Metabolic and pathologic profiles of human LSS deficiency recapitulated in mice

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Lanosterol synthase (LSS) converts (S)-2,3-epoxysqualene to lanosterol in the cholesterol synthesis pathway

- LSS catalyzes the formation of the steroid skeleton from a linear chain terpene compound
- Located in 21q22.3
- 732 a.a. (83 kDa)
- Expression: Ubiquitous
- Location: ER
- Monomer

LSS biallelic pathogenic variants have been previously reported to be associated with cataracts

However, these two points were not confirmed:
1. association between LSS biallelic variants and other phenotypes
2. LSS enzymatic disruption in vivo

This study content is published in “Wada Y, Kikuchi A, et al PLOS Genetics, 2020”
Whole exome sequencing identified biallelic variants of two siblings with hypotrichosis and several anomalies

### Patient II-2
- Preterm low birth weight
- Sub-urethral cleft
- External strabismus

### Patient II-3
- Preterm low birth weight
- Cleft palate
- Umbilical hernia

Hyperplastic sebaceous glands, hypoplastic hair follicles, and psoriasiform acanthosis by histological analysis

LSS metabolic block of the patients was confirmed by LC-MS/MS analysis of forehead sebum

Wada et al, PLOS Genetics 2020
Epidermis-specific Lss knockout mice showed no whiskers and neonatal lethality due to skin barrier dysfunction.

- $Lss^{flox}$-K14 showed no whiskers.
- $Lss^{flox/flox}$; K14-Cre/+ (Lss$^{flox}$-K14) lost the weight and died within a few hours after birth.

The skin barrier dysfunction in Lss$^{flox}$-K14

- Outside-in barrier dysfunction
- Inside-out barrier dysfunction

Hypomorphic desmosome in Lss$^{flox}$-K14

Wada et al, PLOS Genetics 2020
Tamoxifen-inducible epidermis-specific Lss knockout mice showed hypotrichosis corresponding to the patients.

$Lss^{ff}$ - $K14ERT$ reproduced the enzymatic dysfunction and pathological findings in the patients.

Lens-specific Lss knockout mice showed cataracts.

Wada et al, PLOS Genetics 2020
What is the mechanism of hypotrichosis or cataracts in LSS deficiency?
- Shh or Wnt signaling?
  Pathogenesis of Smith-Lemli-Opitz syndrome would be involved in aberrant Shh or Wnt signaling.

Phenotype-genotype correlation?
- A previous report suggested the phenotype may be dependent on the locus of mutations, although phenotypes of our model mice have not been consistent.

Discussion

We confirmed LSS enzymatic inhibition caused by biallelic LSS loss-of-function.

The ratio of (S)-2,3-epoxysqualene to lanosterol in the sebum would be a good biomarker for the diagnosis of LSS deficiency.

Hypotrichosis and cataracts would be caused by LSS enzyme disruption in the affected organs.

Our mouse model of LSS deficiency could help clarify the pathological mechanism and develop novel treatments.

Conclusion

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