Early Onset Diarrhoea

Patient 1

- 7 month old male
- Poor growth, wasted, moderate signs of dehydration
- No other significant findings
- Occasional loose stool (fat malabsorption?)

Patient 1

Special investigations

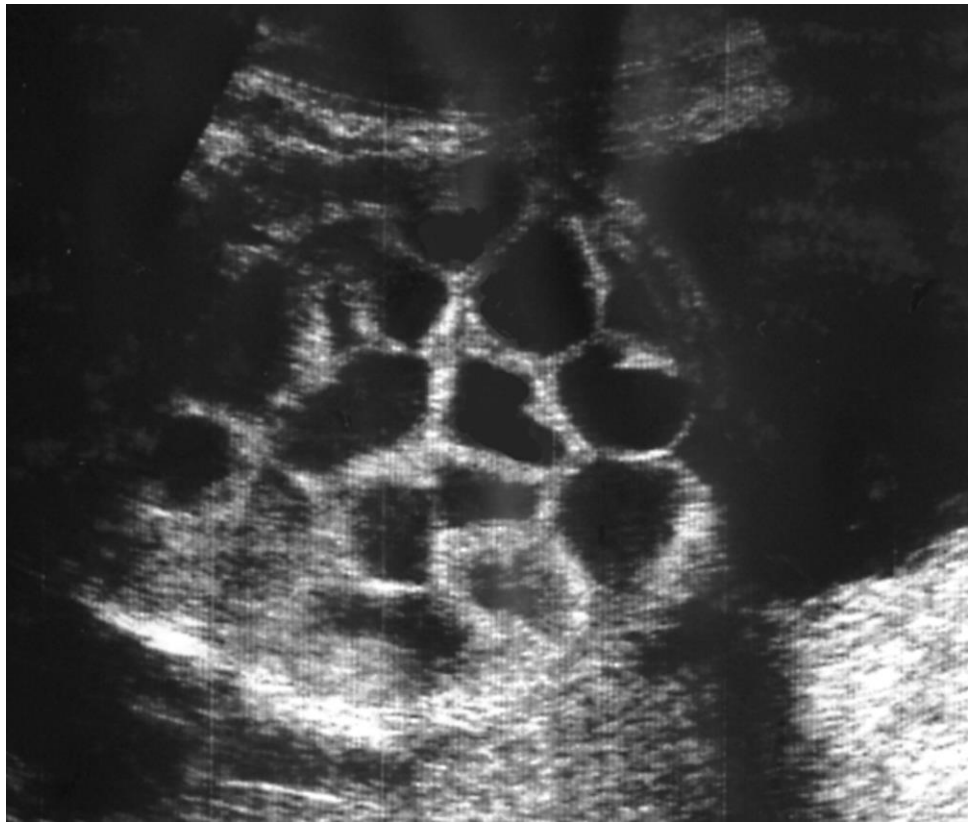
- Electrolytes
  - Na 124 mmol/l
  - Cl 74 mmol/l
  - K 2,8 mmol/l

- Acid Base
  - pH 7,52
  - HCO3 36mmol/l

Antenatal History

Antenatal Sonar

- Polyhydramnios
- Dilated intestinal loops



Clinical course in hospital

- Denies any diarrhoea

- Ward staff: No diarrhoea

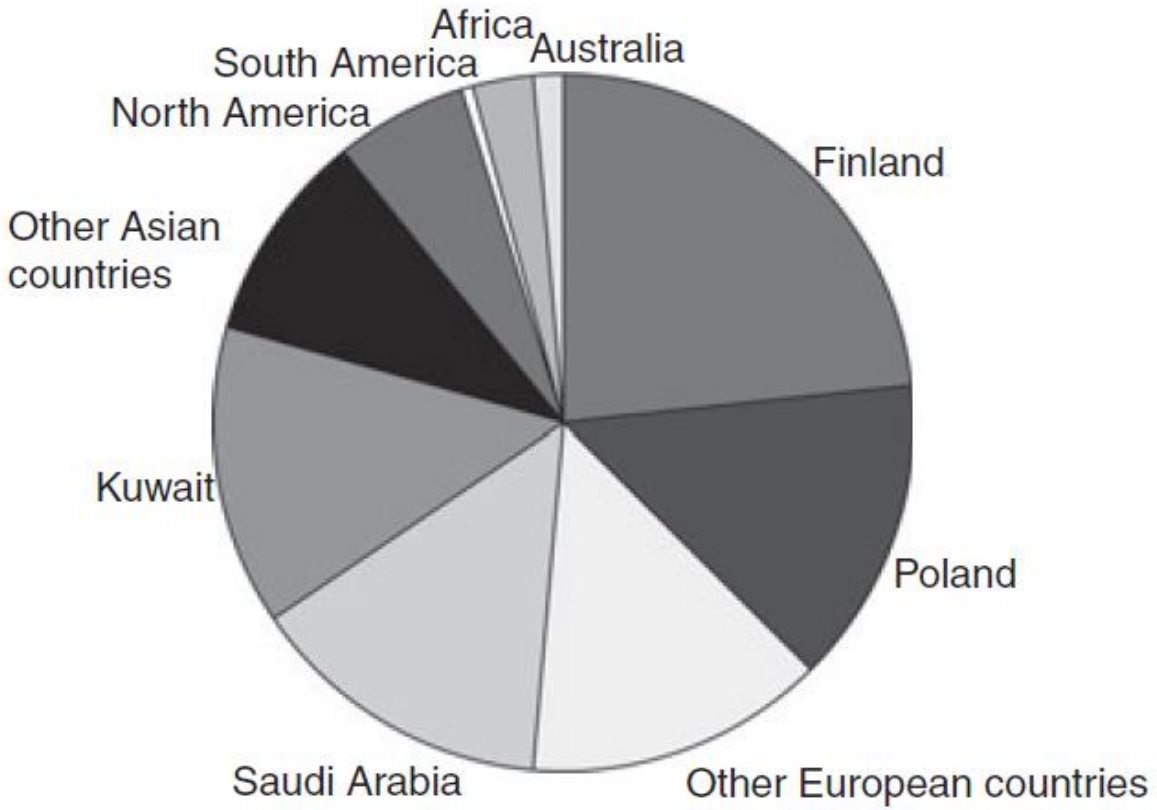
Stool electrolytes

After digital examination of rectum

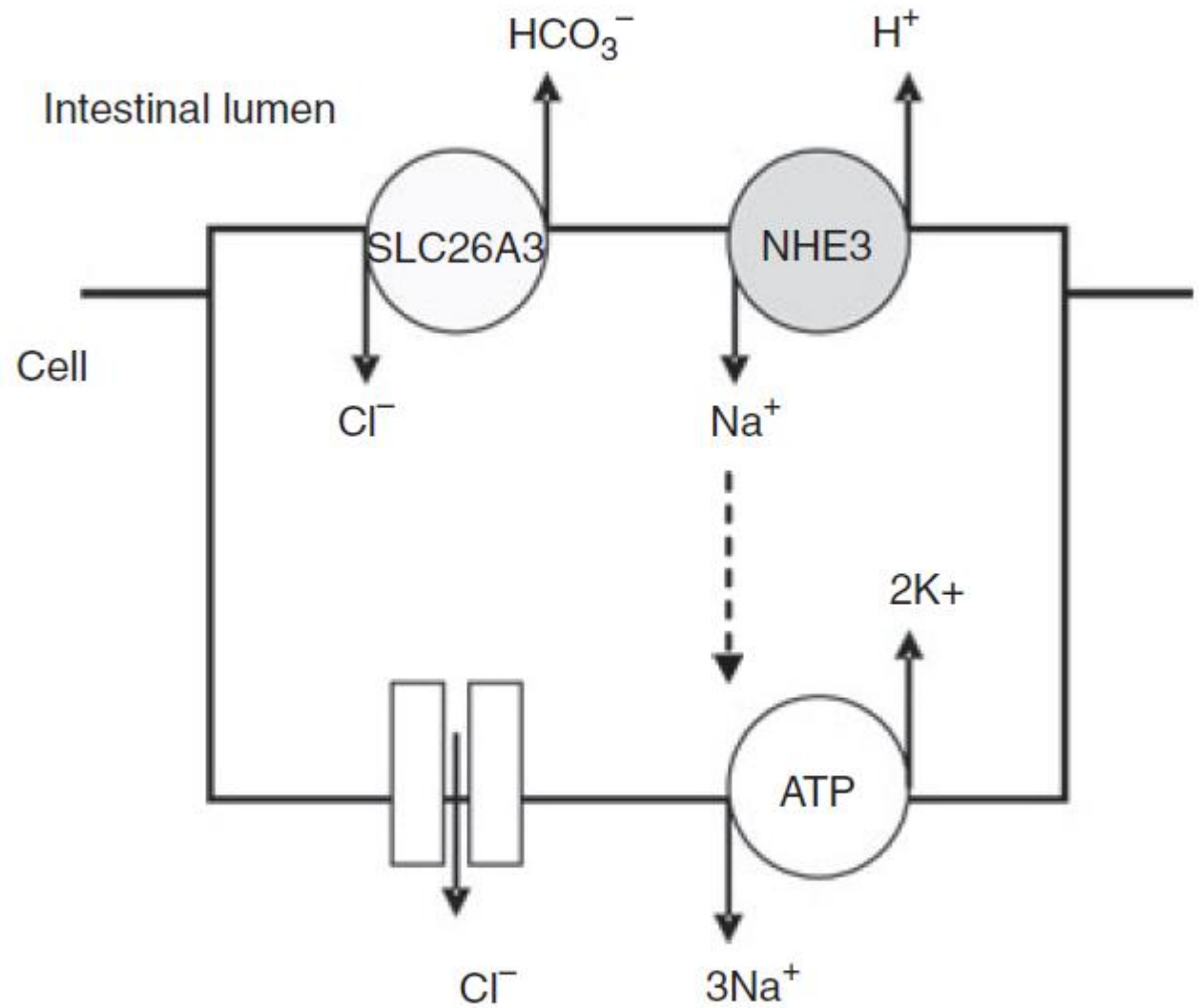
- Na 23 mmol/l
- K 30 mmol/l
- Cl 161 mmol/l

Congenital Chloride Diarrhoea

250 reported cases



Wedenoja 2009



Wedenoja 2009

Patient 2

- 6 week old
- Secretory diarrhoea, vomiting, severe malnutrition
- Dysmorphic features
  - Facial features (triangular face, low set ears, penile hypospadia, bilateral camptodactyly)
  - Hair abnormal
  - Pigmented skin lesions

Patient 2

- Intolerant to any oral feeds
- TPN started

- Recurrent episodes of infection

- Small bowel biopsy: moderate villous atrophy
- 3,5 months in hospital
- Died due to infection

Patient 2

- Metabolic screen: normal
- Normal karyotype

Patient 2 (sib)

- Sibling admitted to PICU at 3 months
- Severe pneumonia (CMV)
- Died on ventilator

- Consanguineous family (first cousins, once removed)

Exome Sequencing

Novel homozygous missense mutation

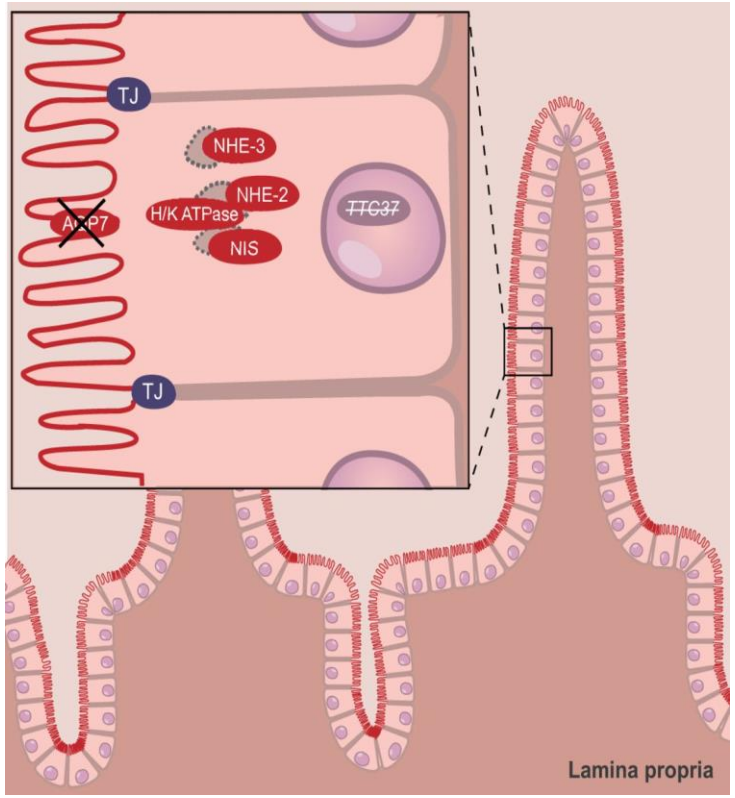
in exon 42 of TTC37

Trichohepatoenteric syndrome

Mutations in TTC37 (THES1) or SKIV2L (THES2)

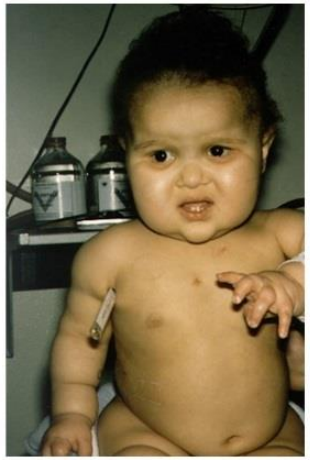
Trafficking or expression of apical proteins

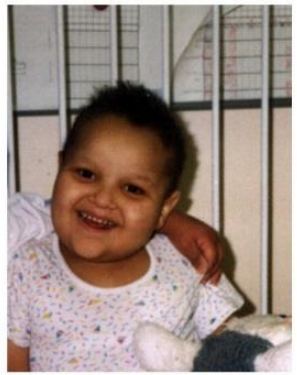
mRNA degradation

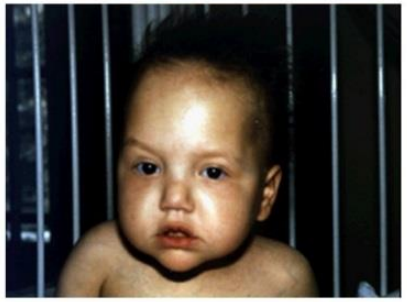


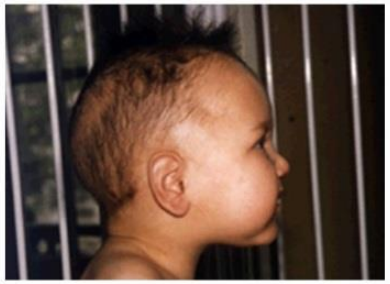
Trichohepatoenteric syndrome

- Severe diarrhoea in infancy
- Hair abnormalities
- Dysmorphic facial features
- Immunodeficiency
- Early onset IBD









Patient 3

- 20 month old boy
- Recurrent infections:
  - Streptococcal infections
  - Septic arthritis
  - CMV
  - Pneumonia
- Additional problems
  - Vasculitic rash
- Laboratory
  - Thrombocytopaenia
  - High IgE

Patient 3

- Intestinal complaints
  - Reaction to cow's milk (improved with extensively hydrolysed formula)
  - Intermittent diarrhoea
  - PR bleeding

Patient 3

Small Bowel Histology

- Duodenum: villous blunting, inflammatory infiltrate (mild, neutrophils and plasma cells)
- Stomach: Chronic gastritis (>50 eosinophils/hpf)
- Oesophagus: 2-3 eosinophils/hpf

Improved on hydrolysed formula

Colon (on MTX & Prednisone)

- Crypt distortion
- Mild cryptitis

Patient 3

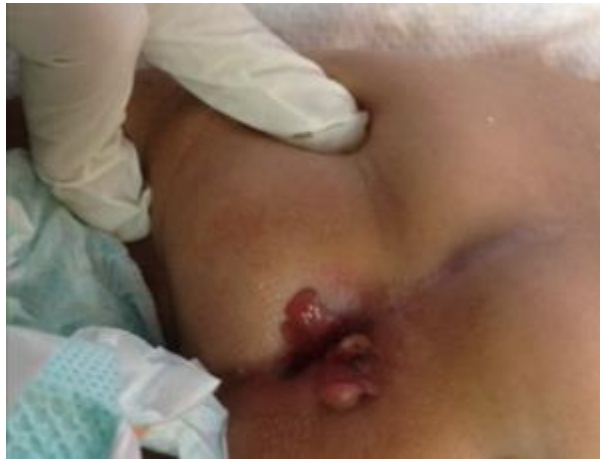
Exome analysis

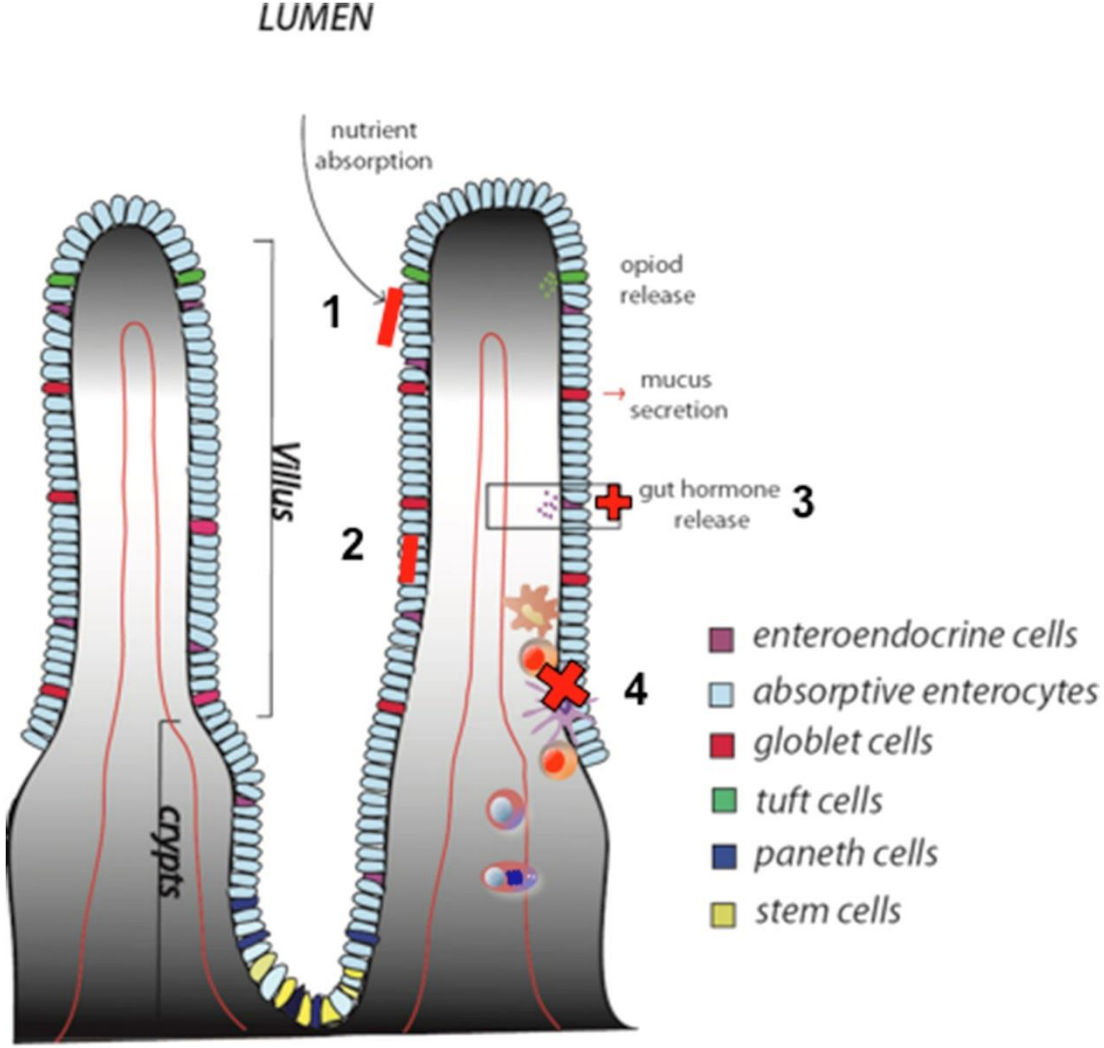
- Wiskott Aldrich syndrome

Classification of Congenital Diarrhoea

Defects in:

- Digestion, Absorption, transport
- Enterocyte differentiation or polarisation
- Enteroendocrine cells
- Primary Immune Deficiency





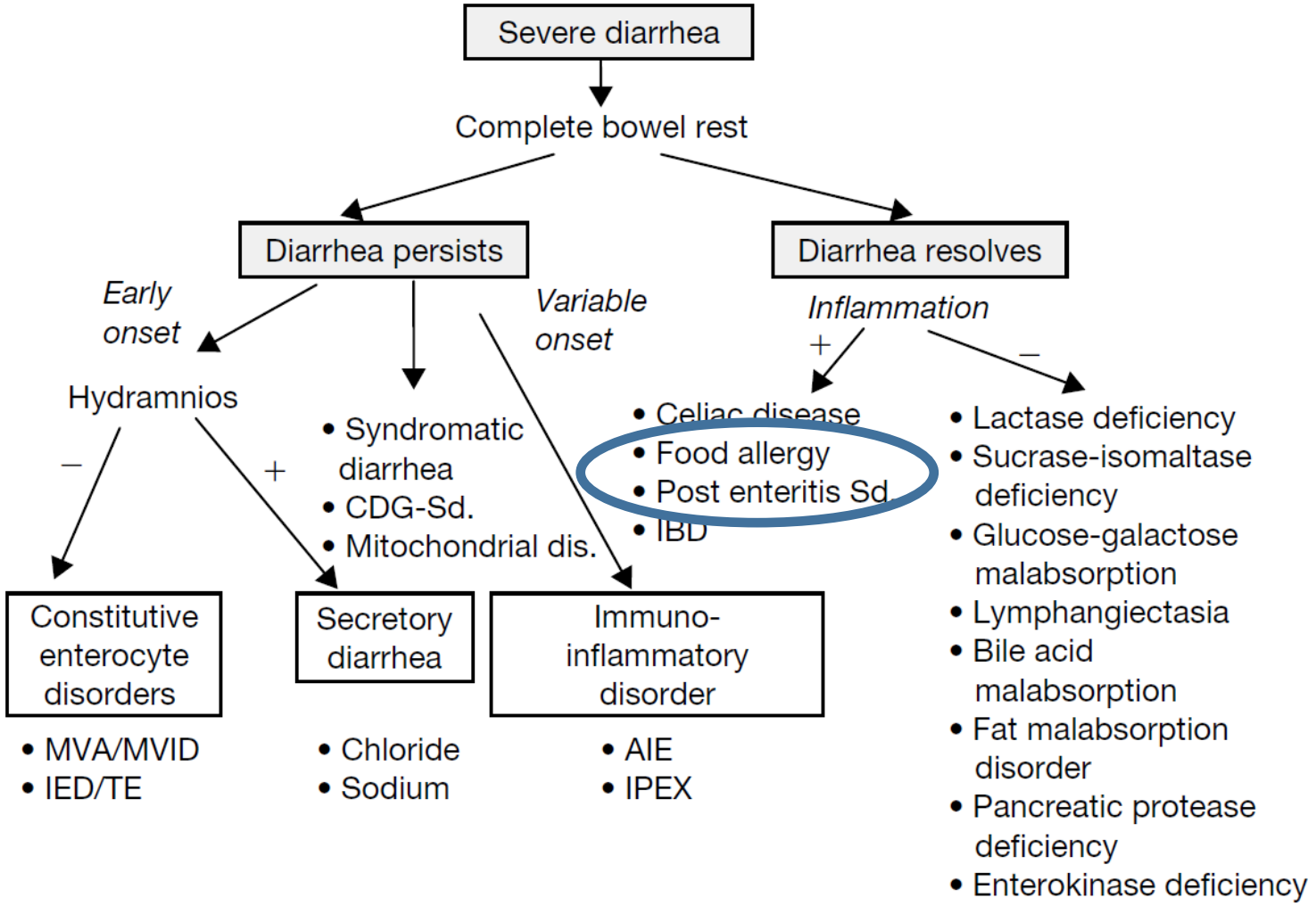
C. Posovszky. 2016

When to Suspect a Congenital Diarrhoea

- Polyhydramnios
- Dilated intestinal loops in utero

- Family history
- Consanguinity
- Dysmorphic features

- Early onset diarrhoea
- No response to standard treatment
- Associated complications/findings
    - Rash
    - Increased eosinophils
    - Increased IgE
    - Recurrent infections
    - Endocrine manifestations
- Histology
    - Often difficult to interpret or non-specific



+ Immnune deficiency:

1. HIV
2. PID

Ruemelle 2007

GENIUS Cohort

Fabienne Charbit-Henrion

Nadine Cerf-Bensussan

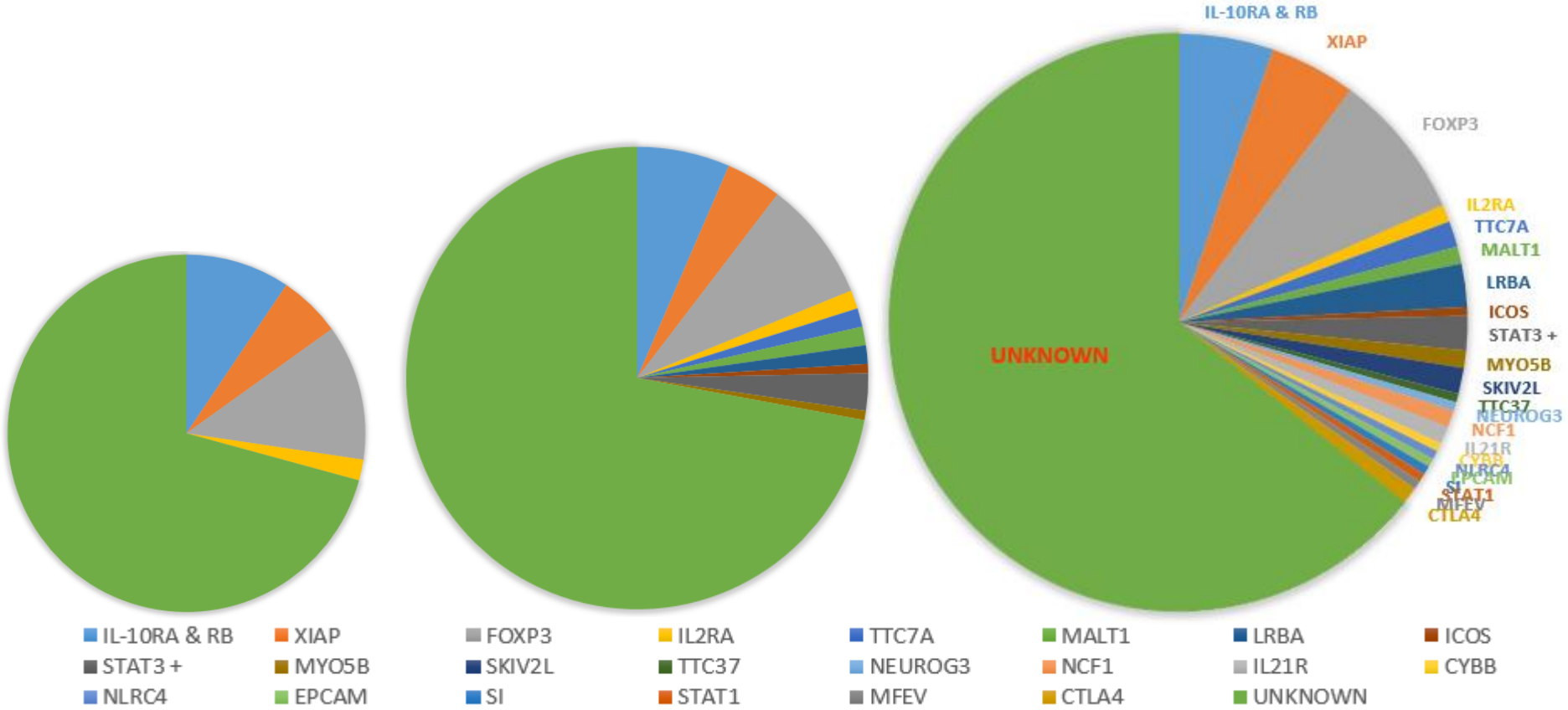
Frank Ruemmele

GENIUS Group's Experience

2009-2013
PHENOTYPE BASED
FUNCTIONAL TESTS
106 patients
Diagnostic: **29%**

2013-2014
GENOTYPE BASED
EXOME SEQUENCING
154 patients
Diagnostic: **28%**

2015
GENOTYPE BASED
TARGETED PANEL SEQUENCING
207 patients
Diagnostic: **36%**



Conclusions

- Genetic diseases causing early onset severe diarrhoea more common than thought
- Next generation sequencing (Exome analysis/target panel) makes definitive diagnosis possible
- Make friends with your geneticist & molecular biologist

Results: new diagnoses (2)

Congenital Diarrhea	Malabsorption	IPEX-like Syndromes	Colitis	Common variable ID	Chronic Granulomatosis	Inflammasome
MYO5B = 2	LCT	FOXP3 = 4	ICOS	CD40	CYBA	MEFV
STX3	SI = 1	IL2RA	IL10	CD40LG	CYBB	NLRC4 = 1
NEUROG3 = 1	MGAM	STAT1 = 1	IL10RA = 1	TNFRSF13C/BAFFR	NCF1 = 2	MVK
EPCAM = 1	SGLT1	STAT3	IL10RB	TNFSF13B/BAFF	NCF2	PLCG2
SPINT2	GLUT5	STAT5B	XIAP = 4	TNFSF13/APRIL	NCF4	
TTC37 = 1	GLUT2	CTLA4 = 2	IL21	TNFRSF13B/TACI	SLC37A4	
SKIV2L = 3	SLC7A7	MALT1	IKBKG	CD19	ITGB2	
SLC26A3	SLC10A2	LRBA = 3	ADAM17		GUCY2C	
SLC39A4	PRSS7	ITCH	NOD2			
DGAT1	PRSS1	DOCK8	IL21R			
PCSK1	PNLIP	WAS	TTC7A = 1			
	MTTP	DOCK2				
	APOB					
	SAR1B					
	SLC5A1					

Patient 3

Male infant
Recurrent presentations to ID service with pneumonia
Initially thought to have PTB
Developed intermittent diarrhoea
Occasional blood in the stool

Patient 3

Stool cultures : no pathogens
OGD : Normal
Histology

Sigmoidoscopy : Normal
Histology

Patient 3

Additional Findings

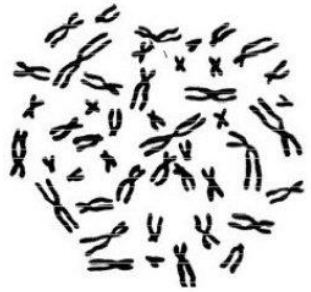
Patient 3

Suspected PID
Extensive discussion with immunologists

Exome analysis:

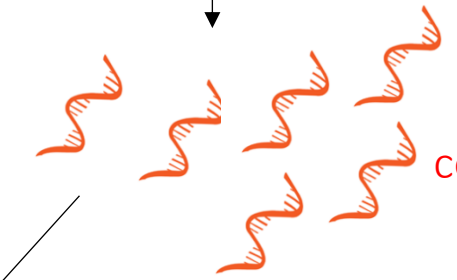
Awaiting BMT

Next Generation Sequencing



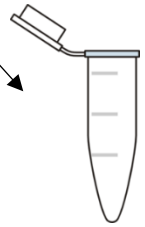
Small fragments of patient's genomic DNA

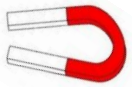
Congenital Diarrhea	Malabsorption	IPEX-like Syndromes	Colitis	Common variable ID	Chronic Granulomatosis	Inflammasome
MYO5B	LCT	FOXP3	ICOS	CD40	CYBA	MEFV
STX3	SI	IL2RA	IL10	CD40LG	CYBB	NLRC4
NEUROG3	MGAM	STAT1	IL10RA	TNFRSF13C/BAFFR	NCF1	MVK
EPCAM	SGLT1	STAT3	IL10RB	TNFSF13B/BAFF	NCF2	PLCG2
SPINT2	GLUT5	STAT5B	XIAP	TNFSF13/APRIL	NCF4	
TTC37	GLUT2	CTLA4	IL21	TNFRSF13B/TACI	SLC37A4	
SKIV2L	SLC7A7	MALT1	IKBKG	CD19	ITGB2	
SLC26A3	SLC10A2	LRBA	ADAM17		GUCY2C	
SLC39A4	PRSS7	ITCH	NOD2			
DGAT1	PRSS1	DOCK8	IL21R			
PCSK1	PNLIP	WAS	TTC7A			
	MTTP	DOCK2				
	APOB					
	SAR1B					
	SLC5A1					



RNA baits complementary to selected genes (Agilent)

CAPTURE by HYBRIDIZATION





SELECTION of TARGETED GENES

HIGH THROUPUT SEQUENCING

Results: new diagnoses (1)

- 173 patients:
  - 100 boys (58%)
  - Median age of onset : 1 year
  - Median duration of disease: 7.5 years