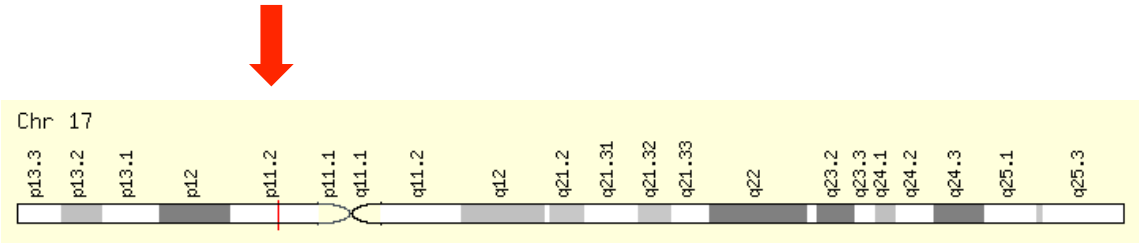
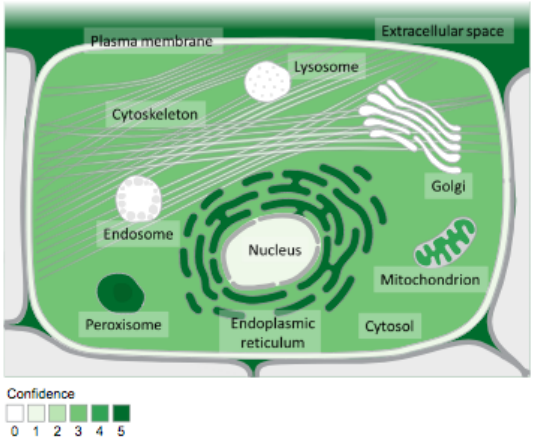
ALDH3A2 Sjogren-Larsson syndrome

Gene name: ALDH3A2 aldehyde dehydrogenase 3 family member A2

Gene localization: 17p11.2



Cellular localization:



Compartment	Confidence
extracellular	5
peroxisome	5
endoplasmic reticulum	5
mitochondrion	4
cytosol	3
plasma membrane	1
nucleus	1

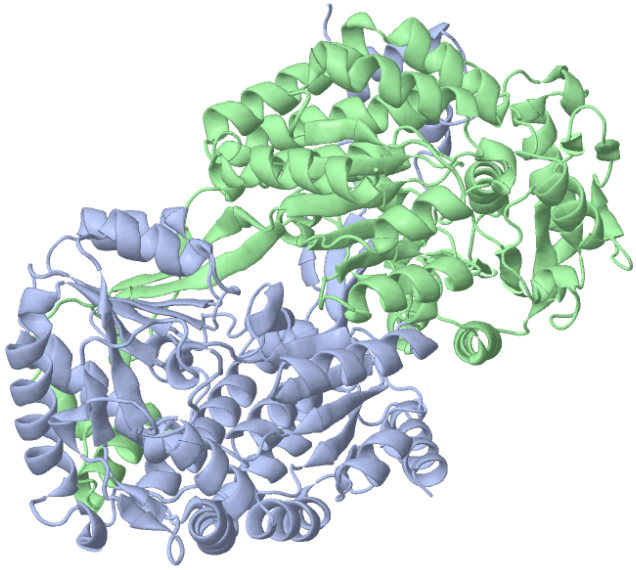
Protein name: Fatty aldehyde dehydrogenase FALDH

Accession uniprot: P51648

Lenght: 485 amino acid

Molecular weight: 54,848 Da

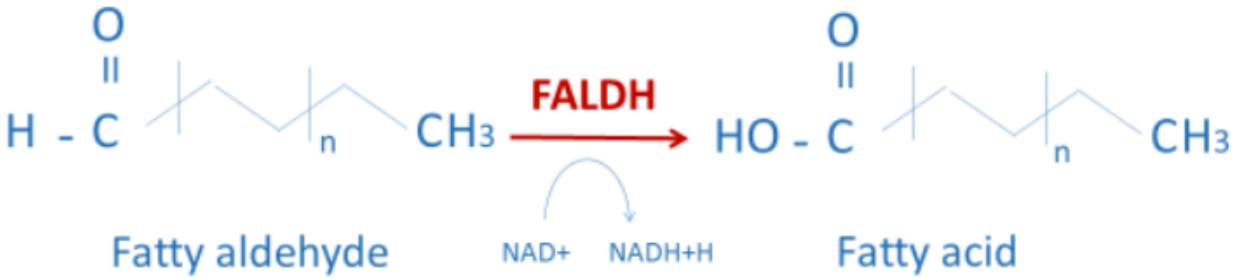
Structure: crystallographic structure of human FALDH, the first model of a membrane-associated aldehyde dehydrogenase.



Protein description: Aldehyde dehydrogenase has a major role in the detoxification of aldehydes generated by alcohol metabolism and lipid peroxidation.

Function

Catalyzes the oxidation of long-chain aliphatic aldehydes derived from lipid metabolism. This enzyme (FALDH) is involved in the breakdown of fats, specifically the breakdown of molecules called fatty aldehydes to fatty acids. This conversion of molecules is part of a multistep process called fatty acid oxidation in which fats are broken down and converted into energy. The FALDH enzyme is found in most tissues, but its activity is highest in the liver. Within cells, the FALDH enzyme is located in the endoplasmic reticulum.



FALDH: NAD+ dependent fatty aldehyde deshydrogenase

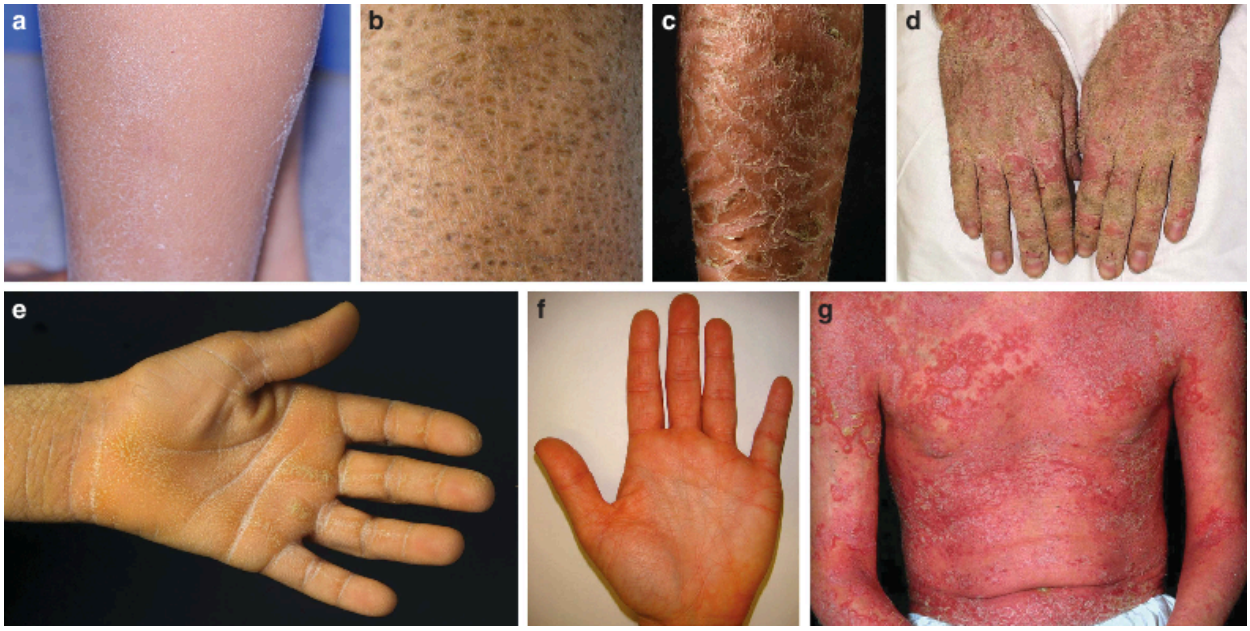
Mutations

At least 80 mutations in the *ALDH3A2* gene have been found; many of these mutations change single amino acids in the FALDH enzyme. The gene mutations that cause Sjögren-Larsson syndrome lead to the production of a FALDH enzyme that is unable to break down fatty aldehyde molecules. As a result, fats that are not broken down can build up in cells. In all affected tissues, excess fat accumulation interferes with the normal formation of protective membranes or materials that are necessary for the body to function normally. These abnormalities underlie the characteristic signs and symptoms of Sjögren-Larsson syndrome.

Sjogren-Larsson syndrome

http://omim.org/entry/270200?search=609523&highlight=609523

Sjogren-Larsson syndrome is an autosomal recessive neurocutaneous disorder characterized by a combination of severe mental retardation, spastic di- or tetraplegia and congenital ichthyosis. Ichthyosis is usually evident at birth with varying degrees of erythema and scaling, neurologic symptoms appear in the first or second year of life. Most patients have an IQ of less than 60. Additional clinical features include glistening white spots on the retina, seizures, short stature and speech defects.



Therapies: The most promising pharmacologic approach to SLS involves blocking the formation of potentially harmful fatty aldehyde adducts using aldehyde scavenging drugs, currently in phase 2 clinical trials. Other approaches needing further investigation include:

1) ALDH-specific activator drugs and PPAR-α agonists to increase mutant FALDH activity;
2) inhibitors of the JNK phosphorylation cascade;
3) antioxidants to decrease aldehyde load;
4) dietary lipid modification;
5) gene therapy.

Prevalence is estimated at 1/250,000 worldwide, but the syndrome is more common in Sweden due to a founder effect.

Curiosity*:* https://www.youtube.com/watch?v=Jyj2mIMeo2M

Associations: UNIAMO, Federazione italiana malattie rare