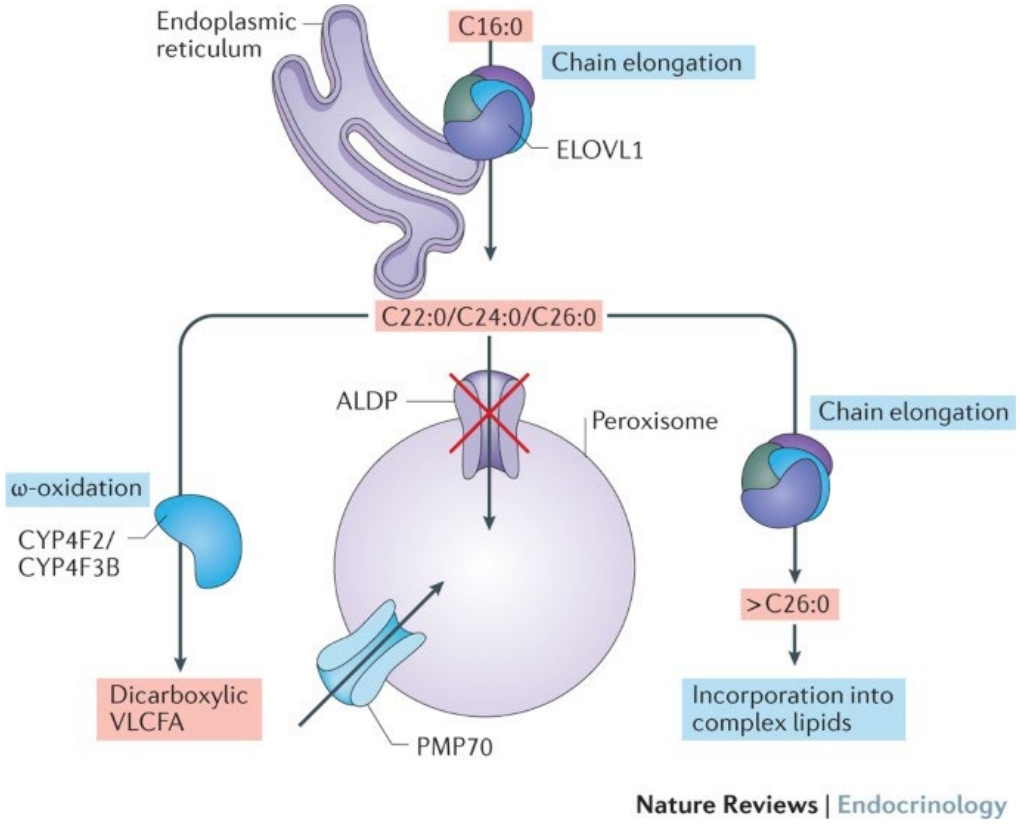
X-linked adrenoleukodystrophy (ALD)



- The very long chains of fatty acids (VLCFAs) is therefore unable to be broken down due to the mutation of the *ABCD1* gene.
- VLCFAs build up in the brain, nervous system + adrenal glands as a result,
- The accumulation is thought to cause inflammation + damage the myelin sheath.

Relevant Literature

Review > Adv Drug Deliv Rev. 2023 Jun:197:114861. doi: 10.1016/j.addr.2023.114861. Epub 2023 May 6.

Lipid nanoparticle-mediated drug delivery to the brain

Purva Khare [1], Sara X Edgecomb [2], Christine M Hamadani [2], Eden E L Tanner [3], Devika S Manickam [4]

Affiliations + expand

PMID: 37150326 DOI: 10.1016/j.addr.2023.114861

Lorenzo's oil inhibits ELOVL1 and lowers the level of sphingomyelin with a saturated very long-chain fatty acid

Takayuki Sassa [1], Takeshi Wakashima, Yusuke Ohno, Akio Kihara

Data we worked with

Note Only variants located in or within 75 base pairs of a coding exon are shown here. To see variants in UTRs or introns, use the region view.

The table below shows the HGVS consequence and VEP annotation for each variant's most severe consequence across all transcripts in this gene. Cases where the most severe consequence occurs in a non-MANE Select transcript (or non-canonical transcript if no MANE Select transcript exists) are denoted with †. To see consequences in a specific transcript, use the transcript view.

Variant ID	Source	HGVS Consequence	VEP Annotation	LoF Curation	Clinical Significance	Flags	Allele Count
X-153725270-C-G	E	p.Pro2Ala	missense				1
X-153725271-C-A	E	p.Pro2Gln	missense				1
X-153725272-G-T	E G	p.Pro2Pro	synonymous				3
X-153725272-G-A	E	p.Pro2Pro	synonymous		Likely benign		1
X-153725275-G-A	E	p.Val3Val	synonymous				5
X-153725278-C-T	E	p.Leu4Leu	synonymous		Likely benign		2
X-153725278-C-G	E	p.Leu4Leu	synonymous		Likely benign		3
X-153725278-C-A	E	p.Leu4Leu	synonymous				1
X-153725280-C-G	E	p.Ser5Cys	missense				1
X-153725284-GC-G	E	p.Arg8GlyfsTer8	frameshift				1
X-153725285-C-T	E G	p.Pro7Ser	missense				3
X-153725285-C-G	E	p.Pro7Ala	missense				1
X-153725288-C-T	E	p.Arg8Trp	missense		Uncertain significa...		1
X-153725289-G-A	E	p.Arg8Gln	missense				1
X-153725293-C-T	E	p.Pro9Pro	synonymous				1
X-153725295-G-A	E	p.Trp10Ter	stop gained		Pathogenic		1
X-153725296-G-C	E G	p.Trp10Cys	missense				36
X-153725297-CG-C	E	p.Asn13ThrfsTer3	frameshift		Pathogenic		2
X-153725297-C-G	E G	p.Arg11Gly	missense		Conflicting interpre...		11
X-153725298-G-C	G	p.Arg11Pro	missense		Conflicting interpre...		4

L11

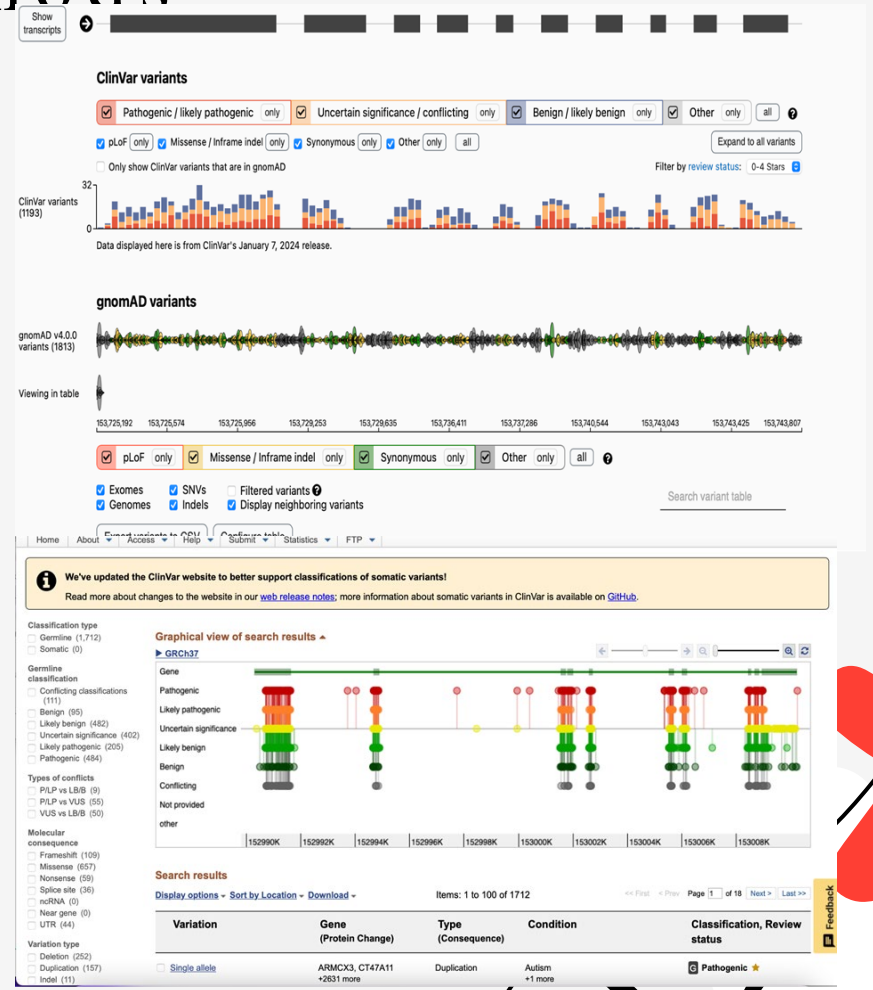
	A	B	C	D	E	F	G	H	I	J
1	Chromosom	Variant	Consequen	Exon	Remark					
2	152990663	c.-59C>T		5′ UTR	Benign					
3	152990698	c.-24_57de	p.0? (no tra	5′ UTR	Likely pathogenic					
4	152990702	c.-20C>T		5′ UTR	Benign					
5	152990705	c.-17_8del	p.0? (no tra	5′ UTR	Pathogenic					
6	152990706	c.-16_10de	p.0? (no tra	5′ UTR	Likely pathogenic					
7	152990712	c.-10C>T		5′ UTR	Benign					
8	152990718	c.-4_5delin	p.?	5′ UTR / exo	Likely pathogenic					
9	152990722	c.1A>G	p.Met1Val (	Exon 1	Pathogenic					
10	152990722	c.1A>T	p.Met1Val (	Exon 1	Pathogenic					
11	152990723	c.2T>A	p.Met1Lys (	Exon 1	Pathogenic					
12	152990724	c.3_19dup	p.Pro7Argfs	Exon 1	Pathogenic					
13	152990724	c.3G>A	p.Met1Ile (r	Exon 1	Pathogenic					
14	152990724	c.3G>C	p.Met1Ile (r	Exon 1	Pathogenic					
15	152990724	c.3G>T	p.Met1Ile (r	Exon 1	Pathogenic					
16	152990730	c.9del	p.Leu4Serfs	exon 1	Pathogenic					
17	152990731	c.10dup	p.Leu4Profs	exon 1	Pathogenic					
18	152990737	c.16del	p.Arg6Glyfs	exon 1	Pathogenic					
19	152990737	c.16_22del	p.Arg6Leufs	exon 1	Pathogenic					
20	152990742	c.21_64del	p.Arg8Glyfs	exon 1	Pathogenic					
21	152990750	c.29G>A	p.Trp10*	exon 1	Pathogenic					
22	152990751	c.30G>A	p.Trp10*	exon 1	Pathogenic					
23	152990751	c.30G>C	p.Trp10Cys	exon 1	Benign					
24	152990752	c.31C>G	p.Arg11Gly	exon 1	Likely benign					
25	152990752	c.31_46del	p.Arg11Ser	exon 1	Pathogenic					
26	152990757	c.36del	p.Asn13Thr	exon 1	Pathogenic					
27	152990757	c.36dupG	p.Asn13Glu	exon 1	Pathogenic					
28	152990759	c.38A>C	p.Asn13Thr	exon 1	Benign based on frequency 3023/1146578 in non-ALD alleles (323)					
29	152990761	c.40A>G	p.Thr14Ala	exon 1	Benign					
30	152990762	c.41C>G	p.Thr14Arg	exon 1	Benign					
31	152990767	c.[46A>T; 7	p.[Lys16*; A	exon 1	Pathogenic					
32	152990771	c.50G>A	p.Arg17His	exon 1	Benign					
33	152990772	c.51_54dup	p.Ala19Hisfs*	exon 1	Pathogenic					

Methods

-Understanding Biological Pathway

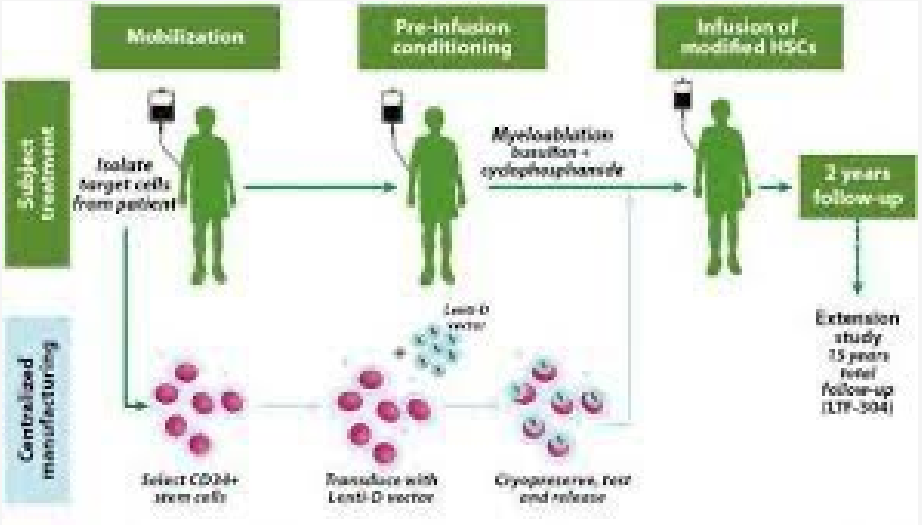
-Analyze possible targets

-Propose less invasive new therapeutics

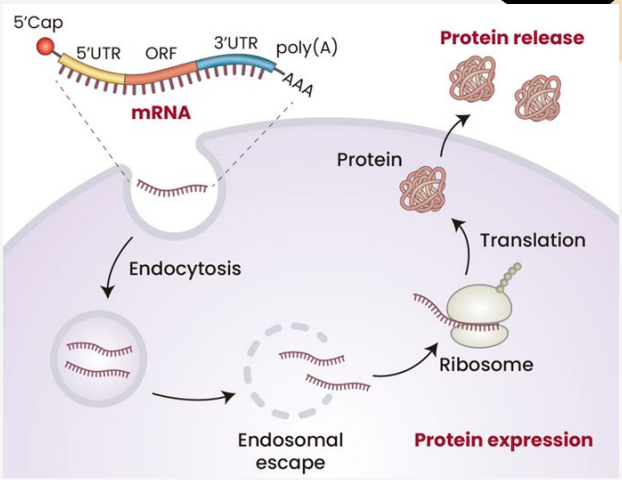


Results

Skysona: The only gene therapy



Home Sunshine Pharmaceutical Technology Co.



Research Gate

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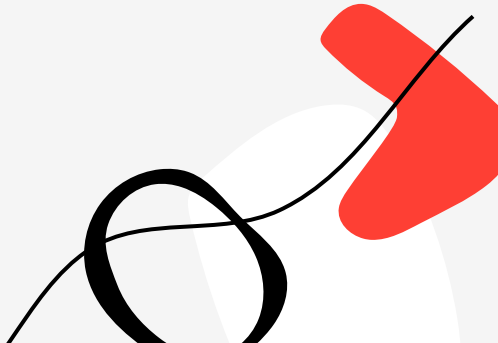
Blood Brain Barrier

Discussion

- **Current Treatment: SkySona Gene Therapy**
- **Lipid nanoparticles for mRNA delivery**
- **Lorenzo's Oil —--| EVOLV1—->VLCFA**



Challenges + future directions

- Struggled to find an idea that would work for ALD
- Pivoted multiple times (diagnostic website, dataset report, prediction model, etc.)
- In the future:
  - We would start the scope of the project sooner
  - Test out a few ideas a day or so beforehand to see what works and doesn't
  - Solidify idea choice + work on it in a timely fashion before judging
- Demyelination, nanoparticle technology immature

References

mRNA therapeutics/vaccines for inducing protein expression.... | Download Scientific Diagram

Rare Diseases.org

OMIM, ABCD1 gene for ALD

OMIM link to ALD characteristics/phenotypes

Drugs.com (Elivaldogene autotemcel)

Skysona: The first gene therapy to treat cerebral adrenal leukodystrophy (CALD)!---2/2 - Knowledge - Hefei Home Sunshine Pharmaceutical Technology Co., Ltd

Pubmed Paper (Long Term Disease Prevention w/Gene Therapy)

ALD Connect .org

Public Datasets document

https://pubmed.ncbi.nlm.nih.gov/24489110/