ORAL COMMUNICATIONS

DECODING THES PATHOGENESIS: HOW TTC37 SHAPES GUT HOMEOSTASIS AND PERISTALSIS

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Trichohepatoenteric Syndrome (THES) is an ultra-rare, multisystem disorder caused by biallelic mutations in the TTC37 or SKIV2L genes, which encode essential subunits of the SKI complex, a cofactor for the RNA exosome. The hallmark of THES is intractable diarrhea, often necessitating parenteral nutrition for survival. THES is a life-threatening condition, with mortality mainly attributed to intestinal failure and infections. Despite its clinical implications, no curative treatment exists, and management is limited to supportive care.

The mechanisms through which TTC37 mutations give rise to such profound gastrointestinal dysfunction and high mortality have remained entirely unclear. The existing body of literature consists largely of clinical descriptions and case reports and provides no mechanistic explanation linking TTC37 deficiency to THES enteropathy. This critical gap in knowledge has hindered the identification of therapeutic targets for a condition in urgent need of effective interventions.

To elucidate the complete unknown pathophysiological basis of THES, we established a ttc37 knockout zebrafish line, the first animal model of the disease reported to date. This model recapitulates major aspects of the human condition and exhibits marked abnormalities in gut architecture and impaired peristalsis, all consistent with the clinical phenotype of THES.

Leveraging the strengths of our disease model, we dissected the impact of the ttc37 mutation on gut cells. We identified marked structural defects associated with increased inflammation and apoptosis, alongside a reduction in stemness markers.

In conclusion, we provide the first insight into the molecular basis of THES symptomatology, enabled by the generation of a disease model. Our data support a pathogenic framework in which structural defects lead to impaired epithelial integrity, chronic inflammation, and reduced regenerative capacity, ultimately driving THES enteropathy.