L-Fucose supplementation as a therapy for FUT8-CDG

JH Park¹, J Reunert¹, M He², RG Mealer³, M Noel³, Y Wada⁴, M Grüneberg¹, J Horváth⁵, RD Cummings³, O Schwartz¹ & T Marquardt¹

¹ University Children’s Hospital Münster, Münster, Germany
² Children’s Hospital of Philadelphia, Philadelphia, USA
³ Harvard Medical School, Boston, USA
⁴ Osaka Women’s and Children’s Hospital, Osaka, Japan
⁵ Institute of Human Genetics, University of Münster, Münster, Germany

Introduction

- FUT8 encodes an α-1,6-fucosyltransferase that mediates core fucosylation
- Mutations in FUT8 cause a severe congenital disorder of glycosylation marked by dysmorphism, skeletal abnormalities and respiratory impairment
- Previous in vitro experiments found no effect of L-fucose supplementation on glycosylation in fibroblasts
- We report on the effects of oral L-fucose supplementation in dizygotic twins

Highlights

- Oral L-fucose supplementation is well tolerated in FUT8-CDG
- Substrate supplementation using L-fucose is associated with clinical improvement in FUT8-CDG
- Glycosylation studies identified a limited, protein specific improvement of fucosylation

Materials & Methods

Patients underwent exome sequencing in addition to glycosylation studies using high-performance liquid chromatography (HPLC) and isoelectric focusing (IEF).

Detailed glycosylation studies were performed in the form of N-glycome profiling using MALDI-TOF MS in addition to lectin blotting and LC-ESI-TOF MS. All procedures were approved by the relevant institutional IRB (University of Münster 2019-199f-a).

L-fucose supplementation was introduced at 15 mg/kg/day and gradually increased to a final dose of 825 mg/kg/day. In addition, D-galactose were added due to hypogalactosylation observed in ESI-TOF MS.
Results

Case reports

- The patients are dizygotic twins presenting with muscular hypotonia, sucking weakness, dysmorphisms, and hypercapnic respiratory failure.
- Exome sequencing identified the compound heterozygous FUT8 variants (c.1403del [p.Ser468Tyrfs*26];(c.1418G > A [p.Arg473Gln]) in both patients.
- No glycosylation abnormalities detected in HPLC or IEF.

Core fucosylation is severely reduced in FUT8-CDG

- N-glycome profiling using MALDI-TOF MS detects preserved antennary fucose structures in FUT8-CDG.
- Core fucosylation is virtually absent in both patients.

Oral L-fucose supplementation results in a limited, protein specific improvement of glycosylation.

- No significant difference was detected in N-glycome profiling using MALDI-TOF MS between pre- and posttherapeutic samples.
- Similarly, lectin blots did not identify major differences following treatment.
Oral L-fucose supplementation results in a limited, protein specific improvement of glycosylation

- ESI-TOF MS detected a decrease in fucosylated and truncated glycan species following therapy
- Transferrin fucosylation increased despite remaining below reference ranges

Clinical improvement associated with L-fucose supplementation in FUT8-CDG

- Both patients showed clinical improvement under L-fucose supplementation therapy
  - Non-invasive ventilation could be discontinued
  - Motor abilities improved with less pronounced muscular hypotonia allowing free sitting
- No adverse effects were noted during the entire duration of therapy

Discussion

- LC-ESI-TOF MS detected partial improvement of core glycosylation following L-Fucose supplementation
- Targeted analysis revealed protein specific improvement of glycosylation
- Differences in sensitivity of analytical methods and tissue specific effects as possible causes of diverging findings
- High concentrations of L-fucose might be needed to improve glycosylation further

Contact:
Dr. med. Julien H. Park
Email: julien.park@ukmuenster.de
@JHPark_MD

Scan to find the paper!