Congenital Tufting Enteropathy

- A Case Presentation and Further Study

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Aims and Objectives

- Presentation of case vignette - confirmed diagnosis and successful management
- Discussion of congenital diarrhoeal disorders
- Discussion of congenital tufting enteropathy
  - Advances in diagnostic processes
  - Management
  - Prognosis

Case Vignette - Part 1

2015 - Baby M born in December

2016

- Intractable diarrhoea (>1.5L per day)
- Diagnosed at 3 months age with upper and lower GI endoscopy, biopsies using histology and electron microscopy proved congenital tufting enteropathy
- Looked after by foster carers from same age due to safeguarding issues
- PICC line, Broviac line and Hickmann line inserted for home total parenteral nutrition (TPN)
- Complications suffered
  - Iron infusions required
  - Line-related infections

Case Vignette - Part 2

2017-2021

- PEG insertion gastrostomy
- Lines required changing every 1-2 years due to repeated infections
- Cholecystectomy due to having acute calculous cholecystitis
- Developed intestinal failure but
- Tolerated larger volumes of feed and growth improved

2022-2025

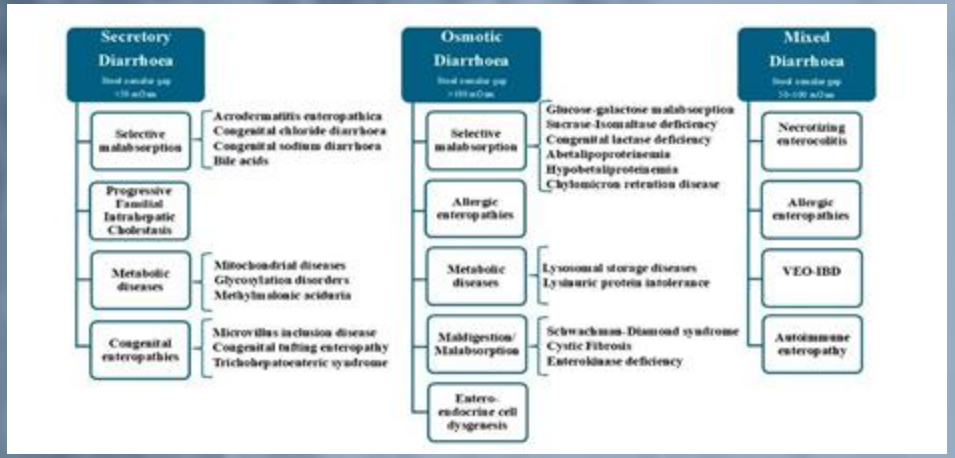
- Developed line-related non-mycobacterium TB abscess in 2023 - one line re-sited
- Diagnosed with ADHD in 2023 following developmental paediatrician assessment after concerns from long-term foster parents and school
- Tolerated good volumes of feed and occasionally ate normal food in small amounts
- Follow up every 6 months

Congenital Diarrhoeal Disorders - History

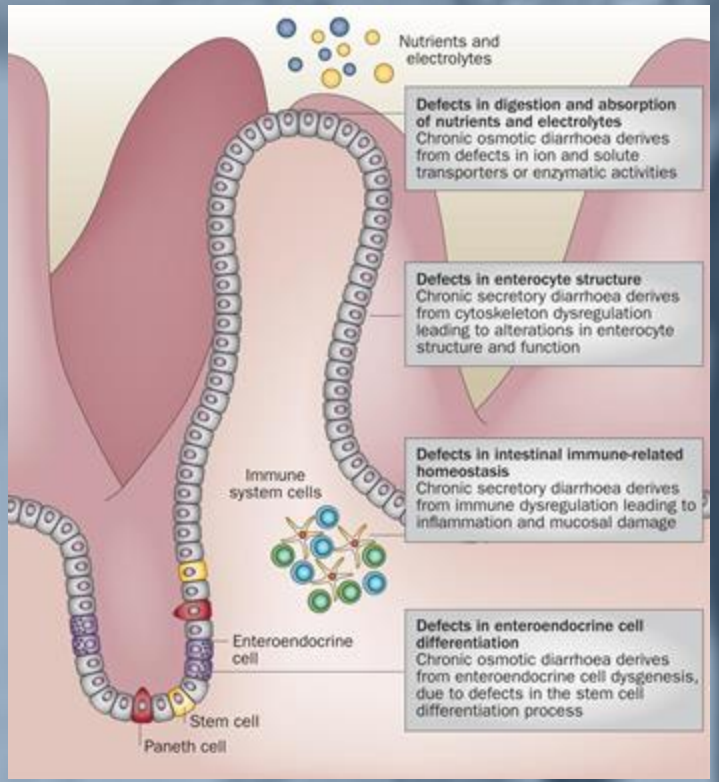
- First described as ‘infantile intractable diarrhea’ (1)
  - Age: Under 3 months old.
  - Duration: Diarrhea persisting for more than two weeks.
  - Negative Cultures: Three or more stool cultures negative for standard pathogenic organisms.
  - Refractory Nature: Prolonged diarrhea despite extensive hospital therapy and intravenous fluids
  - Despite hospital management, diarrhoea was persistent and intractable
  - High mortality
- Why Dr Avery’s 1968 paper mattered (2)
  - Diarrhoea was highly fatal in infants if it could not be pinned to an obvious infection.
  - Highlighted that many of these infants had previously unrecognized underlying conditions.
- Overall classification (3)
  - Failure to make a diagnosis of any kind
  - Specific diagnosis but no therapy
  - Specific diagnosis but therapy of variable efficacy
  - No specific or only partial diagnosis

Congenital Diarrhoeal Disorders - Current concepts

- Number of well-characterized disorders has increased over the last 20 years
- Many new genes identified have been functionally related (4, 5)

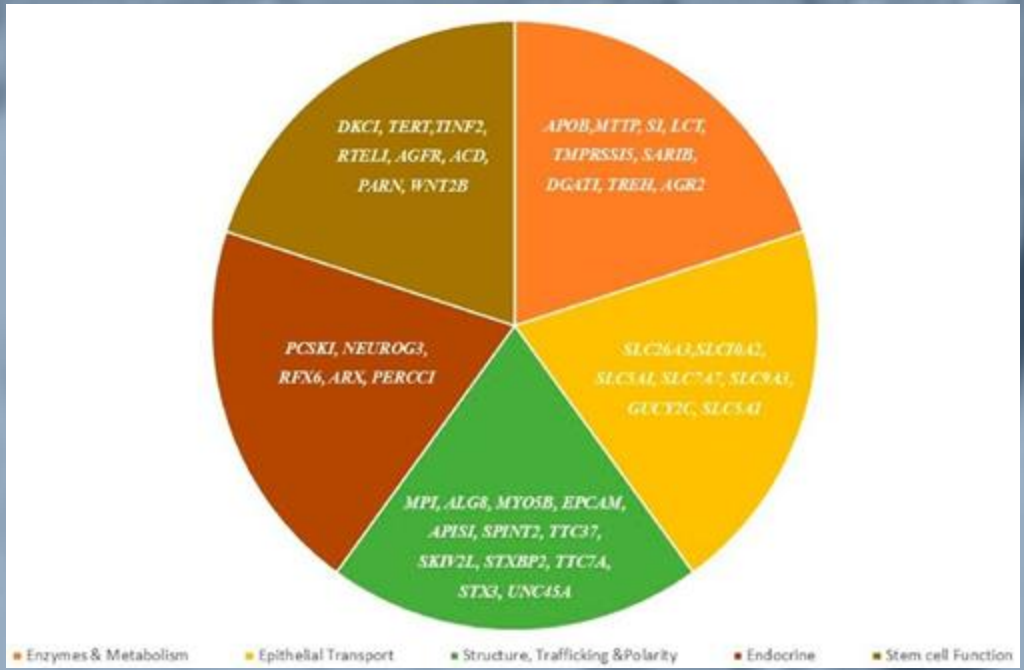


Overview of congenital diarrhoea Abbreviation: VEO-IBD, very early onset inflammatory bowel disease (6)



Congenital Diarrhoeal Disorders - Current concepts Part 2

- Molecular analysis has changed the diagnostic scenario in congenital diarrhoeal disorders.
- Major advances have been made in terms of pathogenesis. (6)



Congenital Tufting Enteropathy - General

- Inheritance - autosomal recessive (7, 8)
- Age of onset - Neonatal period (0-38 days) (8)
- Prevalence at birth - 1-9/1000000 (Europe) and incidence - 1 in 50,000-100,000 (Western Europe)(9)
- Overall mortality rate ~20% (10)
- More common in populations and regions with high rates of consanguinity (11)

First described in 1994 by Reifen et al. (12) as a syndrome of:

- Protracted, watery diarrhea beginning in early infancy
- Cessation of enteral feeding resulted in marked reduction of bowel motion volume and frequency
- Distinct histologic and ultrastructural characteristics
    - Semiquantitative assessment of the epithelial surface in these patients revealed that 80 to 90% contained tufts

Congenital Tufting Enteropathy - Genomics Part 1

It is primarily caused by biallelic mutations in two distinct genes, EPCAM and SPINT2. [13, 14, 15]

Mutations in the *EPCAM* (Epithelial Cell Adhesion Molecule) gene (classic form) are the most common cause, accounting for roughly 73% of CTE cases. These mutations generally lead to isolated intestinal disease. [8]

- Frameshift Mutations: The most frequently reported variant worldwide is the c.499dupC (previously c.498insC) (8, 16, 17, 18)
- Splice Site Mutations: Intron mutations, such as c.556-14A>G (common in Mediterranean populations) and c.491+1G>A (16, 19, 20)
- Nonsense Mutations: Premature stop codons (e.g., p.Trp143*, p.Lys106X) disrupt protein translation(8, 21, 22)
- Missense Mutations: Amino acid substitutions (e.g., p.Gln109Arg) cause misfolding and endoplasmic reticulum (ER) retention of the protein (8, 23, 24)

Congenital Tufting Enteropathy - Genomics Part 2

Mutations in the *SPINT2* (Serine Peptidase Inhibitor Kunitz Type 2) gene (syndromic form)

- Account for about 21% of CTE cases
- Present alongside extraintestinal symptoms like anal and choanal atresia (blockages in the nasal or anal passages)
- Ophthalmologic (eye) abnormalities. (8, 25, 26)
- These mutations are usually homozygous or compound heterozygous changes
    a. Loss of HAI-2, a Kunitz-type serine protease inhibitor. Without it,
        i. enzymes like matriptase become hyperactivated
        ii. hepatocyte growth factor activator (HGFA) is inhibited (25, 27)

Congenital Tufting Enteropathy - Pathogenesis Part 1

Regardless of mutation type, the consequence is a severe disruption of intestinal epithelial integrity. (13, 21, 26, 28)

Probable Signaling Mechanisms

- The EpCAM Pathway: Mutations in the Epithelial Cell Adhesion Molecule (EPCAM) gene destabilize the EpCAM protein, which is vital for cell-cell adhesion and homeostasis.
- The SPINT2 Pathway: Mutations in SPINT2 (Serine Peptidase Inhibitor Kunitz Type 2) act indirectly on the EpCAM pathway.
- Notch Signalling: Aberrant differentiation is strongly tied to overactive notch signalling. Studies utilising murine models have shown that treatment with Notch pathway inhibitors (such as DAPT) can reverse these differentiation defects (6, 13, 29)

Congenital Tufting Enteropathy - Pathogenesis Part 2

Role of Intestinal Homeostasis in CTE

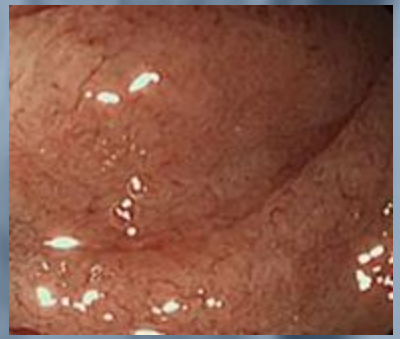
- Aberrant Cell Differentiation: Intestinal stem cells fail to properly differentiate into functional absorptive enterocytes and critical secretory cells (e.g., goblet and Paneth cells).
- Disrupted Barrier Function: The defining characteristic of CTE—focal epithelial "tufts"—consists of densely packed, disorganized enterocytes.
- Cell-Matrix Adhesion Defects: Impaired interactions between intestinal epithelial cells and the underlying extracellular matrix lead to structural collapse.(13, 31, 32)

Congenital Tufting Enteropathy - Diagnostic Imaging

- Oesophageogastroduodenoscopy or enteroscopy
  - Most appropriate for obtaining biopsies
- Appearance: varying degrees of subtotal to total villous atrophy in the duodenal and jejunal mucosa.
- Gross Mucosa: mucosa may appear relatively smooth, flat, or minimally altered.
- Distribution: Characteristic lesions are often patchy
  - Entire small intestine
  - Occasionally large intestine (19, 33, 34, 35)



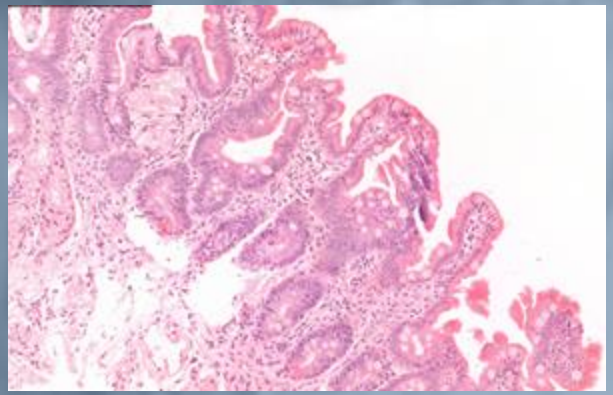


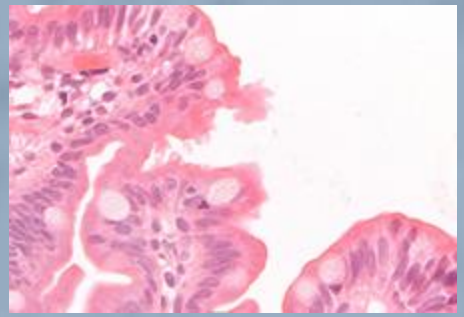


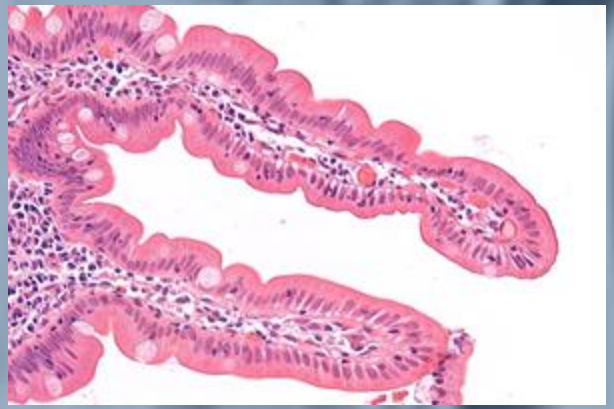
Congenital Tufting Enteropathy - Histopathology

Biopsy

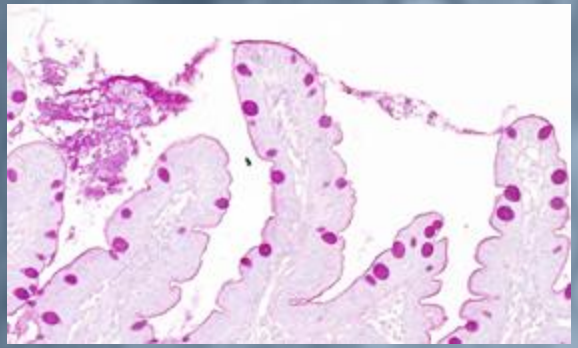
- Crypt distortion
- Villous blunting
- Multifocal epithelial tuft-like appearance
- Nuclear pseudostratification and loss of polarity



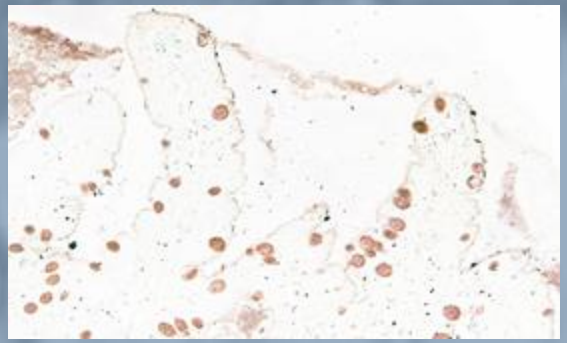




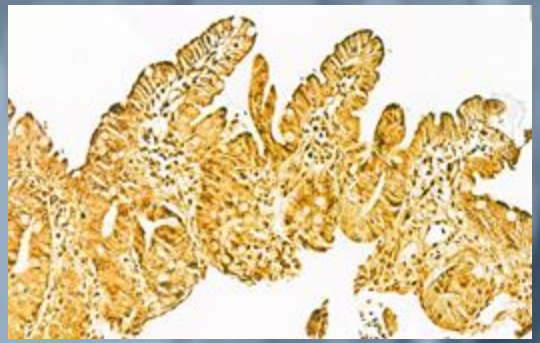
Congenital Tufting Enteropathy - Further Work



PAS

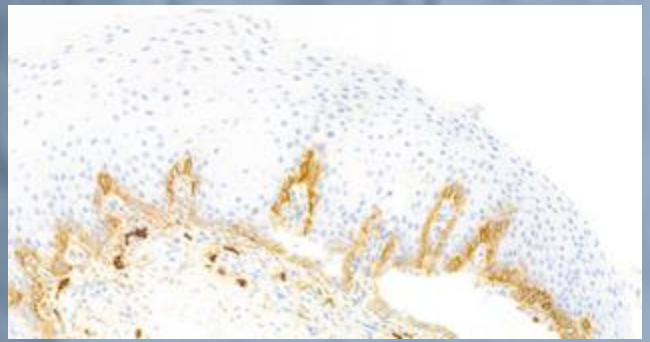


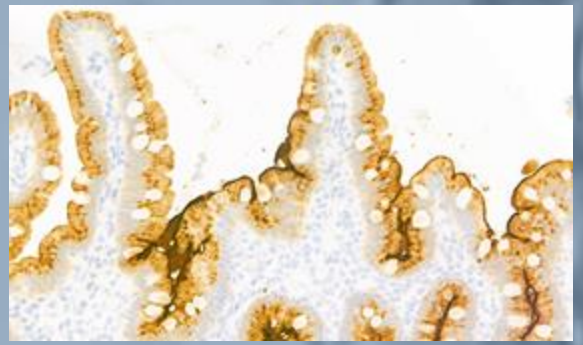
Grocott



Warthin-Starry

D2-40

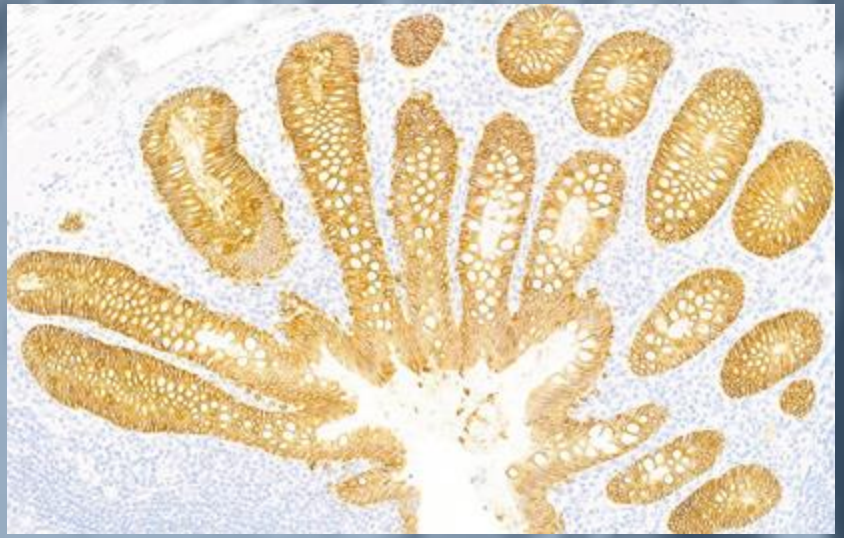




CD10

Congenital Tufting Enteropathy - Further Work contd.



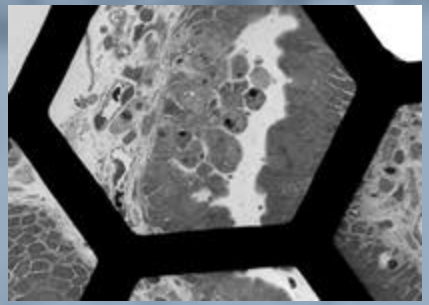


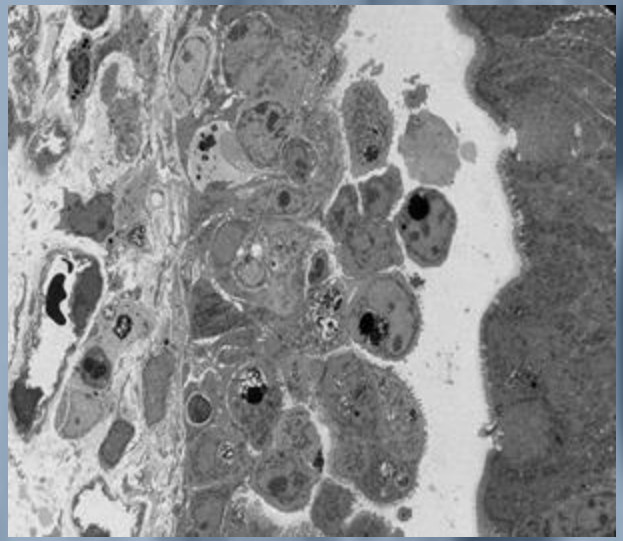
MOC-31: loss of expression of EPCAM in congenital tufting enteropathy

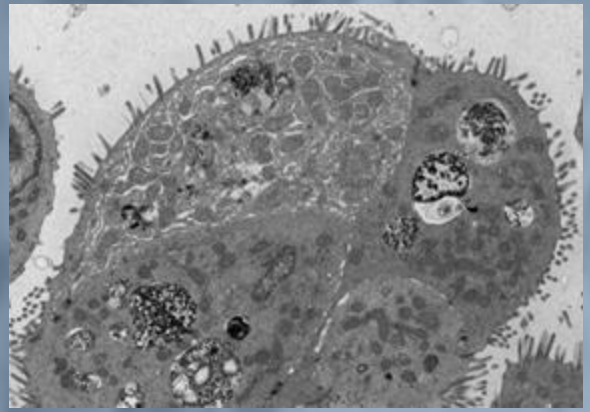
Congenital Tufting Enteropathy - Electron Microscopy

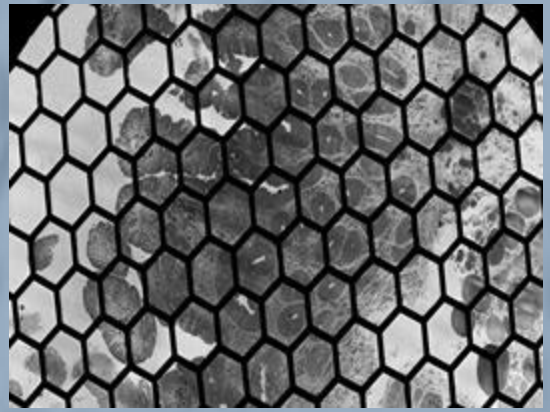
Vital diagnostic tool - provides critical ultrastructural imaging to confirm the disease.

- Visualizing epithelial tufts (14, 25, 36)
- Assessing the brush border (36, 37, 38)
- Ruling out mimics (6, 38, 39, 40)









Congenital Tufting Enteropathy - Genomics testing

United Kingdom (41)

- Genomics England specialised gene panel, since 2019
- V3.11 latest, clinical indication R331
- 49 proteins implicated and therefore tested for

United States of America

- Congenital Diarrhea Panel by Labcorp Genetics (formerly Invitae) – tufting enteropathy testing not included (42)
- Congenital Diarrhea Panel by Blueprint Genetics - tufting enteropathy testing included (43)

Congenital Tufting Enteropathy - Management

Supportive, not curative (8, 13, 24, 34)

- Short-term - fluid resuscitation
- Long-term parenteral nutrition (PN) for survival (44)
- Minimal enteral feeding
- Monitoring for intestinal failure complications
  - Cholestasis
  - Use of GLP-2 agonists such as Teduglutide
- Small Bowel transplantation (45)
- Regular MDT input - crucial!

Congenital Tufting Enteropathy - Prognosis

- Intestinal failure & parenteral nutrition dependence (15, 46, 47)
- Mortality rates - case series of over 100 CTE patients show overall mortality ~27% (48)
    - from PN-related complications such as sepsis, thrombosis, or liver failure.
- Intestinal or multivisceral transplantation - viable but challenging therapeutic option, with historical 3-year survival rates around 30%
- Genotype-Phenotype Variables - numerous and can cause broad clinical heterogeneity, meaning the severity of the disease varies from patient to patient
    - EPCAM c.757G>A can present with a milder course

Conclusion

- Congenital Tufting Enteropathy is a complex disorder with heterogeneity in presentation and underlying genetics
- All testing modalities prior to genetic testing are still required for successful diagnosis
- Crucial to have good ongoing patient education and wide variety of MDT members in order to facilitate ongoing management
- Consider the need for availability of a broad panel of tests or referrals at your centre to ensure correct diagnosis is reached for optimal management and monitoring

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Questions?

