. (2011). Sjögren–Larsson syndrome due to a novel mutation in the *FALDH* gene. *European Journal of Dermatology*, *21*, 412–413.
- Boyd, R. N., & Kerr Graham, H. (1999). Objective measurement of clinical findings in the use of botulinum toxin type A for the management of children with cerebral palsy. *European Journal of Neurology*, *6*, s23–s35.
- Burgueño-Montañés, C., Garcia-Fernández, M., Colunga-Cueva, M., & Garcia-López, A. (2014). Sjögren–Larsson syndrome: Optical coherence tomography and a novel mutation. *Archivos de la Sociedad Española de Oftalmología*, *89*, 504–507.
- Carney, G., Wei, S., & Rizzo, W. B. (2004). Sjögren–Larsson syndrome: Seven novel mutations in the fatty aldehyde dehydrogenase gene *ALDH3A2*. *Human Mutation*, *24*, 186–186.
- Cubo, E., & Goetz, C. G. (2000). Dystonia secondary to Sjögren–Larsson syndrome. *Neurology*, *55*, 1236–1237.
- Davis, K., Holden, K. R., S'Aulis, D., Amador, C., Matheus, M. G., & Rizzo, W. B. (2013). Novel mutation in Sjögren–Larsson syndrome is associated with divergent neurologic phenotypes. *Journal of Child Neurology*, *28*, 1259–1265.
- 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 Sjögren–Larsson syndrome. *Journal of Human Genetics*, *52*, 865–870.
- van Domburg, P. H., Willemsen, M. A., Rotteveel, J. J., deJong, J. G., Thijssen, H. O., Heerschap, A., ... Steijlen, P. M. (1999). Sjögren–Larsson syndrome: Clinical and MRI/MRS findings in *FALDH*-deficient patients. *Neurology*, *52*, 1345–1352.
- den Dunnen, J. T., Dalgleish, R., Maglott, D. R., Hart, R. K., Greenblatt, M. S., McGowan-Jordan, J., ... Taschner, P. E. M. (2016). HGVS recommendations for the description of sequence variants: 2016 Update. *Human Mutation*, *37*, 564–569.
- 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*, 356–361.
- Ezzedine, K., Droitcourt, C., Ged, C., Diallo, A., Hubiche, T., de Verneuil, H., ... Boralevi, F. (2012). Usefulness of a global clinical ichthyosis vulgaris scoring system for predicting common *FLG* null mutations in an adult Caucasian population. *British Journal of Dermatology*, *167*, 1165–1169.
- Fuijkschot, J., Theelen, T., Seyger, M., Van der Graaf, M., Groot, I., Wevers, R., ... Willemsen, M. (2012). Sjögren–Larsson syndrome in clinical practice. *Journal of Inherited Metabolic Disease*, *35*, 955–962.
- Gaboon, N. E. A., Jelani, M., Almrhamhi, M. M., Mohamoud, H. S. A., & Al-Aama, J. Y. (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*, 706–709.
- Gånemo, A., Jagell, S., & Vahlquist, A. (2009). Sjögren–Larsson syndrome: A study of clinical symptoms and dermatological treatment in 34 Swedish patients. *Acta Dermato-Venereologica*, *89*, 68–73.
- Garcia-Peris, E., Latour-Álvarez, I., Pestana-Eliche, M., & Sánchez, R. (2017). Expanding the genotype of Sjögren–Larsson syndrome: A new case due to two novel mutations. *Actas Dermo-Sifiliograficas*, *108*, 601–603.
- Hidalgo, E. T., Orillac, C., Hersh, A., Harter, D. H., Rizzo, W. B., & Weiner, H. L. (2017). Intrathecal Baclofen therapy for the treatment of spasticity in Sjögren–Larsson syndrome. *Journal of Child Neurology*, *32*, 100–103.
- Incecik, F., Herguner, O. M., Ozbek, M. N., Gungor, S., Yilmaz, M., Rizzo, W. B., & Mert, G. G. (2018). Neuro-ichthyotic syndromes: A case series. *Journal of Pediatric Neurosciences*, *13*, 34–38.
- Incecik, F., Herguner, O. M., Rizzo, W. B., & Altunbasak, S. (2013). A Turkish family with Sjögren–Larsson syndrome caused by a novel *ALDH3A2* mutation. *Annals of Indian Academy of Neurology*, *16*, 425–427.
- Jain, P., Sharma, S., Drunat, S., Samaan, S., Goel, S., Gulati, P., & Aneja, S. (2015). Clinico-radiological and genetic features of a common neuro-ichthyotic syndrome. *Indian Journal of Pediatrics*, *82*, 487–489.
- James, P. F., & Zoeller, R. A. (1997). Isolation of animal cell mutants defective in long-chain fatty aldehyde dehydrogenase. *Journal of Biological Chemistry*, *272*, 23532–23539.
- Jean-François, E., Low, J. Y., Gonzales, C. R., & Sarraf, D. (2007). Sjögren–Larsson syndrome and crystalline maculopathy associated with a novel mutation. *Archives of Ophthalmology*, *125*, 1582–1583.
- Kamalpour, L., Rice, Z. P., Pavlis, M., Veledar, E., & Chen, S. C. (2010). Reliable methods to evaluate the clinical severity of ichthyosis. *Pediatric Dermatology*, *27*, 148–153.
- Kariminejad, A., Barzgar, M., Bozorgmehr, B., Keshavarz, E., Kariminejad, M. H., S'Aulis, D., & Rizzo, W. B. (2017). Novel mutations and a severe neurological phenotype in Sjögren–Larsson syndrome patients from Iran. *European Journal of Medical Genetics*, *61*, 139–144.

- Keller, M. A., Piedrafita, G., & Ralser, M. (2015). The widespread role of non-enzymatic reactions in cellular metabolism. *Current Opinion in Biotechnology*, 34, 153–161.
- Keller, M. A., Watschinger, K., Golderer, G., Maglione, M., Sarg, B., Lindner, H. H., ... Werner, E. R. (2010). Monitoring of fatty aldehyde dehydrogenase by formation of pyrenedecanoic acid from pyrenedecanal. *Journal of Lipid Research*, 51, 1554–1559.
- Keller, M. A., Watschinger, K., Golderer, G., Werner-Felmayer, G., & Werner, E. R. (2013). Fatty aldehyde dehydrogenase, the enzyme downstream of tetrahydrobiopterin-dependent alkylglycerol monooxygenase. *Pteridines*, 24, 105–109.
- Keller, M. A., Watschinger, K., Lange, K., Golderer, G., Werner-Felmayer, G., Hermetter, A., ... Werner, E. R. (2012). Studying fatty aldehyde metabolism in living cells with pyrene-labeled compounds. *Journal of Lipid Research*, 53, 1410–1416.
- Keller, M. A., Zander, U., Fuchs, J. E., Kreutz, C., Watschinger, K., Mueller, T., ... Marquez, J. A. (2014). A gatekeeper helix determines the substrate specificity of Sjögren–Larsson syndrome enzyme fatty aldehyde dehydrogenase. *Nature Communications*, 5, 4439.
- Kim, J. Y., Kim, S.-H., Park, M.-J., Kim, S. H., Cho, W. H., Choi, J., ... You, S. J. (2018). Identification of homozygous likely pathogenic variant of ALDH3A2 in a Korean boy with Sjögren–Larsson syndrome. *Annals of Laboratory Medicine*, 38, 80–82.
- Köhler, S., Doelken, S. C., Mungall, C. J., Bauer, S., Firth, H. V., Bailleul-Forestier, I., ... Eppig, J. T. (2014). The Human Phenotype Ontology project: Linking molecular biology and disease through phenotype data. *Nucleic Acids Research*, 42, D966–D974.
- Köhler, S., Vasilevsky, N. A., Engelstad, M., Foster, E., McMurry, J., Aymé, S., ... Buske, O. J. (2017). The human phenotype ontology in 2017. *Nucleic Acids Research*, 45, D865–D876.
- Kraus, C., Braun-Quentin, C., Ballhausen, W. G., & Pfeiffer, R. A. (2000). RNA-based mutation screening in German families with Sjögren–Larsson syndrome. *European Journal of Human Genetics*, 8, 299–306.
- De Laurenzi, V., Rogers, G. R., Hamrock, D. J., Marekov, L. N., Steinert, P. M., Compton, J. G., ... Rizzo, W. B. (1996). Sjögren–Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. *Nature Genetics*, 12, 52–57.
- Lossos, A., Khoury, M., Rizzo, W. B., Gomori, J. M., Banin, E., Zlotogorski, A., ... Rosenmann, H. (2006). Phenotypic variability among adult siblings with Sjögren–Larsson syndrome. *Archives of Neurology*, 63, 278–280.
- Marukian, N. V., Deng, Y., Gan, G., Ren, I., Thermidor, W., Craiglow, B. G., ... Choate, K. A. (2017). Establishing and validating an ichthyosis severity index. *Journal of Investigative Dermatology*, 137, 1834–1841.
- Möhrenschlager, M., Braun-Falco, M., & Ring, J. (2005). Sjögren–Larsson syndrome: Indian and Central European similarities. *Pediatric Dermatology*, 22, 574–575.
- Nagappa, M., Bindu, P. S., Chiplunkar, S., Gupta, N., Sinha, S., Mathuranath, P. S., ... Taly, A. B. (2017). Child neurology: Sjögren–Larsson syndrome. *Neurology*, 88, e1–e4.
- Nakajima, K., Sano, S., Uchida, Y., Akiyama, M., Morita, Y., & Shimizu, H. (2011). Altered lipid profiles in the stratum corneum of Sjögren–Larsson syndrome. *Journal of Dermatological Science*, 63, 64–66.
- Nakano, H., Akasaka, E., Rokunohe, D., Yokoyama, S., Toyomaki, Y., Umegaki, N., ... Sawamura, D. (2008). A novel homozygous missense mutation in the fatty aldehyde dehydrogenase gene causes Sjögren–Larsson syndrome. *Journal of Dermatological Science*, 53, 136–138.
- de Paiva, A. R. B., Melo, U. S., Freua, F., Dória, D., Cabral, K. S. S., Macedo-Souza, L. I., ... Dória, D., (2018). Typical clinical and neuroimaging features in Sjögren–Larsson syndrome. *Arq Neuropsiquiatr* 76:283–283.
- Paller, A. S., Renert-Yuval, Y., Suprun, M., Esaki, H., Oliva, M., Huynh, T. N., ... Estrada, Y. D. (2017). An IL-17-dominant immune profile is shared across the major orphan forms of ichthyosis. *Journal of Allergy and Clinical Immunology*, 139, 152–165.
- Papathemeli, D., Mataftsi, A., Patsatsi, A., Sotiriadis, D., Samouilidou, M., Chondromatidou, S., & Evangeliou, A. (2017). Atypical presentation of Sjögren–Larsson syndrome. *Case Reports in Pediatrics*, 2017, 7981750.
- Rafai, M. A., Boulaajaj, F. Z., Seito, A., Suga, Y., Slassi, I., & Fadel, H. (2008). Sjögren–Larsson syndrome: A novel mutation in a Moroccan child. *Archives De Pediatrie*, 15, 1648–1651.
- Regier, D. A., Kuhl, E. A., & Kupfer, D. J. (2013). The DSM-5: Classification and criteria changes. *World Psychiatry*, 12, 92–98.
- Rizzo, W. (2001). *Sjögren–Larsson syndrome: Fatty aldehyde dehydrogenase deficiency. The metabolic & molecular bases of inherited disease* (pp. 2239–2258). New York: NY: McGraw-Hill.
- Rizzo, W. B. (2014). Fatty aldehyde and fatty alcohol metabolism: Review and importance for epidermal structure and function. *Biochimica et Biophysica Acta*, 1841, 377–389.
- Rizzo, W. B. (2016). Genetics and prospective therapeutic targets for Sjögren–Larsson syndrome. *Expert Opinion on Orphan Drugs*, 4, 395–406.
- Rizzo, W. B., & Carney, G. (2005). Sjögren–Larsson syndrome: Diversity of mutations and polymorphisms in the fatty aldehyde dehydrogenase gene (ALDH3A2). *Human Mutation*, 26, 1–10.
- Rizzo, W. B., Craft, D. A., Somer, T., Carney, G., Trafrova, J., & Simon, M. (2008). Abnormal fatty alcohol metabolism in cultured keratinocytes from patients with Sjögren–Larsson syndrome. *Journal of Lipid Research*, 49, 410–419.
- Rizzo, W. B., Heinz, E., Simon, M., & Craft, D. A. (2000). Microsomal fatty aldehyde dehydrogenase catalyzes the oxidation of aliphatic aldehyde derived from ether glycerolipid catabolism: Implications for Sjögren–Larsson syndrome. *Biochimica et Biophysica Acta, Molecular Basis of Disease*, 1535, 1–9.
- Rizzo, W. B., S'Aulis, D., Jennings, M. A., Crumrine, D. A., Williams, M. L., & Elias, M. (2010). Ichthyosis in Sjögren–Larsson syndrome reflects defective barrier function due to abnormal lamellar body structure and secretion. *Archives of Dermatological Research*, 302, 443–451.
- Rogers, G. R., Markova, N. G., De Laurenzi, V., Rizzo, W. B., & Compton, J. G. (1997). Genomic organization and expression of the human fatty aldehyde dehydrogenase gene (FALDH). *Genomics*, 39, 127–135.
- Sakai, K., Akiyama, M., Watanabe, T., Sanayama, K., Sugita, K., Takahashi, M., ... Shimizu, H. (2006). Novel ALDH3A2 heterozygous mutations in a Japanese family with Sjögren–Larsson syndrome. *Journal of Investigative Dermatology*, 126, 2545–2547.
- Sakai, K., Akiyama, M., Yanagi, T., Nampoothiri, S., Mampilly, T., Sunitha, V., & Shimizu, H. (2010). An Indian family with Sjögren–Larsson syndrome caused by a novel ALDH3A2 mutation. *International Journal of Dermatology*, 49, 1031–1033.
- Sanabria, M. R., & Coco, R. M. (2011). Sjögren–Larsson syndrome. *Ophthalmology*, 118, 2101–2102.
- Sarret, C., Rigal, M., Vaurs-Barrière, C., Dorboz, I., Eymard-Pierre, E., Combes, P., & Boespflug-Tanguy, O. (2012). Sjögren–Larsson syndrome: Novel mutations in the ALDH3A2 gene in a French cohort. *Journal of the Neurological Sciences*, 312, 123–126.
- Shah, K., Mehmood, S., Jan, A., Abbe, I., Hussain Ali, R., Khan, A., ... Nickerson, D. A. (2017). Sequence variants in nine different genes underlying rare skin disorders in 10 consanguineous families. *International Journal of Dermatology*, 56, 1406–1413.
- Shamriz, O., Molho-Pessach, V., Shaag, A., Daum, H., & Stepensky, P. (2016). Coexistence of two rare autosomal recessive disorders: Activation-induced cytidine deaminase deficiency and Sjögren–Larsson syndrome. *The Israel Medical Association Journal*, 18, 636–638.

- Shibaki, A., Akiyama, M., & Shimizu, H. (2004). Novel ALDH3A2 heterozygous mutations are associated with defective lamellar granule formation in a Japanese family of Sjögren–Larsson syndrome. *Journal of Investigative Dermatology*, 123, 1197–1199.
- Sijens, P. E., Westerlaan, H. E., de Groot, J. C., Boon, M., Potze, J. H., van Spronsen, F. J., ... Oudkerk, M. (2009). MR spectroscopy and diffusion tensor imaging of the brain in Sjögren–Larsson syndrome. *Molecular Genetics and Metabolism*, 98, 367–371.
- Sillén, A., Anton-Lamprecht, I., Braun-Quentin, C., Kraus, C. S., Sayli, B. S., Ayuso, C., ... Wadelius, C. (1998). Spectrum of mutations and sequence variants in the FALDH gene in patients with Sjögren–Larsson syndrome. *Human Mutation*, 12, 377–384.
- Sjogren, T., & Larsson, T. (1957). Oligophrenia in combination with congenital ichthyosis and spastic disorders: A clinical and genetic study. *Acta Psychiatrica et Neurologica Scandinavica, Supplementum*, 113, 1–112.
- Staps, P., Hogeveen, M., Fuijkschot, J., Van Drongelen, J., & Willemsen, M. A. (2018). Understanding fetal factors that contribute to preterm birth: Sjögren–Larsson syndrome as a model. *Journal of Perinatal Medicine*, 46, 523–529.
- Tachibana, Y., Aida, N., Enomoto, K., Iai, M., & Kurosawa, K. (2012). A case of Sjögren–Larsson syndrome with minimal MR imaging findings facilitated by proton spectroscopy. *Pediatric Radiology*, 42, 380–382.
- Taghdiri, M., Kashef, A., Fardaei, M., & Miryounesi, M. (2018). Identification of a novel deletion within ALDH3A2 gene in an Iranian family with Sjögren–Larsson syndrome. *Clinical Case Reports*, 6, 32–36.
- Takeichi, T., Sugiura, K., Arai, H., Ishii, K., Kono, M., & Akiyama, M. (2013). Sporadic VACTERL association in a Japanese family with Sjögren–Larsson syndrome. *Acta Dermato-Venereologica*, 93, 579–580.
- Tanteles, G. A., Nicolaou, M., Patsia, N., Delikurt-Tuncalp, T., Spanou-Aristidou, E., Leonidou, E., ... Christophidou-Anastasiadou, V. (2015). A rare cause of pruritic ichthyosis: Sjögren–Larsson syndrome in the first reported patients of Cypriot descent. *European Journal of Dermatology*, 25, 495–496.
- Tavasoli, A., Sayyahfar, S., & Behnam, B. (2016). A rare case of Sjogren–Larsson syndrome with recurrent pneumonia and asthma. *Korean Journal of Pediatrics*, 59, 276–279.
- Tsakamoto, N., Chang, C., & Yoshida, A. (1997). Mutations associated with Sjögren–Larsson syndrome. *Annals of Human Genetics*, 61, 235–242.
- Van der Veen, R. L., Fuijkschot, J., Willemsen, M. A., Cruysberg, J. R., Berendschot, T. T. & Theelen, T. (2010). Patients with Sjögren–Larsson syndrome lack macular pigment. *Ophthalmology*, 117, 966–971.
- Vural, S., Vural, A., Akçimen, F., Bağcı, I. S., Tunca, C., Gündoğdu Eken, A., ... Başak, A. N. (2018). Clinical and molecular characterization and response to acitretin in three families with Sjögren–Larsson syndrome. *International Journal of Dermatology*, 57, 843–848.
- Willemsen, M. A., Cruysberg, J. R., Rotteveel, J. J., Aandekerck, A. L., Van Domburg, P. H., & Deutman, A. F. (2000). Juvenile macular dystrophy associated with deficient activity of fatty aldehyde dehydrogenase in Sjögren–Larsson syndrome. *American Journal of Ophthalmology*, 130, 782–789.
- Willemsen, M. A., IJlst, L., Steijlen, P. M., Rotteveel, J. J., de Jong, J. G. N., van Domburg, P. H., ... Wanders, R. J. (2001). Clinical, biochemical and molecular genetic characteristics of 19 patients with the Sjögren–Larsson syndrome. *Brain*, 124, 1426–1437.
- Yiş, U., & Terrinoni, A. (2012). Sjögren–Larsson syndrome: Report of monozygote twins and a case with a novel mutation. *The Turkish Journal of Pediatrics*, 54, 64–66.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Weustenfeld M, Eidelpes R, Schmuth M, Rizzo WB, Zschocke J, Keller MA. Genotype and phenotype variability in Sjögren–Larsson syndrome. *Human Mutation*. 2019;40:177–186. <https://doi.org/10.1002/humu.23679>