Adeno-associated virus vectors are able to restore fatty aldehyde dehydrogenase-deficiency. Implications for gene therapy in Sjogren-Larsson syndrome.

Abstract: Sjogren-Larsson Syndrome (SLS) is caused by an autosomal recessive defect in the gene coding for fatty aldehyde dehydrogenase (FALDH), an enzyme necessary for the oxidation of long-chain aliphatic aldehydes to fatty acid as one enzyme of the fatty alcohol:nicotinamide-adenine dinucleotide (NAD+) -oxidoreductase complex (FAO). The impaired activity of FALDH leads to the clinical symptom triad of generalized ichthyosis, mental retardation, and spastic diplegia or tetraplegia. Treatment options are primarily symptomatic. Gene therapy by means of genetic reintroduction of the functional FALDH gene into defective cells has so far not been considered as a therapeutic modality. In order to pursue such an approach for SLS, we constructed a recombinant adeno-associated virus-2 vector containing the human cDNA of functional FALDH and evaluated its capability to restore the enzyme-deficiency in a FALDH-deficient cell line resembling the gene defect of SLS. rAAV-2 transduction of FALDH-deficient cells, usually exhibiting less than 10% of normal FALDH activity, resulted in an increase of FALDH activity within the range of unaffected cells. Moreover, FALDH-transduced cells regained resistance over exposure to long chain aldehydes, which are otherwise toxic to FALDH-deficient cells. These results indicated that rAAV-2 vectors are able to restore FALDH-deficiency.
in a cell system resembling SLS. The findings give the first support to the concept that gene therapy might be a future option for the treatment of SLS.