# Monogenic IBD
# WCPGHAN 2016

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www.neopics.org

# Disclosures

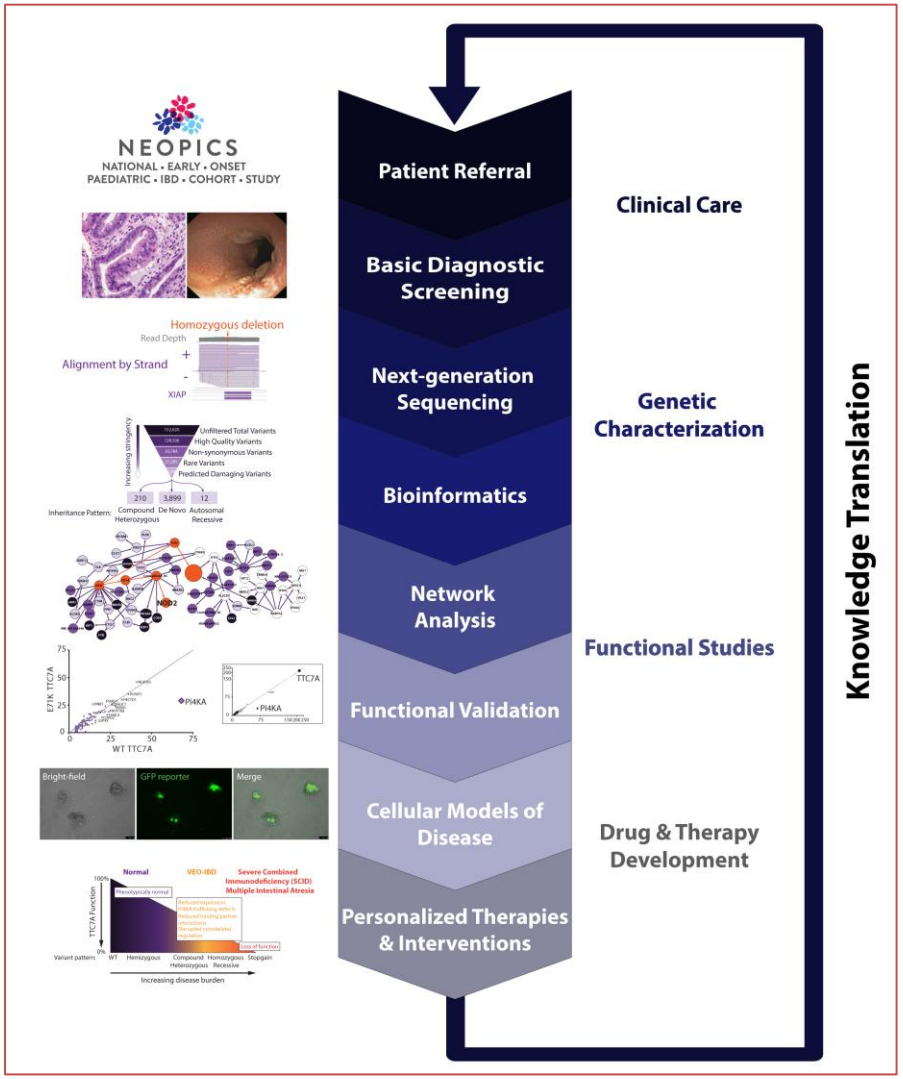
- None

# Learning Objectives

- To know which patients are appropriate for whole exome sequencing
- To be able to identify  the most common forms of monongenic IBD including IL10R, XIAP, and LRBA deficiency
- To determine appropriate therapies for monogenic forms of IBD including stem cell transplant

- **Upon completion of this session, the learner will be able to identify IBD patients that are likely to have monogenic forms of the disease and understand the appropriate therapies**

# Goal: to identify novel genes and understand their function to better treat patients with severe intestinal disease



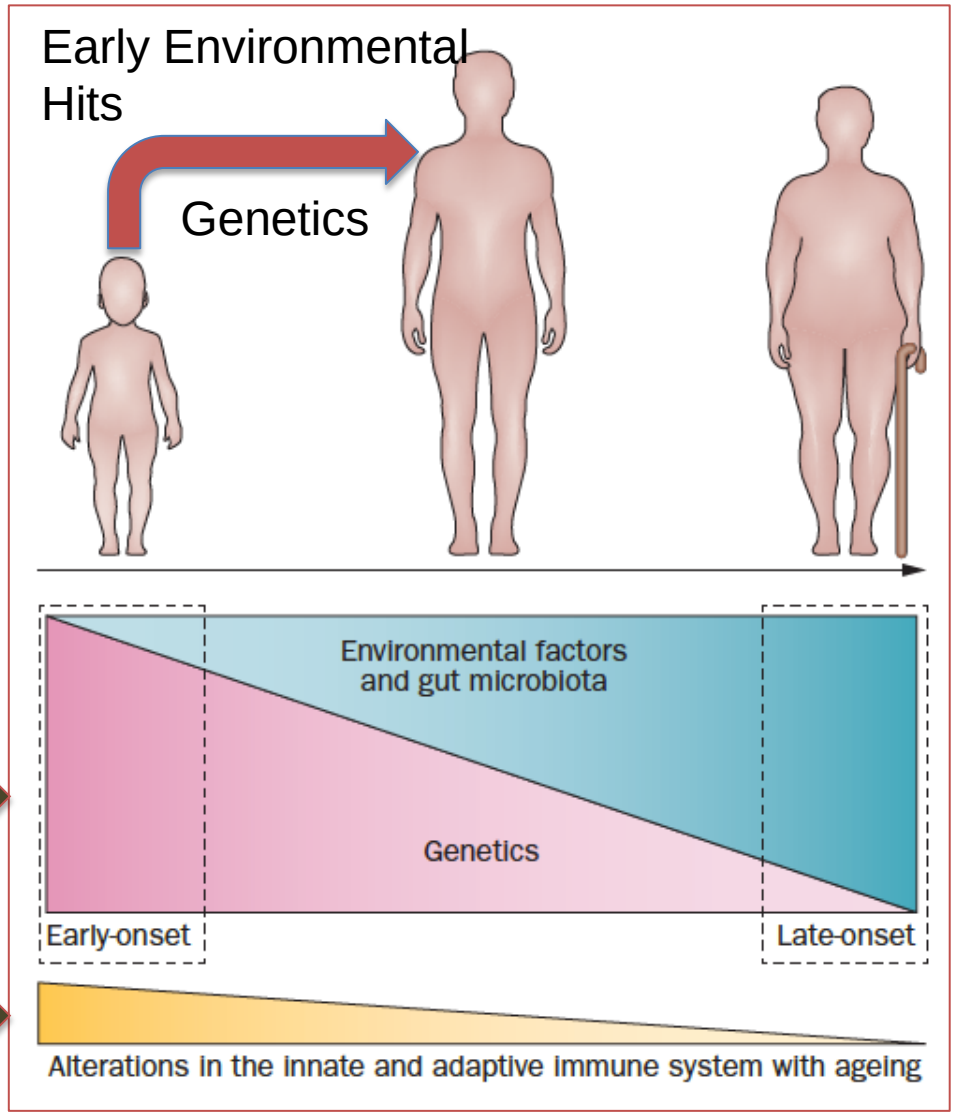
# Rapid increase incidence of VEOIBD

- Canada – increase in incidence not severity
  - Benchimol et al (2009) Gut 48:1490-97
  - **Benchimol…….Muise, Gastroenterology, 2014**
- Ireland – increase in incidence and severity
  - Rising incidence and increasing severity of very early onset IBD in Ireland – Wylde.. Hussey ECCO 2014
- Scotland - increase in incidence and severity
  - Henderson P et al. ECCO 2015 oral abstract OP027.
- Northern France – stable at 3% of Pediatric IBD
  - C. Gower-Rousseau on behalf of Epimad Registry, EUG 2015

# What causes IBD? Does it Vary with Age?

Do single genes cause IBD?

Can we influence the microbiome? Antibiotics?




Modified from Ruel…. Colombel, 2013

# Diagnostic Challenges of VEOIBD

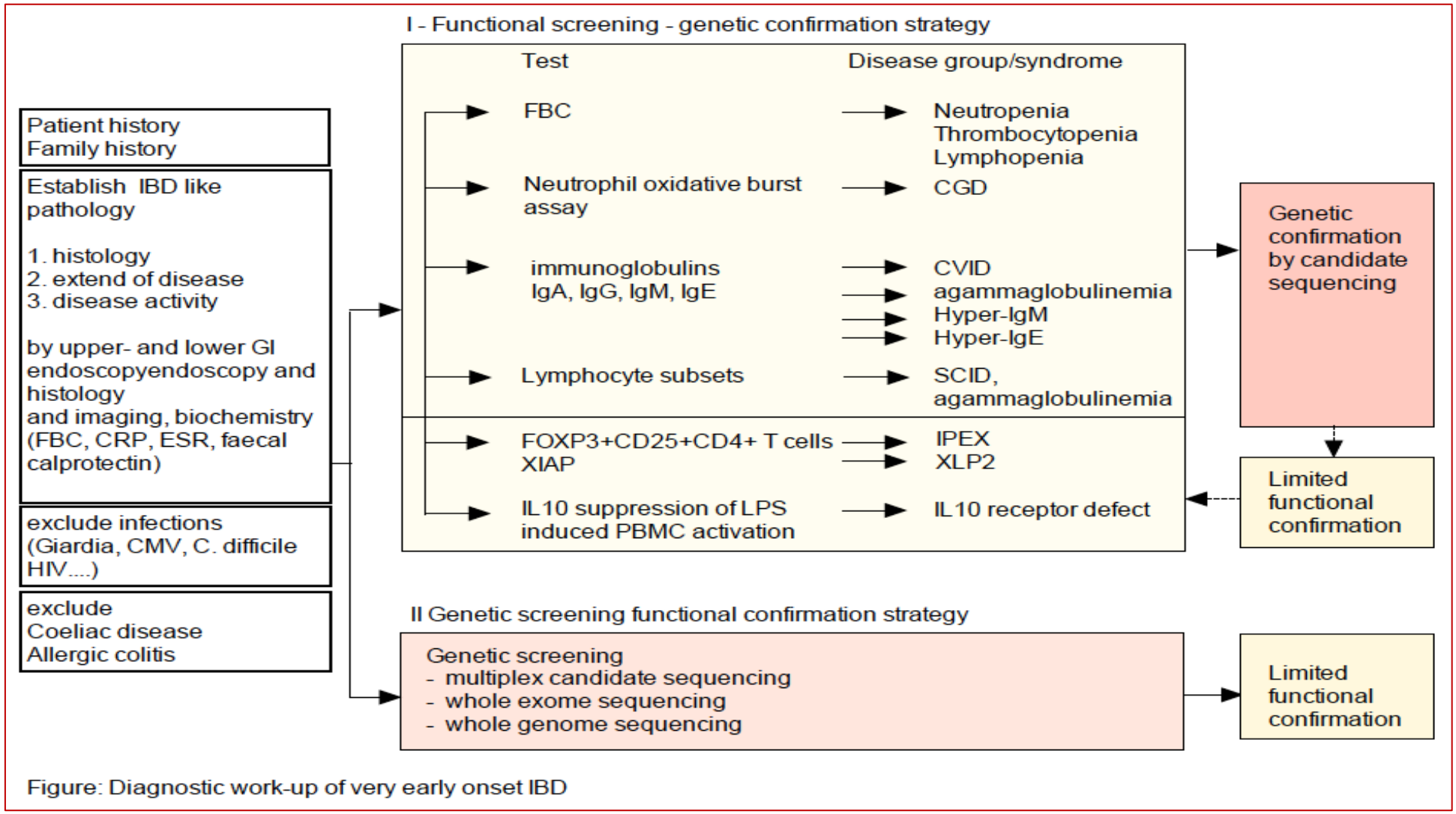



Figure: Diagnostic work-up of very early onset IBD

# NEOPICS – Defining VEOIBD

- CLINICAL - **SickKids VEOIBD Clinic**
  - Following over 100 active VEOIBD patients
  - 35 new patients – last 12 months (almost all < 2 years of age)
  - Once confirmed dx VEOIBD……research WES – standard of care?

- RESEARCH - **NEOPICS** (www.NEOPICS.org)
  - 18 member lab – all studying VEOIBD – known and novel genes
  - 535 VEOIBD patients have participated in NEOPICS from 26 countries (now completed WES on all 535 patients and 1000 older pediatric patients)
  - **41** confirmed known genetic diagnosis
    - Canada, United States, Chile, Uruguay, China, Australia, Sweden, New Zealand, Israel, and others
  - 4 patients had successful bone marrow transplant
    - others now listed for transplant
  - 8 new genes discovered
    - 4 published
- **Helmsley Trust VEOIBD Consortium** (www.VEOIBD.org; PI's Muise, Snapper, Klein)

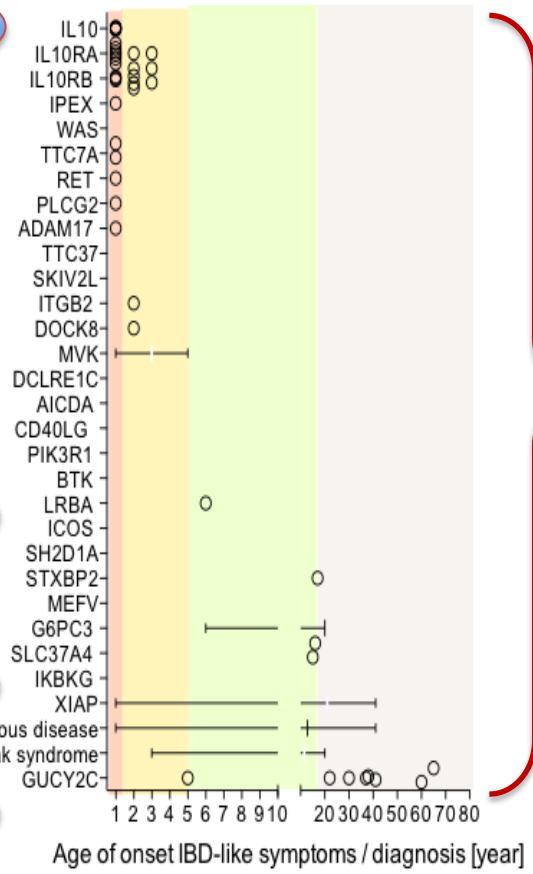
# VEOIBD WES - Pipeline

IL10R

LRBA

XIAP

CGD




Uhlig …. Muise, Gastroenterology 2014

Research WES – all VEOIBD Cases

Screen for 50 Known Genes

No

No known genes
Common pathways
Novel genes

Yes

Examine Novel Variants

CLIA-Approved Validation

Functional Examination of Variants

Therapies including BMT

www.neopics.org

# NEOPICS – Defining VEOIBD

- Novel Risk
  - IL10RA (IBDJ, 2013)
  - NADPH oxidase (NOX2)
    - RAC1/2 (Gut, 2012 and Gastro, 2011 and 2014)
    - NCF1,2,4 (Gastro, 2014)
    - NOX2 (Gastro, 2014)
  - NOX1 (CMGH, 2015)
  - DUOX2 (CMGH, 2015)
  - NOS2A (Clin Gastro Hep, 2014)

- Known Monogenic
  - IL10RA/B, LRBA, XIAP and others

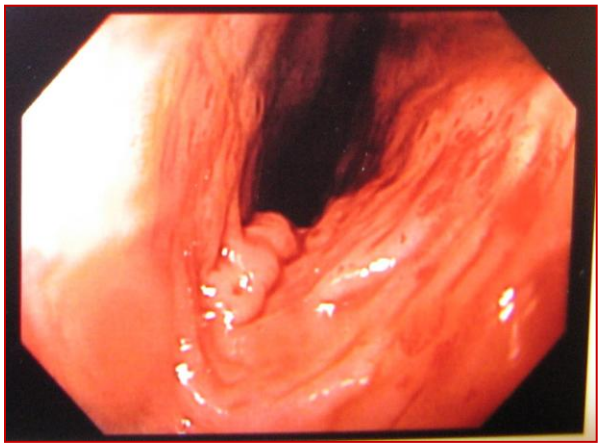
- Novel Monogenic
  - TTC7A (Gastro, 2014)
  - TRIM22 (Gastro, 2016)
  - SLC9A3/NHE3 (Human Mol. Gen. 2015)
  - PLVAP (CMGH, 2015)

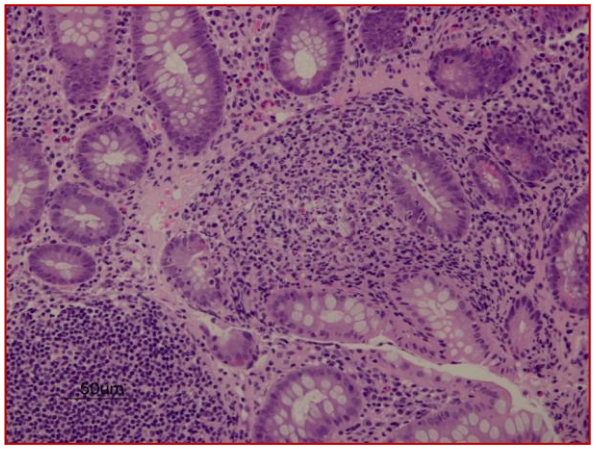
# NEOPICS – Defining VEOIBD

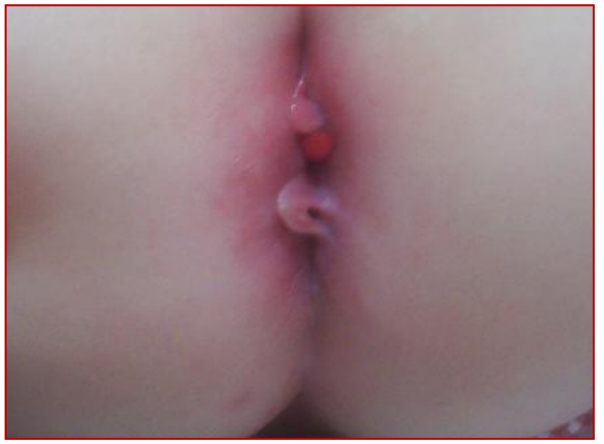
- Cases we cannot miss in 2016
  1. IL10/R mutations (Glocker et al, NEJM 2009 and Lancet 2010)
  2. XIAP mutations (Worthey et al, 2011 – 1st severe IBD disease)
  3. LRBA/CTLA4 (Lo et al, Science, 2015 – mechanism; )

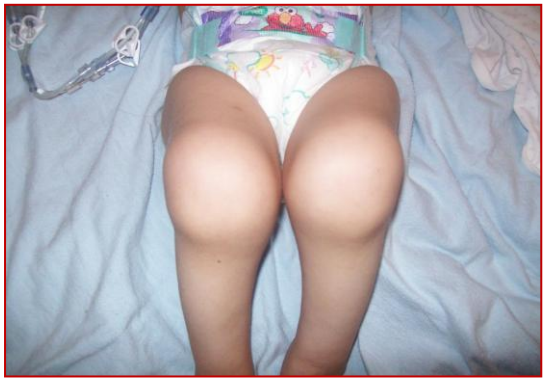
- Novel genes – clinical outcomes
  1. TTC7A (Avitzur et al, Gastro 2014)
  2. TRIM22 (Li et al, Gastro 2016)

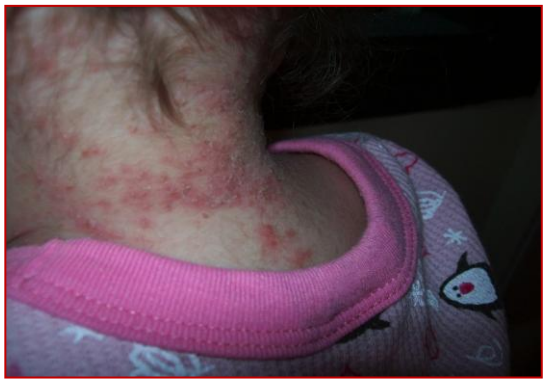
# Case 1 – Severe Pancolitis











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Moran, … Muise. IBD, 2013.

The NEW ENGLAND JOURNAL of MEDICINE

# Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor

Erik-Oliver Glocker, M.D., Daniel Kotlarz, M.D., Kaan Boztug, M.D., E. Michael Gertz, Ph.D., Alejandro A. Schäffer, Ph.D., Fatih Noyan, Ph.D., Mario Perro, M.Sc., Jana Diestelhorst, B.Sc., Anna Allroth, M.D., Dhaarini Murugan, M.Sc., Nadine Hätscher, B.Sc., Dietmar Pfeifer, M.D., Karl-Walter Sykora, M.D., Martin Sauer, M.D., Hans Kreipe, M.D., Martin Lacher, M.D., Rainer Nustede, M.D., Cristina Woellner, M.Sc., Ulrich Baumann, M.D., Ulrich Salzer, M.D., Sibylle Koletzko, M.D., Neil Shah, M.D., Anthony W. Segal, M.D., Axel Sauerbrey, M.D., Stephan Buderus, M.D., Scott B. Snapper, M.D., Ph.D., Bodo Grimbacher, M.D., and Christoph Klein, M.D., Ph.D.

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

# Dx Prior to Disease
# Low Intensity Conditioning
# Stem Cell Transplant


"Diya never suffered like her sister Gayathri. Even the transplant was much smoother than what Gayathri had to go through."



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# Lessons from Brygette and Diya - **IL10R**

- Diagnosis (> 100 cases)
  - symptoms < 3 months of age
  - severe colitis, perianal disease, folliculitis, +/- joint disease
  - non-responsive to standard IBD therapy
  - B-cell Lymphoma
- Maybe older children/adults?
- Definitive Treatment
  - stem cell transplant
- Subtle defects in IL10 pathway
  - treat with IL10?



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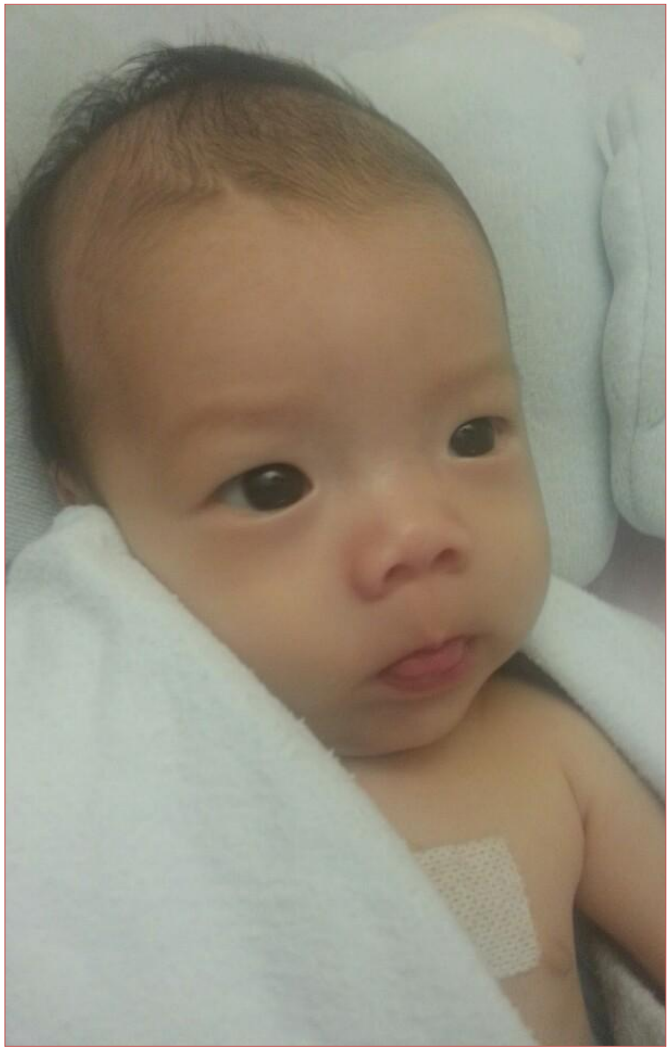
Muise, Snapper, Kugathasan. Gastro 2012

# Case 2 – Jayden

- Presented at 3 wks of age with severe  bloody diarrhea
- Requiring TPN and steroids with no response to treatment
- Worsening clinically
- Provisional dx – congenital diarrhea (Tufting, MVID…..)





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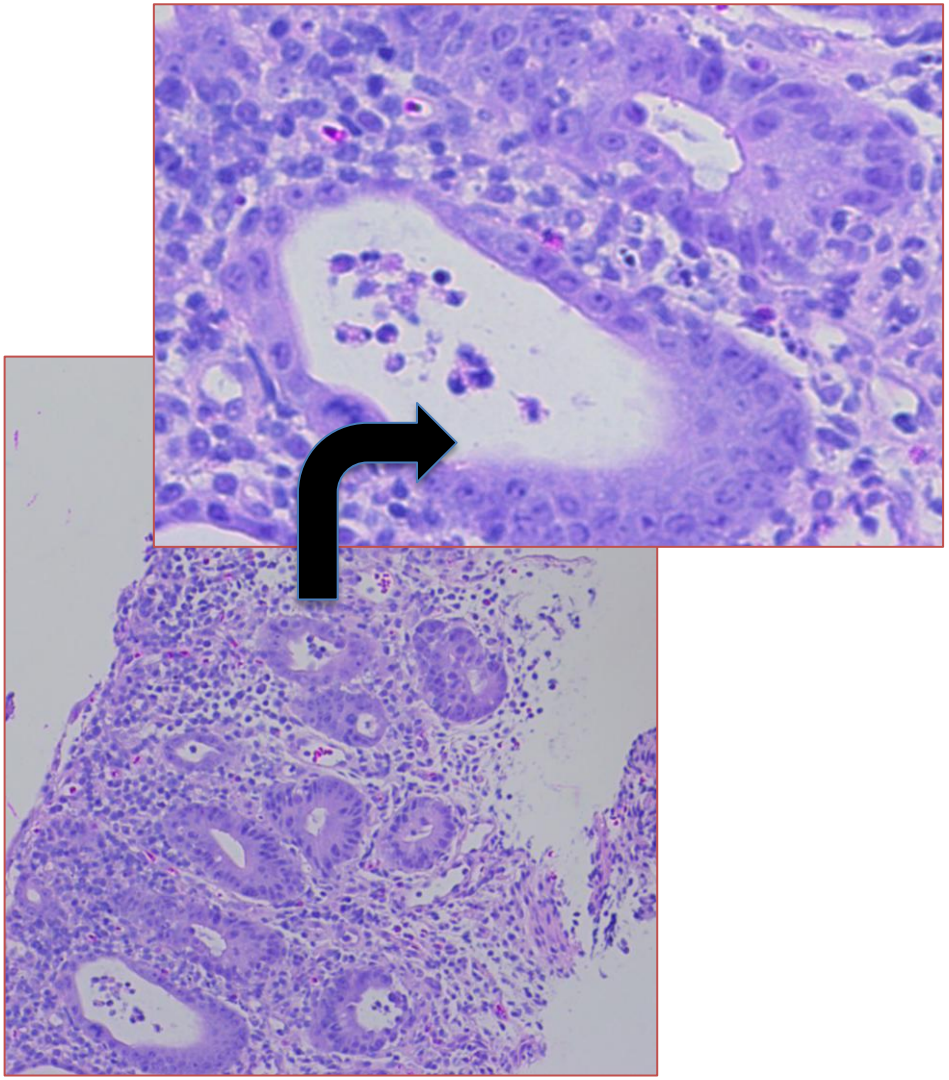
# Case 2 – Jayden

- Scope:
  - Upper – consistent with autoimmune enteropathy
  - Lower – severe colitis (unusual)
- Enteroids:
  - completely normal
  - suggests PID and not an enterocyte defect such as Tufting or MVID





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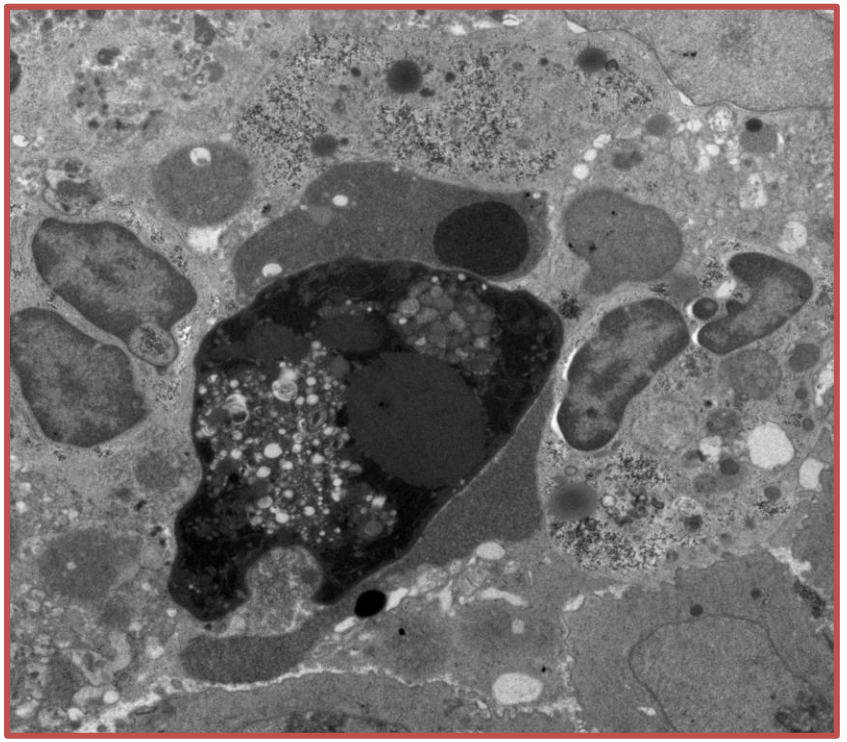
# Diagnosis -XIAP

- Blood work:
  - elevated inflammatory markers
  - elevated liver function tests
  - decreased cell lines (Platelets, RBC, WBC)
- Liver biopsy:
  - **Macrophage Activations Syndrome** (HLH)
- WES:
  - SickKid (10 day) diagnosis of XIAP
- Treatment:
  - stem cell transplant - < 1 year of age

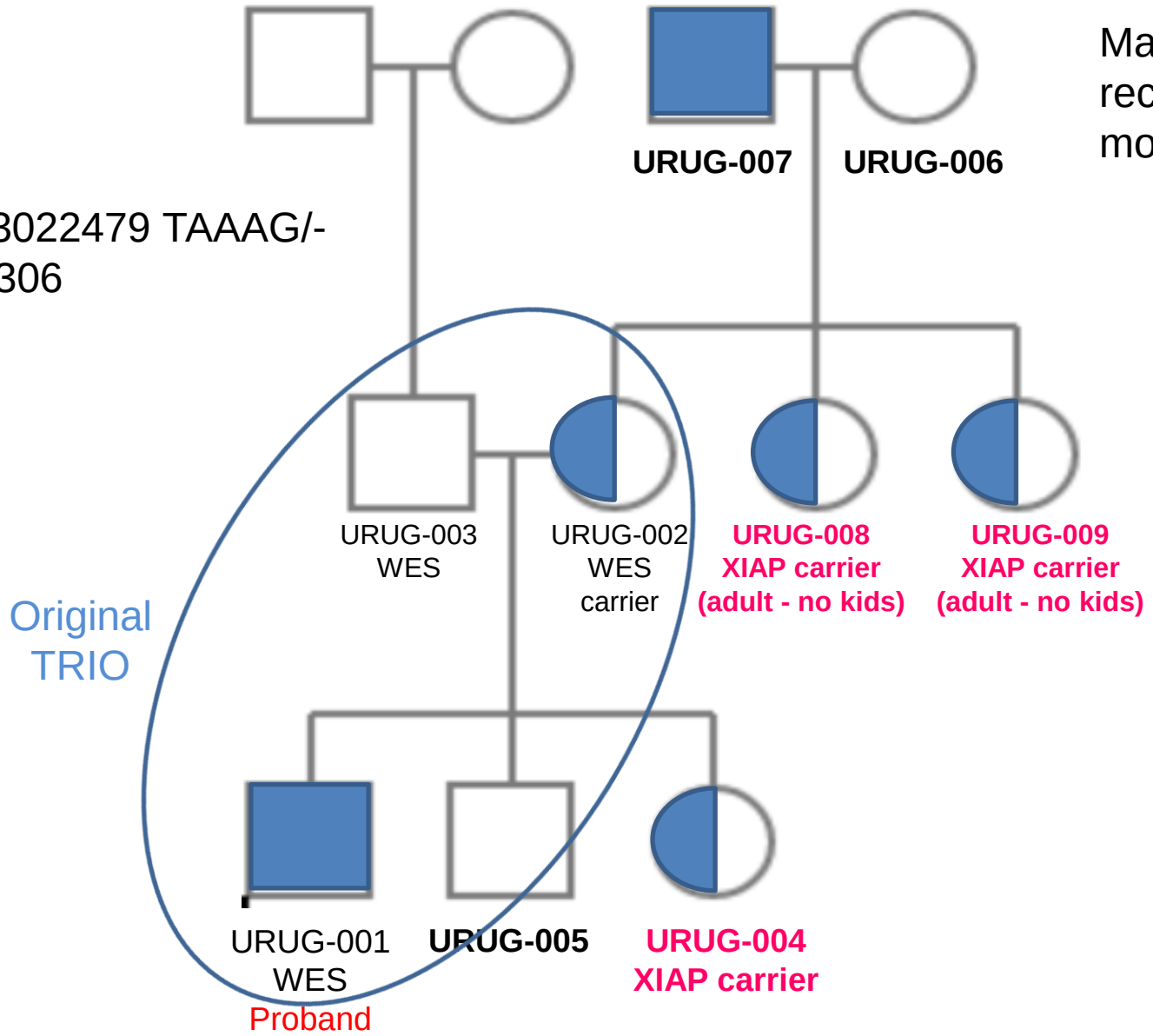



# Ulises from Uruguay

- Gender: male
- Age symptom onset: **2 mos**
- Age diagnosis: **10 mos**

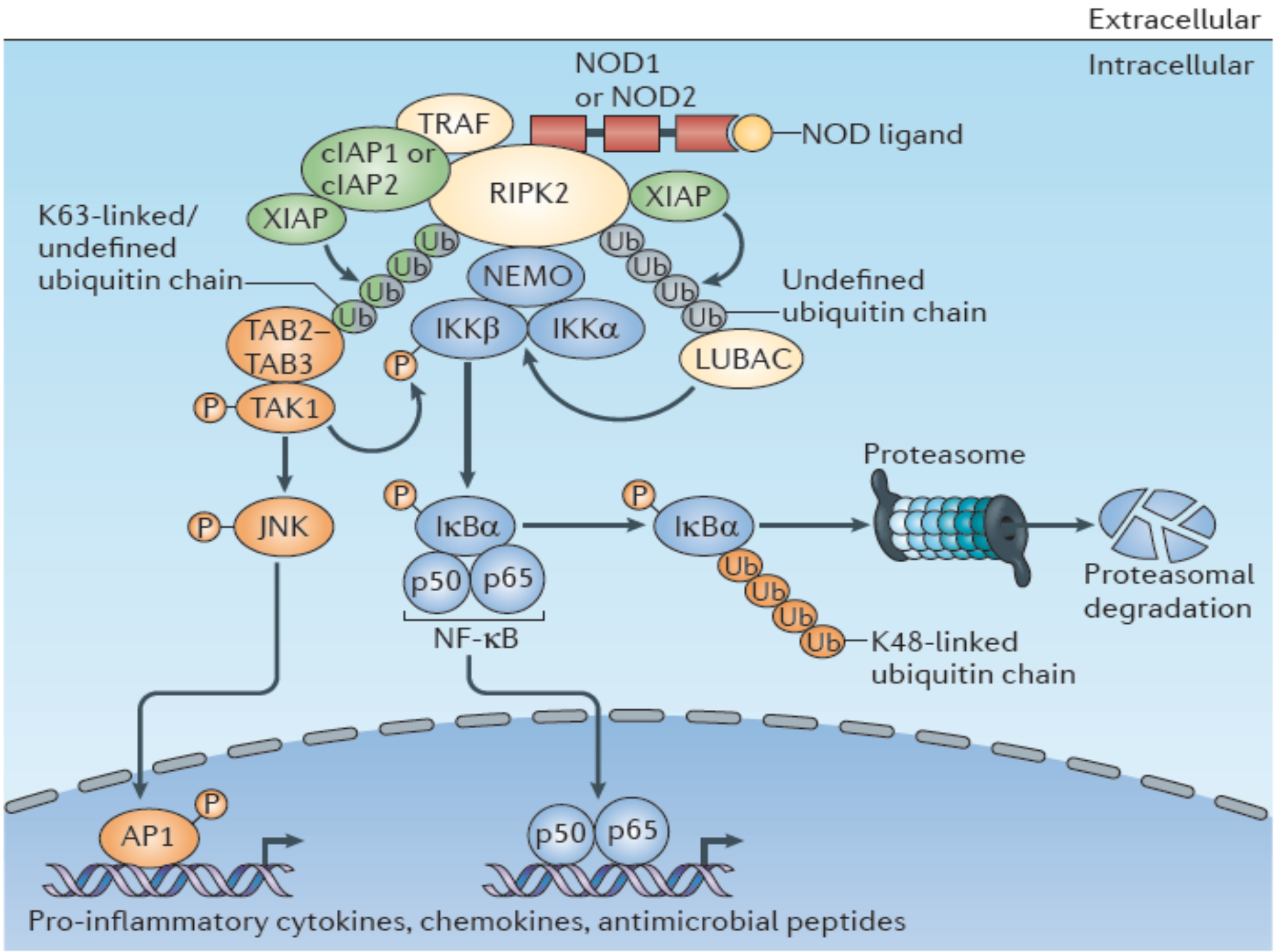
- Current age: 10 yrs
- Disease Type: Crohn's
- Clinical severity: severe
- Disease location: pan-enteric
- Perianal involvement: severe, fistulas, abscesses
- Ethnicity: Hispanic
- Consanguinity: no
- Family Hx IBD: no
- Prior GI surgery: colostomy
- Current Rx: failed conventential

# Ulises - extended pedigree



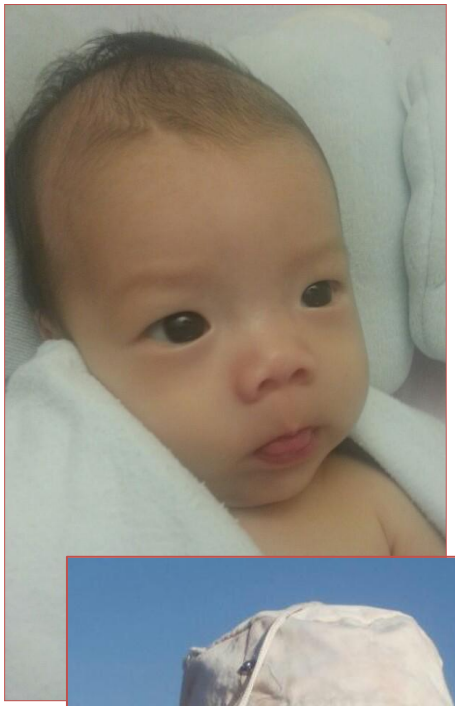

Maternal Grandpa
recurrent skin abscesses
mononucleosis

ChrX:123022479 TAAAG/-
V298fsX306


Extracellular
Intracellular
NOD1
or NOD2
TRAF
NOD ligand
cIAP1 or
cIAP2
XIAP
RIPK2
XIAP
K63-linked/
undefined
ubiquitin chain
Ub
NEMO
Undefined
ubiquitin chain
IKKβ
IKKα
TAB2–
TAB3
LUBAC
P
TAK1
JNK
IκBα
p50
p65
NF-κB
Proteasome
Proteasomal
degradation
K48-linked
ubiquitin chain
AP1
Pro-inflammatory cytokines, chemokines, antimicrobial peptides

# Lessons from Jayden and Ulises - **XIAP**

- X-linked recessive disorder ( > 50 males)
  - Granulomatous colitis
  - Perianal disease
  - Non-responsive to typical therapies including biologics
  - High morbidity and mortality
  - +/- HLH/MAS
- We do NOT understand the phenotype –
  - Onset of disease - months to 40 years of age
- Maybe common?
  - 4% of male Pediatric IBD patients (Zessig, Gut 2014)
  - Sickkids sequencing – lower - validation stage
- X-chromosome inactivation – female carriers
- Colitis may be the first or only manifestation
- Stem cell transplant is curative





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# Case 3 - Kaeden

**Infancy**
- 'Gassy', frequent stooling
- Switched to soy milk formula – symptoms settled

**4 years**
- Poor weight gain
- Linked in with community pediatrician

**9 years Ref to Gen Paeds HSC**
- Frequent loose stool
- Frequent URTIs
- Frequent GE
- Weight loss (0.1c Wt, 15th c Ht)



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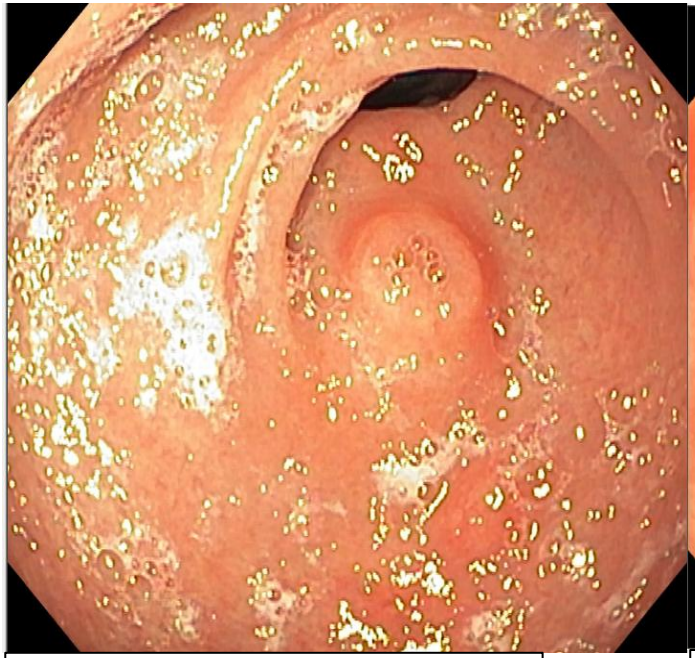
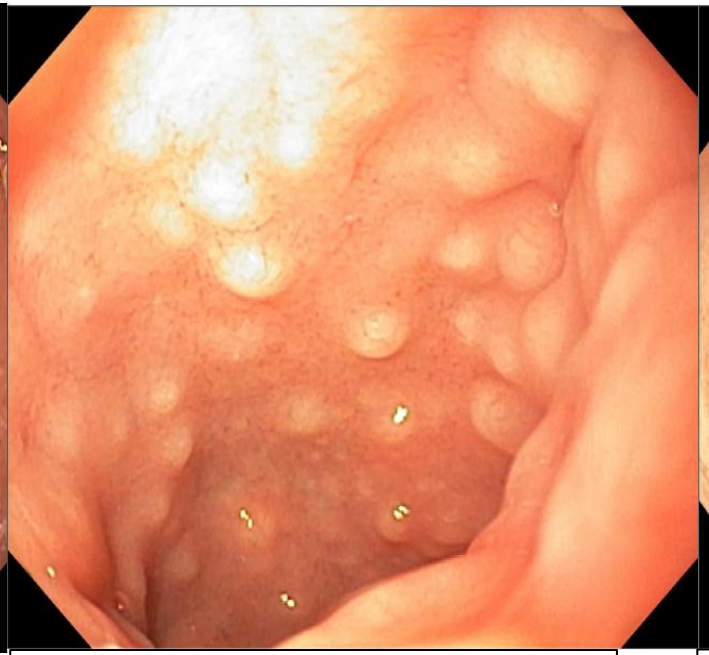
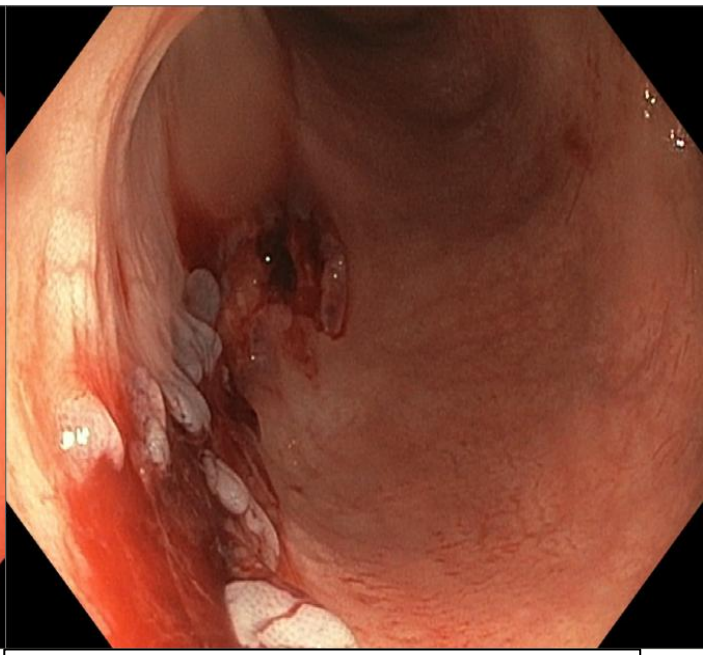


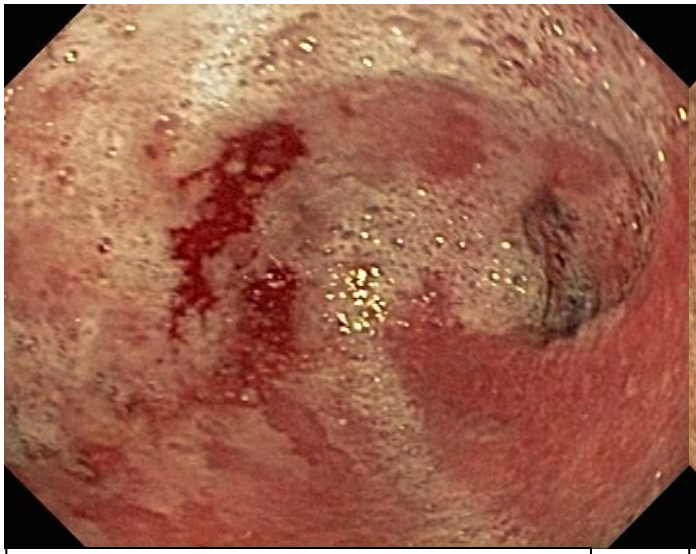
Stomach



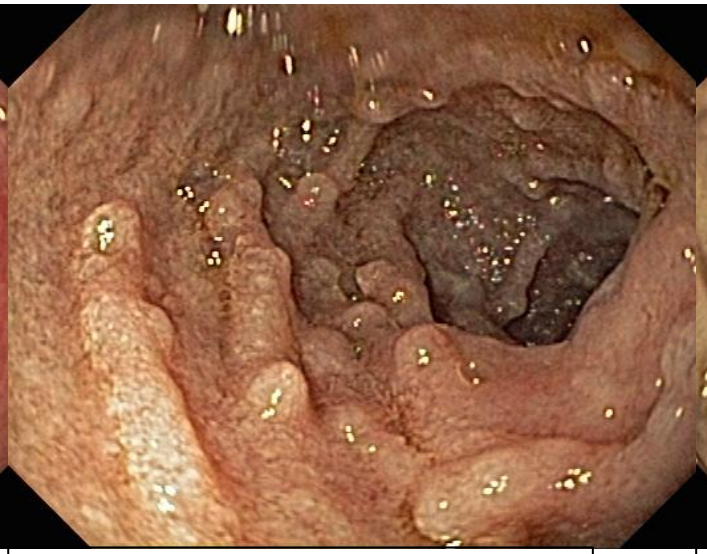
Duodenum



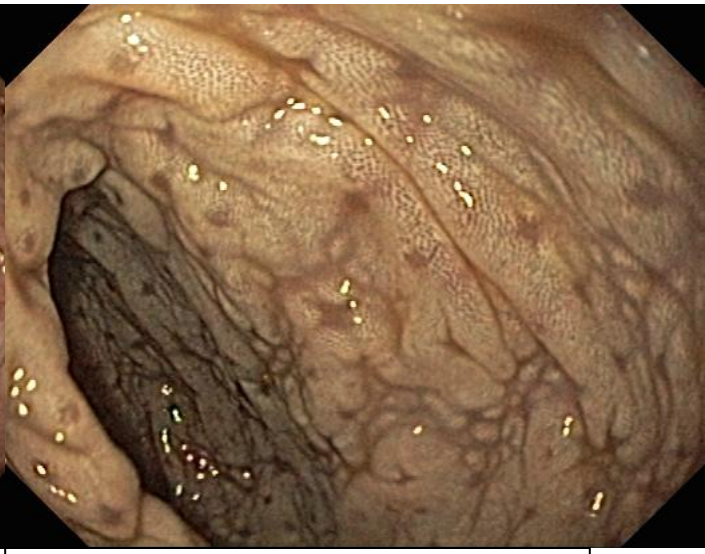
Rectum



Stomach



Duodenum



Colon

# Pathology
# Apoptosis and loss of goblet and Paneth Cells

- Gastric mucosa
  - Increased **apoptosis**
- Duodenal mucosa
  - no intraepithelial lymphocytosis
  - diffuse and **severe loss of goblet and Paneth cells**
- Bowel (small and large)
  - marked **loss of goblet and Paneth cells** (proximally) present extending through the terminal ileum to the rectum
  - mild to moderate active inflammation in cecum and ascending colon
  - marked increase in basal crypt **apoptosis**

# WES - LRBA

- LIPOPOLYSACCHARIDE-RESPONSIVE, BEIGE-LIKE ANCHOR PROTEIN (LRBA)
- widely expressed multiple human tissues, both immune-related and non-immune-related
- multi-domain protein that contains a highly conserved BEACH domain
- implicated in regulating endosomal trafficking, particularly endocytosis of ligand-activated receptors

# LRBA-deficiency

- Common variable immunodeficiency-8 with autoimmunity (CVID8; 614700), Lopez-Herrera et al. (2012)
- Predominant clinical phenotypes
  - hypogammaglobulinemia
  - autoimmune cytopenias
  - autoimmune enteropathy
- Many patients suffer from
  - chronic diarrhea
  - inflammatory bowel disease (described as both UC and CD)
- Other clinical features can include :
  - hepatosplenomegaly, reoccurring warts, growth retardation, allergic dermatitis, and arthritis (also diabetes)

nature medicine

# Autosomal dominant immune dysregulation syndrome in humans with *CTLA4* mutations

Desirée Schubert[1,2,15], Claudia Bode[1,15], Rupert Kenefeck[3,15], Tie Zheng Hou[3,15], James B Wing[4], Alan Kennedy[3], Alla Bulashevska[1], Britt-Sabina Petersen[5], Alejandro A Schäffer[6], Björn A Grüning[7], Susanne Unger[1], Natalie Frede[1], Ulrich Baumann[8], Torsten Witte[8], Reinhold E Schmidt[8], Gregor Dueckers[9], Tim Niehues[9], Suranjith Seneviratne[3], Maria Kanariou[10], Carsten Speckmann[1], Stephan Ehl[1], Anne Rensing-Ehl[1], Klaus Warnatz[1], Mirzokhid Rakhmanov[1], Robert Thimme[11], Peter Hasselblatt[11], Florian Emmerich[12], Toni Cathomen[1,12], Rolf Backofen[7], Paul Fisch[13], Maximilian Seidl[13], Annette May[13], Annette Schmitt-Graeff[13], Shinji Ikemizu[14], Ulrich Salzer[1], Andre Franke[5], Shimon Sakaguchi[4], Lucy S K Walker[3,15], David M Sansom[3,15] & Bodo Grimbacher[1,3,15]

**Table 1 Clinical phenotype of patients with *CTLA4* mutations**

| Clinical manifestations | Patients | Frequency |
|---|---|---|
| Diarrhea/enteropathy | A.II.5, A.II.8, A.II.9, A.III.1, A.III.3, B.II.1, B.II.2, B.II.4, C.II.4, E.II.3, F.II.2 | 11/14 (78%) |
| Hypogammaglobulinemia | A.II.5, A.II.8, A.II.9, A.III.1, A.III.3, C.II.3, B.III.2, D.II.1, E.II.3, F.II.2 | 10/13 (76%) |
| Granulomatous lymphocytic interstitial lung disease | A.II.8, A.II.9, A.III.3, B.II.4, B.III.2, C.II.3, D.II.1, E.II.3 | 8/12 (66%) |
| Respiratory infections[a] | A.II.5, A.II.8, A.II.9, B.II.4, B.III.2, C.II.3, E.II.3, F.II.2 | 8/14 (57%) |
| Organ infiltration (bone marrow, kidney, brain, liver) | A.II.9, A.III.1, A.III.3, B.II.2, B.II.4, C.II.3, D.II.1 | 7/14 (50%) |
| Splenomegaly | A.II.5, A.II.9, A.III.3, C.II.3, D.II.1, E.II.3 | 6/12 (50%) |
| Autoimmune thrombocytopenia | A.III.1, A.III.3, C.II.3, E.II.3, F.II.2 | 5/14 (35%) |
| Autoimmune hemolytic anemia | C.II.3, D.II.1, E.II.3, F.II.2 | 4/14 (28%) |
| Lymphadenopathy | A.III.3, C.II.3, D.II.1, E.II.3 | 4/14 (28%) |
| Psoriasis and other skin diseases[b] | A.III.1, B.II.1, B.II.2 | 3/14 (21%) |
| Autoimmune thyroiditis | A.II.5, D.II.1 | 2/13 (15%) |
| Autoimmune arthritis | A.II.5, A.III.1 | 2/14 (14%) |
| Solid cancer | B.II.4 | 1/14 (7%) |

AUTOIMMUNE DISEASE

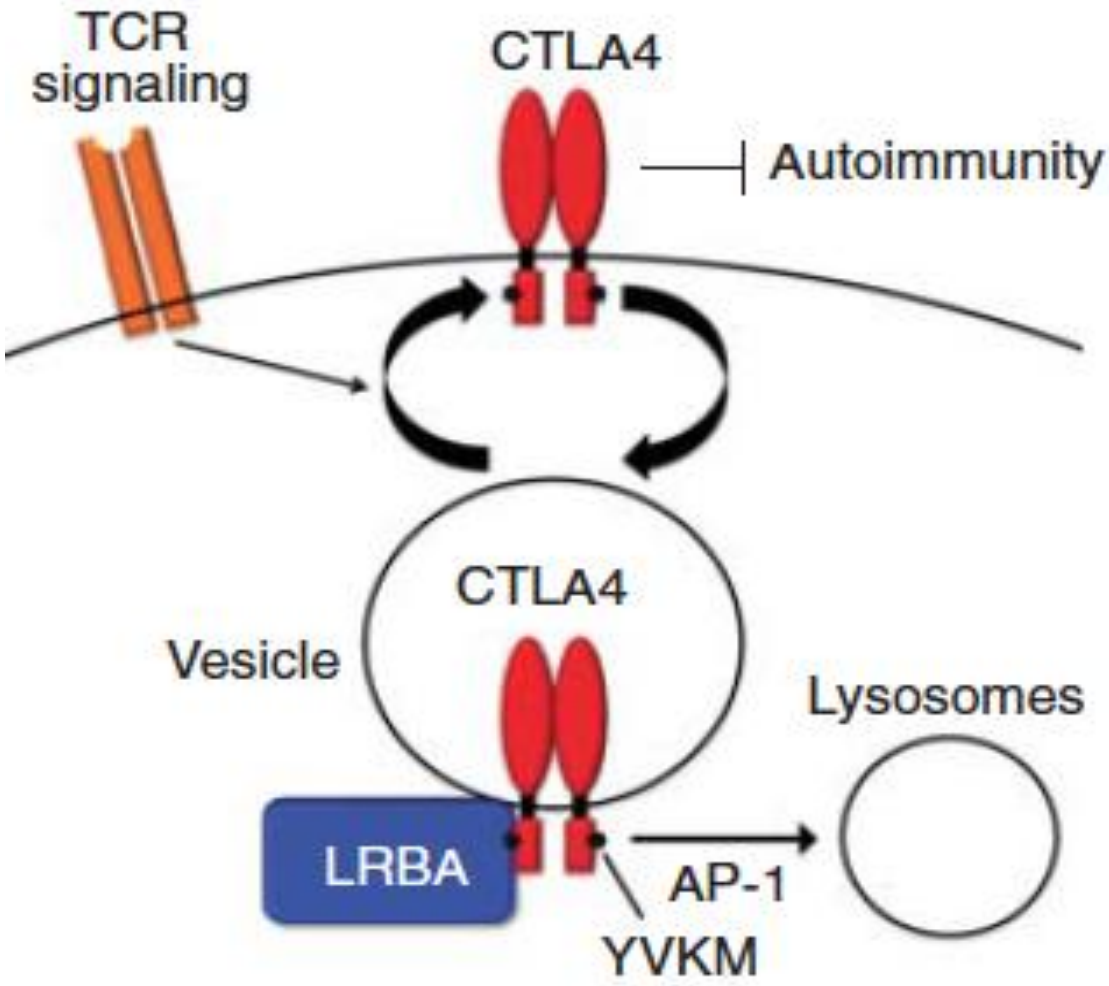
# Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy

Bernice Lo,[1,2]* Kejian Zhang,[3]* Wei Lu,[1,2] Lixin Zheng,[1,2] Qian Zhang,[2,4] Chrysi Kanellopoulou,[1,2] Yu Zhang,[2,4] Zhiduo Liu,[5] Jill M. Fritz,[1,2] Rebecca Marsh,[6] Ammar Husami,[3] Diane Kissell,[3] Shannon Nortman,[3] Vijaya Chaturvedi,[6] Hilary Haines,[7] Lisa R. Young,[8] Jun Mo,[9] Alexandra H. Filipovich,[6] Jack J. Bleesing,[6] Peter Mustillo,[10] Michael Stephens,[11] Cesar M. Rueda,[12] Claire A. Chougnet,[12] Kasper Hoebe,[12] Joshua McElwee,[13] Jason D. Hughes,[13] Elif Karakoc-Aydiner,[14] Helen F. Matthews,[1,2] Susan Price,[1,2] Helen C. Su,[2,4] V. Koneti Rao,[1,2] Michael J. Lenardo,[1,2]† Michael B. Jordan[6,12]†‡

24 JULY 2015 • VOL 349 ISSUE 6246

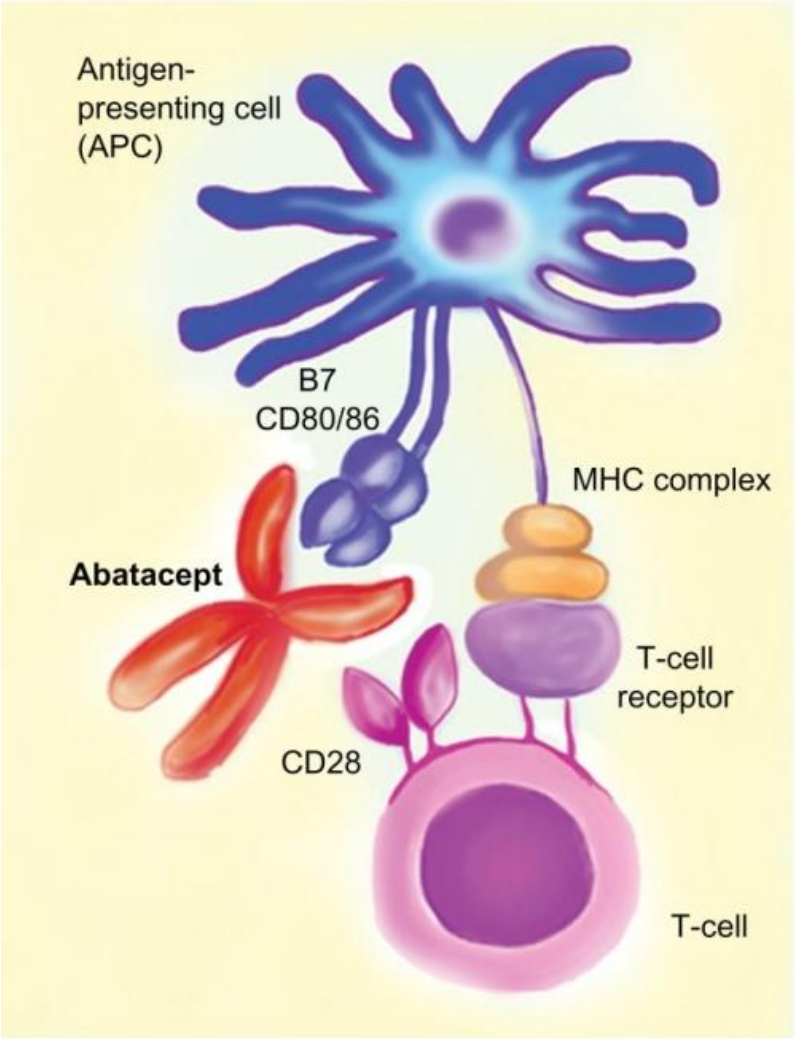
# Role of LRBA in CTLA4 Signaling

SCIENCE sciencemag.org 24 JULY 2015 • VOL 349 ISSUE 6246



# Abatacept

- Abatacept, in effect, replaces natural CTLA4 function, with the caveat that CD80 and CD86 ligands are covered up by the drug rather than physically removed from the surface of antigen-presenting cells
- Used commonly for RA and Psoriasis
- Tx for IBD – phase III trial
  - Conclusion - not efficacious for the treatment of moderate-to-severe CD or UC (Gasto, 2012)
- One case series for treatment for autoimmune enteropathy (J Clin Gastro, 2014)
- Standard treatment for both LRBA and CTLA4 deficiency (Science, 2015, JACI, 2016)
- Numerous cases – most not yet reported
- Variable response but if works – very good response



# Lessons - Kaeden

- LRBA and CTLA4 – phenocopies
- LRBA – AR and CTLA4 – AD with variable expression of disease (both maybe difficult to identify)
- High suspicion – features:
  - atypical IBD, autoimmune enteropathy, other autoimmune features, apoptosis on biopsy, lung disease, diabetes
- **Treatment:**
  - Abatacept – more difficult with gut disease – may require steroids +/- biologics…..
  - stem cell transplant – considered – outcomes still unclear with significant bowel disease

# Case 4 - Apoptotic Enterocolitis

- Case History
  - female patient born at term
  - Caucasian mother and Sudanese father
  - high output secretory hematochezia starting almost immediately after birth
- Colonoscopy
  - severe inflammation with severe friability
  - sloughed mucosa within the colonic lumen
- Pathology – similar
  - chronic inflammation
  - **crypt apoptosis** and exploding crypts
    - acute gastrointestinal graft-versus-host disease
    - intestine allograft rejection

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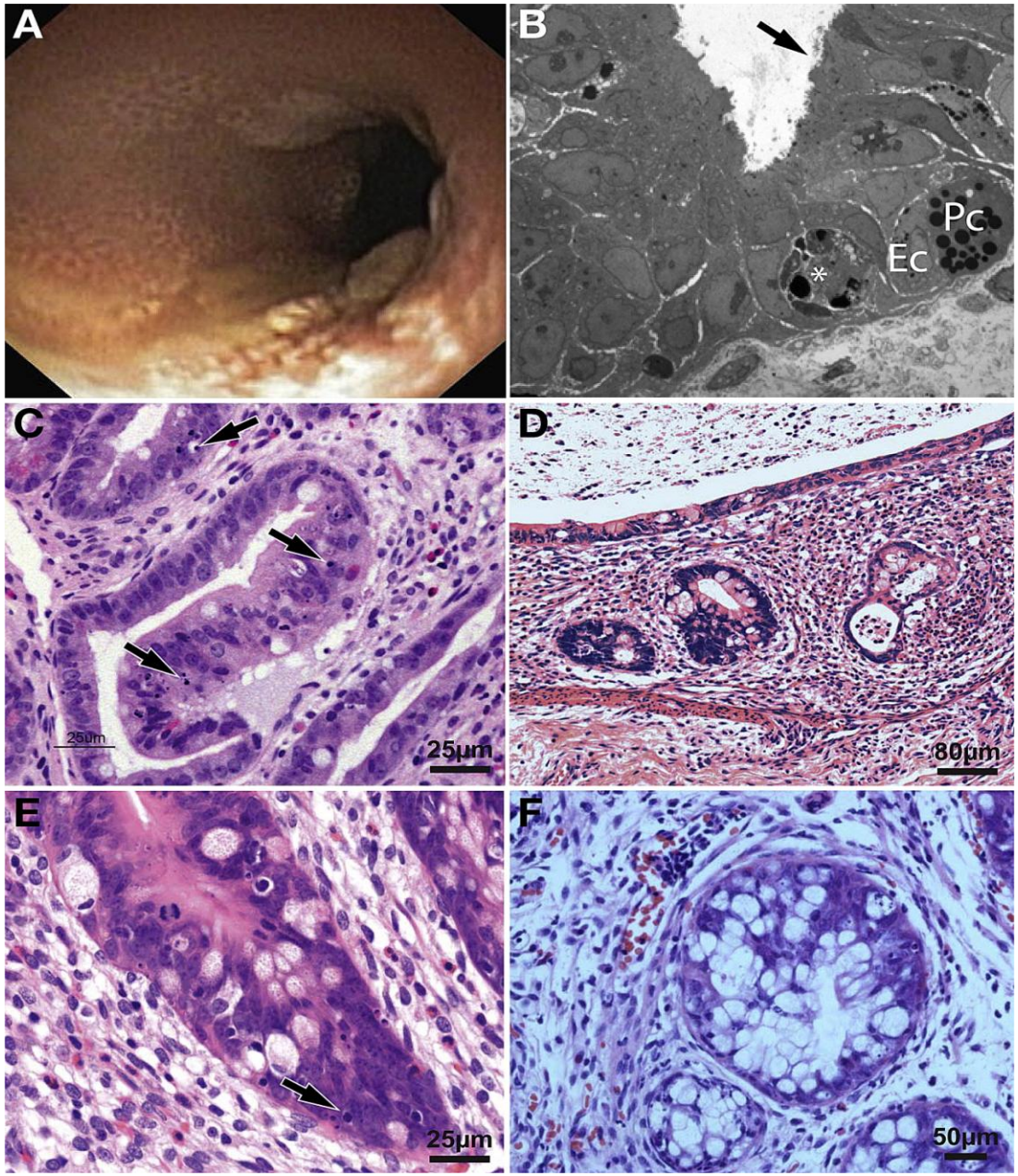
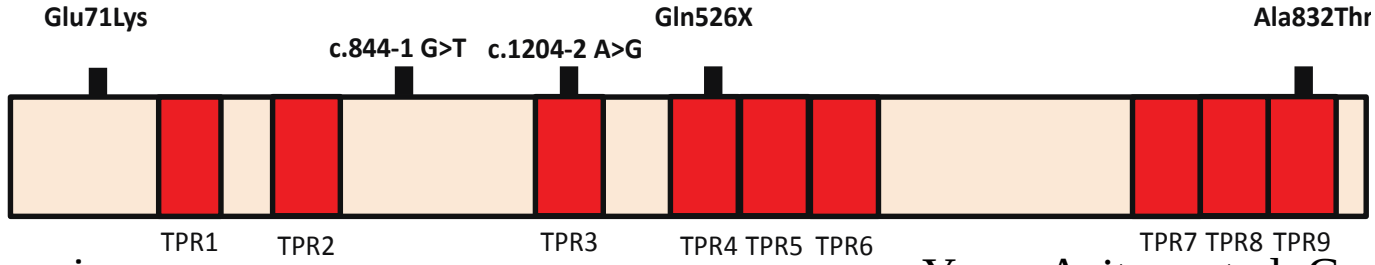
Yaron Avitzur et al. Gastro 2014

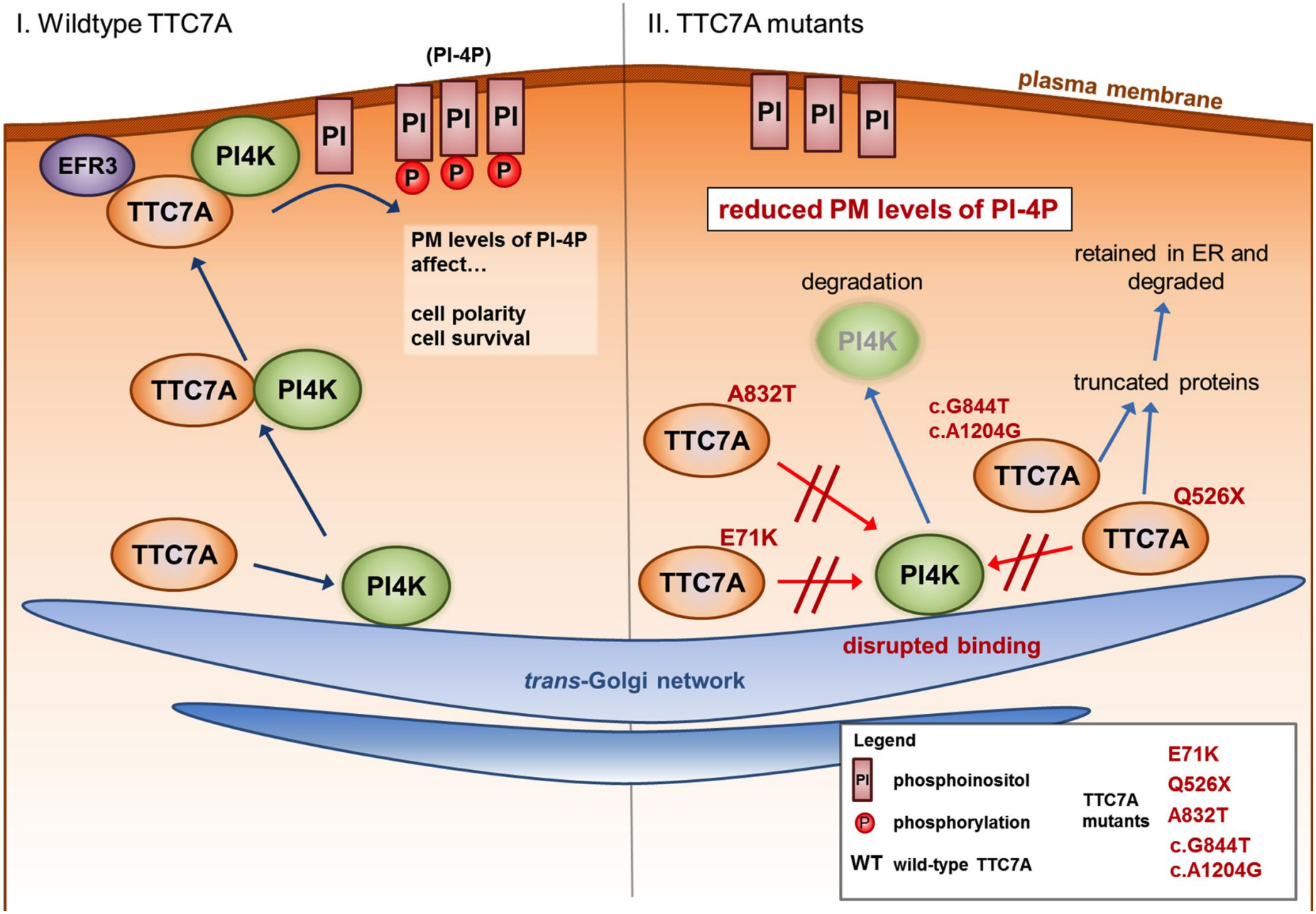

A
B
Pc
Ec
*
C
25µm
25µm
D
80µm
E
25µm
F
50µm

# TTC7A Mutations in 5 Patients

| | Age at Presentation | Gender | CS | Clinical Features | Immune Work-up | Outcome | *TTC7A* Mutation | TTC7A Mutated Protein |
|---|---|---|---|---|---|---|---|---|
| **Patient 1 (Family-1)** | At Birth | Female | N | Bloody Diarrhea; AE | Lymphopenia, hypogamma-globulinemia | Died at 11 months of age | c.211 G>A<br>c.1944 C>T | p.E71K<br>p.Q526X |
| **Patient 2 (Family-2)** | At Birth | Male | N | Obstruction, Stricture, AE | lymphopenia | Died at 3 months of age | c.844-1 G>T<br>c.1204-2 A>G | Loss of the splice acceptor sites for exons 7 and 10 |
| **Patient 3 (Family-2)** | At Birth | Female | N | Obstruction, Stricture, AE | lymphopenia | Died at 1 month of age | c.844-1 G>T<br>c.1204-2 A>G | Loss of the splice acceptor sites for exons 7 and 10 respectively |
| **Patient 4 (Family-3)** | At Birth | Female | Y | Bloody Diarrhea; AE | N/A | Died at 1 month of age | c.2494 G>A | p.A832T |
| **Patient 5 (Family-3)** | At Birth | Female | Y | Bloody Diarrhea; AE | N/A | Alive, TPN for Partial Control | c.2494 G>A | p.A832T |

**D** TTC7A Domain Architecture

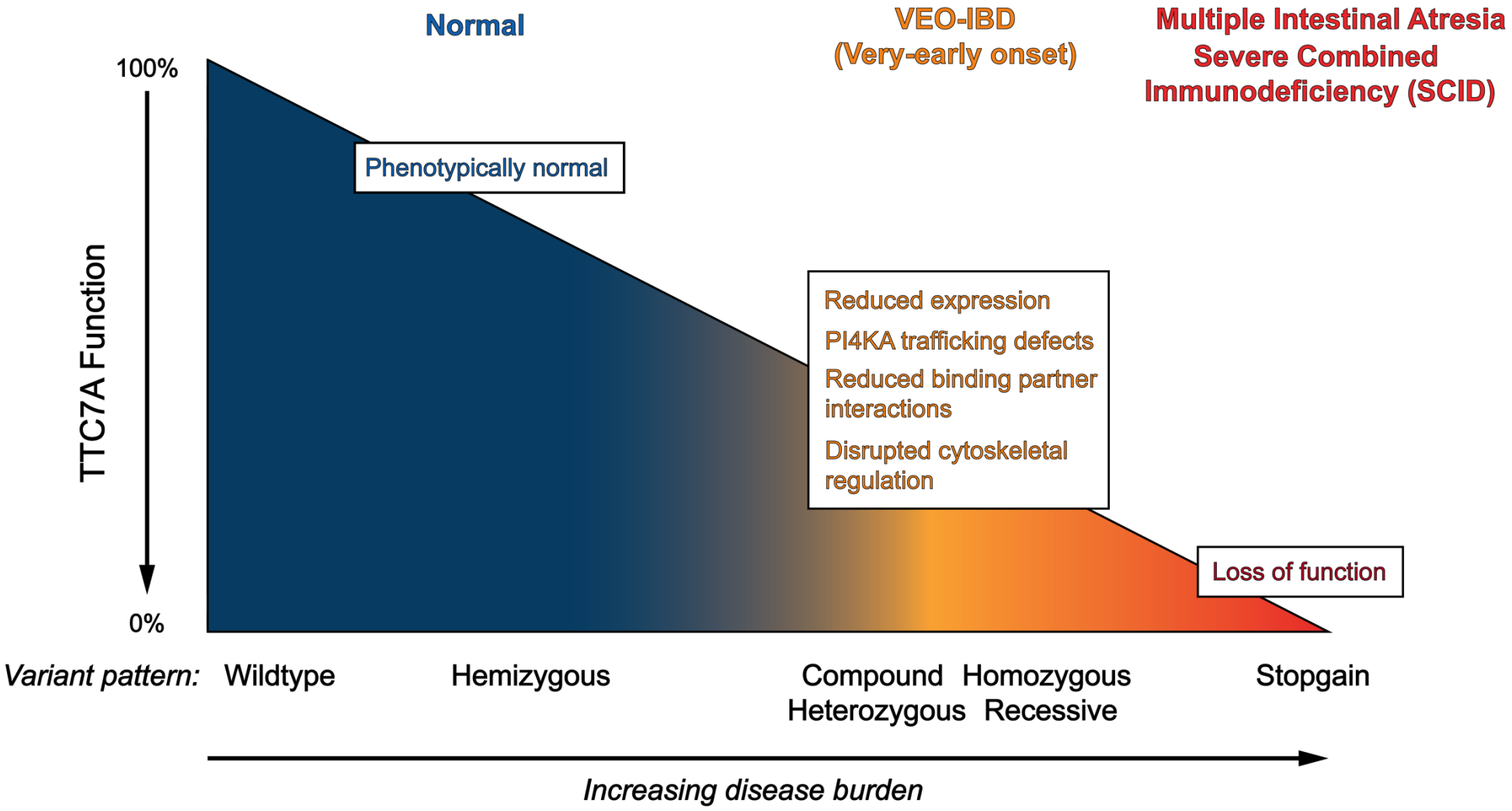







Yaron Avitzur et al. Gastro 2014

# TTC7A Disease Spectrum






Murchie unpublished

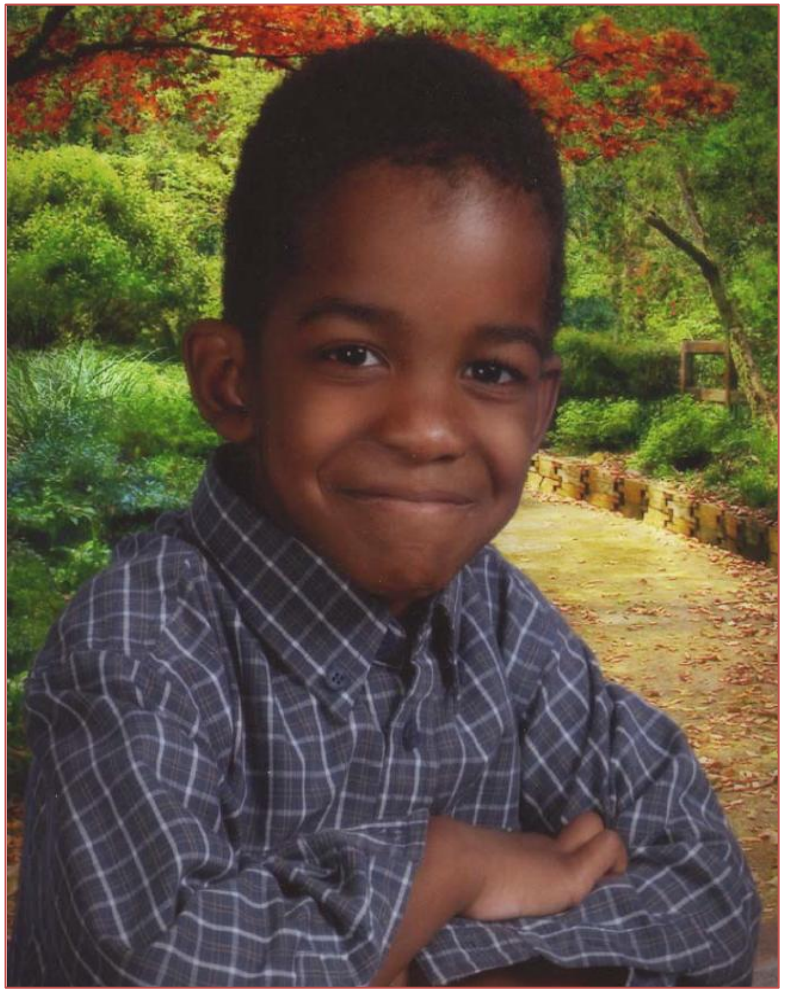
# Lessons from Atap and others

- Severe intestinal inflammatory process driven by
  - primary epithelial defect (apoptosis and mucosal shedding)
  - immune defect (SCID phenotype)
- Post-resection of atretic regions
  - bowel disease recurs
- Hematopoietic stem cell transplant (prior to genetic dx)
  - minimal short-term improvement (<1 year) – recurrence of gut disease
  - does NOT cure intestinal disease
- 1 case of bowel transplant (Blood, 2004) - ?? Successful at age 20 ??
- > 53 cases identified (Avitzur, 2014; Bigorgne, 2014; Samuels. 2013; Chen, 2013; and other case series or unpublished)
  - majority of patients do not survive beyond 2 years of age
  - lung disease develops
- How common is less severe – hypomorphic mutations?
- Urgent need to develop novel therapies…..

# Case 6
# Granulomatous Colitis and Severe Perianal Disease

- Presented at 3.5 months of age
  - Viral meningitis (rash, T°, irritability)
  - Microcytic anemia (Hgb 67; MCN 60)
  - Hypoalbuminemia
  - Thrombocytosis
- Multiple admissions to PICU
- Developed severe granulomatous colitis
  - non-responsive to medical therapy (IFX)
- Severe perianal disease
  - Non-responsive to surgery
  - Required plastic surgery

- Other Dx
  - E. coli. UTI, RSV (+), Rotavirus (+), urine (+) CMV
  - No known VEOIBD monogenic mutations
    - IL10R, XIAP, NOD2….



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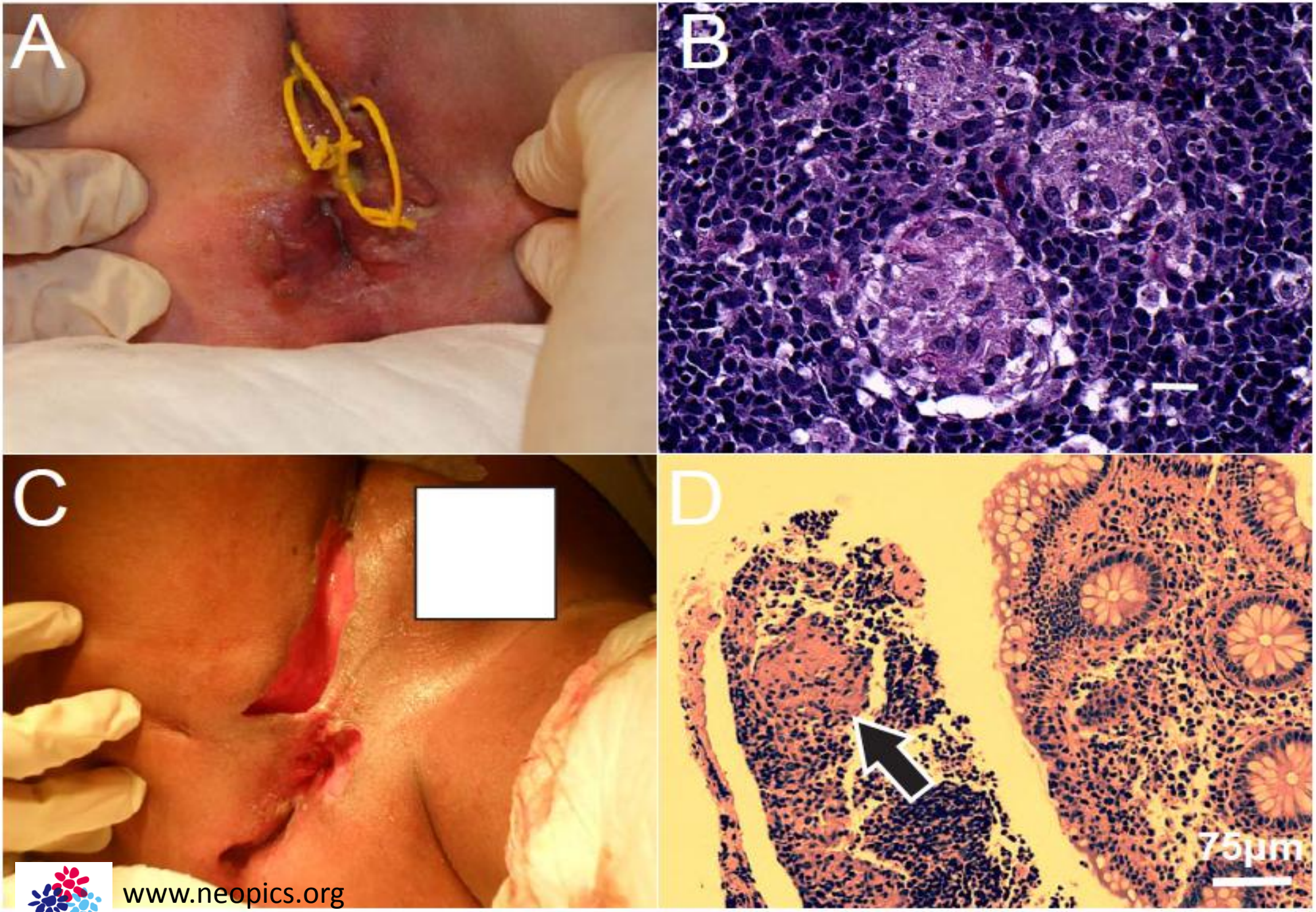
Qi Li et al., Gastro, 2016

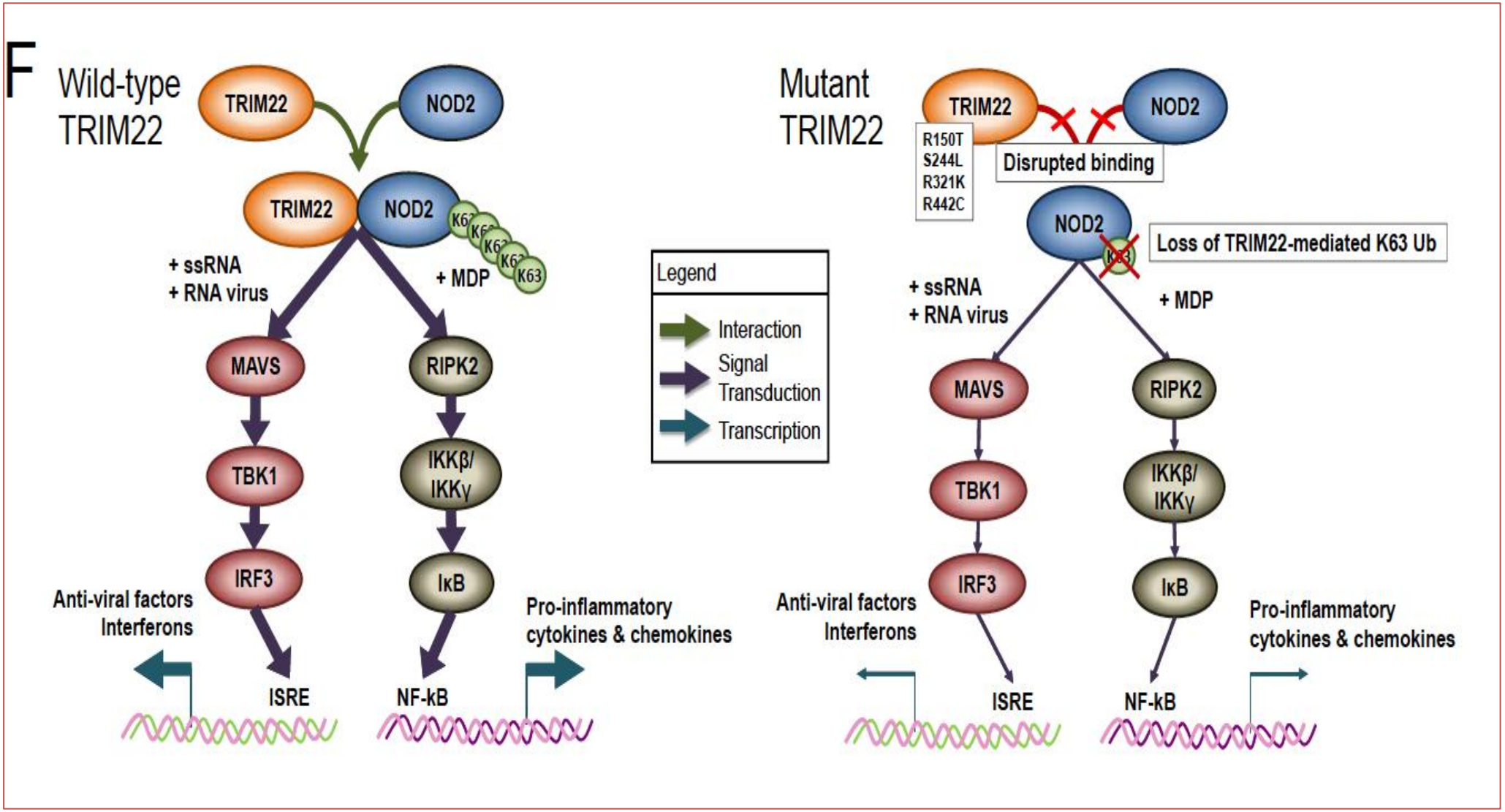



www.neopics.org

Gastroenterology 2016;150:1196–1207

# Variants in *TRIM22* That Affect NOD2 Signaling Are Associated With Very-Early-Onset Inflammatory Bowel Disease

**Qi Li,**[1,2,*] **Cheng Hiang Lee,**[3,4,*] **Lauren A. Peters,**[5,6,*] Lucas A. Mastropaolo,[2] Cornelia Thoeni,[1,2] Abdul Elkadri,[1,2,7] Tobias Schwerd,[8] Jun Zhu,[6] Bin Zhang,[6] Yongzhong Zhao,[6] Ke Hao,[6] Antonio Dinarzo,[6] Gabriel Hoffman,[6] Brian A. Kidd,[6] Ryan Murchie,[1,2] Ziad Al Adham,[1,2,7] Conghui Guo,[2] Daniel Kotlarz,[9] Ernest Cutz,[10] Thomas D. Walters,[1,2] Dror S. Shouval,[11] Mark Curran,[12] Radu Dobrin,[12] Carrie Brodmerkel,[12] Scott B. Snapper,[11,13] Christoph Klein,[9] John H. Brumell,[1,7,14] Mingjing Hu,[3,4] Ralph Nanan,[3,4] Brigitte Snanter-Nanan,[3,4] Melanie Wong,[15] Francoise Le Deist,[16] Elie Haddad,[17] Chaim M. Roifman,[18] Colette Deslandres,[19] Anne M. Griffiths,[1,2] Kevin J. Gaskin,[3,4] Holm H. Uhlig,[8] Eric E. Schadt,[6,§] and Aleixo M. Muise[1,2,7,§]

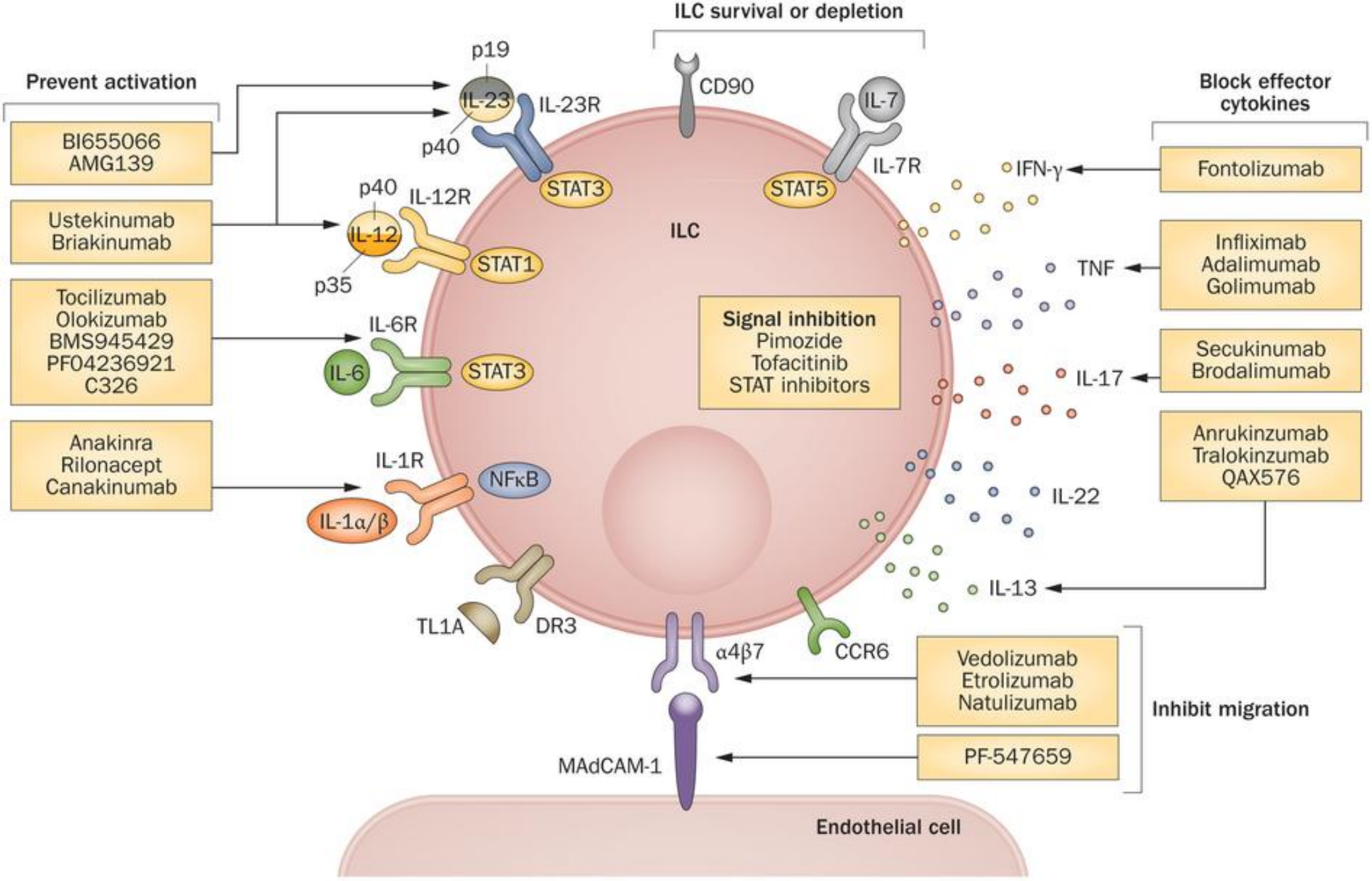





Qi Li et al., Gastro, 2016

# Final Conclusions

- Very young children and infants – with severe disease
  - more likely - genetic form of the disease
  - Look for other features – PID, autoimmune disease, lung, diabetes, treatment failure, HLH, apoptosis on biopsy…
  - identified using current available genetic approaches
- Understanding VEOIBD - will lead to novel therapeutic approaches (and define treatments not to use)
  - Stem cell transplant (specific cases with defined defect)
  - Surgery (diversion vs colectomy in IL10R-deficiency…)
  - Better use of known treatments:
    - Abatacept
    - IL10, IL1RA, GMCSF….others
  - Novel treatment strategies on the horizon….


ILC survival or depletion
Prevent activation
Block effector cytokines
BI655066
AMG139
Ustekinumab
Briakinumab
Tocilizumab
Olokizumab
BMS945429
PF04236921
C326
Anakinra
Rilonacept
Canakinumab
p19
IL-23
p40
IL-23R
STAT3
p40
IL-12
p35
IL-12R
STAT1
IL-6R
IL-6
STAT3
IL-1R
IL-1α/β
NFκB
TL1A
DR3
CD90
IL-7
IL-7R
STAT5
ILC
Signal inhibition
Pimozide
Tofacitinib
STAT inhibitors
IFN-γ
TNF
IL-17
IL-22
IL-13
Fontolizumab
Infliximab
Adalimumab
Golimumab
Secukinumab
Brodalimumab
Anrukinzumab
Tralokinzumab
QAX576
α4β7
CCR6
MAdCAM-1
Vedolizumab
Etrolizumab
Natulizumab
PF-547659
Inhibit migration
Endothelial cell

# More Information

- Please see
  - www.NEOPICS.org
  - www.VEOIBD.org

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  - Lin Wang - WES in Chinese patients
  - Neil Warner – NOD2 networks and WES
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  - Khalid Hossain - TRIM22 binding partners
  - Lucus Mastropaolo – role iNOS in IBD
  - **Karoline Fiedler** – NEOPICS Project Co-ordinator

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C S

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Boston Children's Hospital Early Childhood IBD Initiative

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