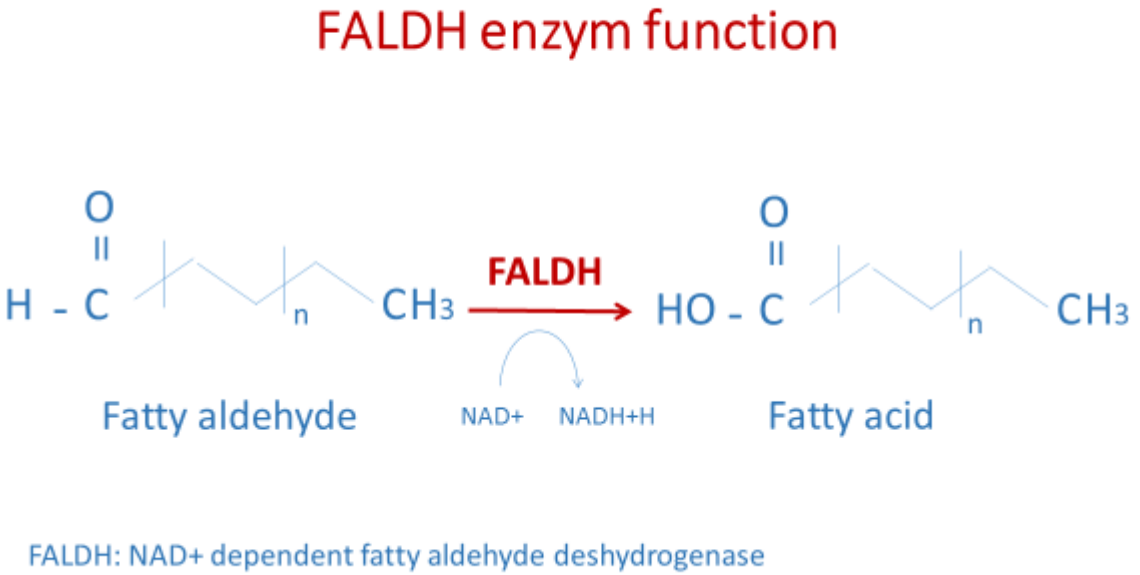
SJOGREN-LARSSON SYNDROME

WHAT IS SJÖGREN-LARSSON SYNDROME (SLS)?

Sjögren-Larsson syndrome (SLS) is an inborn **error of lipid (fat) metabolism**, caused by mutations in the ***ALDH3A2* gene**, which encodes the enzyme fatty aldehyde dehydrogenase (FALDH). FALDH deficiency causes the accumulation of fatty aldehydes, its precursor fatty alcohols and leukotriene B4. SLS mainly presents with **ichthyosis** (dry, scaly, rough skin) in combination with **neurological symptoms**: Spastic diplegia (increased tone in the lower limbs with movement) and severe learning difficulties. Its incidence has been estimated at 0.4: 100,000 live births.

WHAT IS THE FUNCTION OF FATTY ALDEHYDE DEHYDROGENASE?

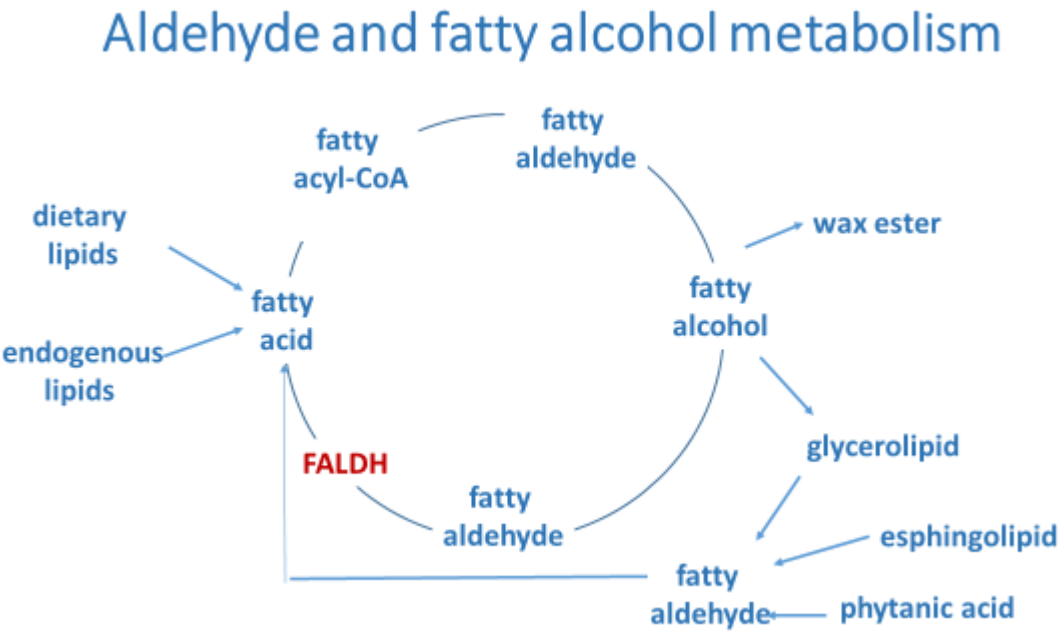


FALDH: NAD+ dependent fatty aldehyde deshydrogenase

The function of FALDH enzyme is to oxidize **long chain fatty aldehydes** (6-24 carbon atoms) to **fatty acids** in a NAD^+-dependent irreversible reaction. FALDH is expressed in most cells and tissues and is present in keratinocytes (cells that produce keratin) of the epidermis (surface layer of the skin). Its genetic deficiency results in an alteration of the oxidation of fatty aldehydes, with accumulation of these and other related lipids (such as fatty alcohols and B4-leukotriene) with serious consequences in the epidermis.

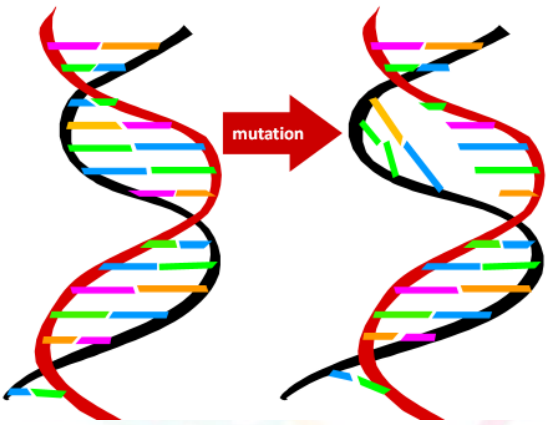
WHAT ARE FATTY ALDEHYDES AND FATTY ALCOHOLS?

Long chain fatty aldehydes are produced in the catabolism of other complex lipids (glycerolipids, fatty alcohols, wax esters and sphingolipids).



Fatty aldehyde and fatty alcohol metabolism of is closely related, since the first ones are intermediates in the conversion of fatty alcohols to fatty acids of similar structure. The cells synthesize fatty alcohols from fatty acids, using fatty aldehydes as intermediates and recycling the excess of fatty alcohols to fatty acids by means of the fatty alcohol cycle (see figure). Fatty alcohols are used to produce wax esters and glycerolipids.

WHY DOES FALDH DEFICIENCY OCCUR?

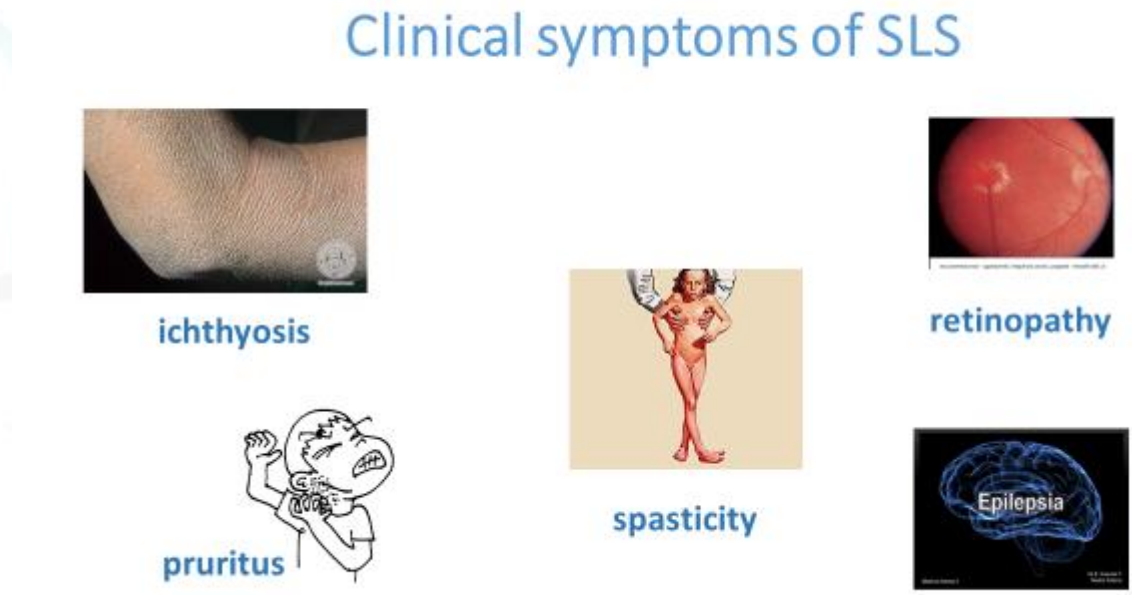


FALDH deficiency occurs due to **mutations** (stable and heritable changes) in the ***ALDH3A2* gene** encoding this enzyme protein.

FALDH deficiency is transmitted with an **autosomal recessive inheritance**, ie, both parents often carry a mutation in the ***ALDH3A2* gene**, although not suffering from any clinical manifestation for it. If both parents transmitted the child a mutated allele of this gene, the child will suffer **Sjögren-Larsson syndrome**.

CLINICAL SYMPTOMS OF SJÖGREN-LARSSON SYNDROME

The SLS presented with a combination of **ichthyosis with neurologic symptoms**.



Usually **hyperkeratosis** (excess keratinized skin cells that gives the rough and scaly appearance) is present at birth and appears more pronounced in the next few months. Hyperkeratosis varies in appearance from a fine scale to large squamous sheets, depending on the body part. There is often a seasoned and thickened skin (lichenification) at the point of bending of the arms and legs. **Pruritus** (itch) is a common sign.

Neurological symptoms appear later in the first or second year of life and include developmental delay, mental retardation, spastic diplegia or quadriplegia, seizures, retinopathy (retina involvement) and photophobia. Other common signs include short stature, kyphoscoliosis, pigmentary degeneration of the retina, crystalline inclusions in the retina and fine hair.

Patients with SLS show impaired sweating, which results in heat and exercise intolerance.

The **pathogenic mechanisms** of FALDH deficiency have not yet been elucidated. The metabolic pathways leading to the production of fatty aldehydes, which are transformed into fatty acids by FALDH are multiple and any of them can contribute to the epidermal alteration observed in the SLS. An alteration in the formation and secretion of the skin layers has been demonstrated, which results in intracellular lipid deposits, altering the permeability of the epidermal barrier, which explains the ichthyosis. Moreover, the metabolism of B4-leukotriene, a potent mediator of inflammation, is altered in the SLS, because it is normally inactivated by FALDH. This could explain the pruritus (itching).

During embryonic development the nervous system and the skin derive from the same layer. Thus, considering the common origin who share the skin and nervous system, the understanding of the biochemical mechanisms of epidermal dysfunction resulting in SLS can also help determine the neurological symptoms associated with this syndrome.

DIAGNOSIS OF FALDH DEFICIENCY

In front of the clinical suspicion of SLS, the detection of an **abnormal urinary excretion of B4-leukotriene** is a biochemical marker of this syndrome.

The demonstration of the **enzymatic FALDH defective activity** in cultured fibroblasts from a skin biopsy or in leukocytes confirms the diagnosis.

The definitive diagnosis is based on the **mutational study of the *ALDH3A2* gene**, which allows genetic counselling and prenatal diagnosis if required.

TREATMENT OF SLS

SLS management involves the intervention of a **multidisciplinary team of neurologists, dermatologists, ophthalmologists, orthopedic surgeons and physiotherapists.**

Treating ichthyosis involves topical application of **keratolytics** or **systemic retinoids** administration.

Generally, seizures respond favorably to **antiepileptic treatments** and spasticity is alleviated by muscle relaxants and **surgery**, ultimately.

A **special diet** with reduced total fat intake and medium

chain fatty acid supplements can improve ichthyosis, although its effects are moderate.

Neurological symptoms and intellectual deficits do not evolve more after puberty. Patients with early symptoms tend to be more severely affected.

Patients often live into adulthood but require lifelong care.

The **Sjögren-Larsson syndrome** causes severe **neuroectodermal disease**. Early diagnosis and treatment improve the prognosis and quality of life of patients.

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