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 36 mmol/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
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
  • Thrombocytopenia
  • 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
- Immune deficiency:
  1. HIV
  2. PID
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%

Graphs showing the diagnostic success rates for different genotyping methods across different years.
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)

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<th>Congenital Diarrhea</th>
<th>Malabsorption</th>
<th>IPEX-like Syndromes</th>
<th>Colitis</th>
<th>Common variable ID</th>
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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

CAPTURE by HYBRIDIZATION

RNA baits complementary to selected genes (Agilent)

HIGH THROUPUT SEQUENCING

SELECTION of TARGETED GENES

- CAPTURING by HYBRIDIZATION
  - Small fragments of patient’s genomic DNA
  - 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