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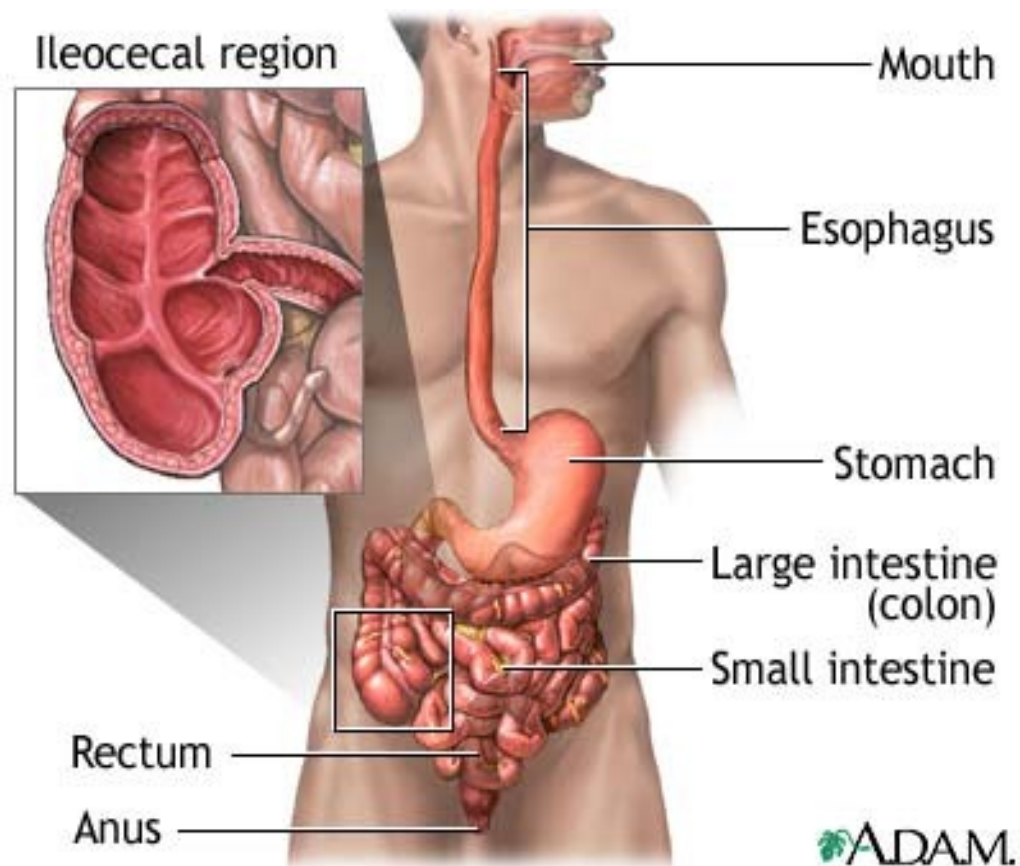
The Genetic Basis of Crohn's Disease

Suzi Alvarez



What is Crohn's Disease?

- A form of Inflammatory Bowel Disease involving chronic inflammation of the intestinal tract
 - Crohn's: anywhere, deepest layers of the lining, discontinuous
 - Ulcerative Colitis: colon and rectum, inner lining, continuous
- Usual onset 15-35 years
- Prevalent in U.S. and western Europe
 - 200 / 100,000, 1 million Americans

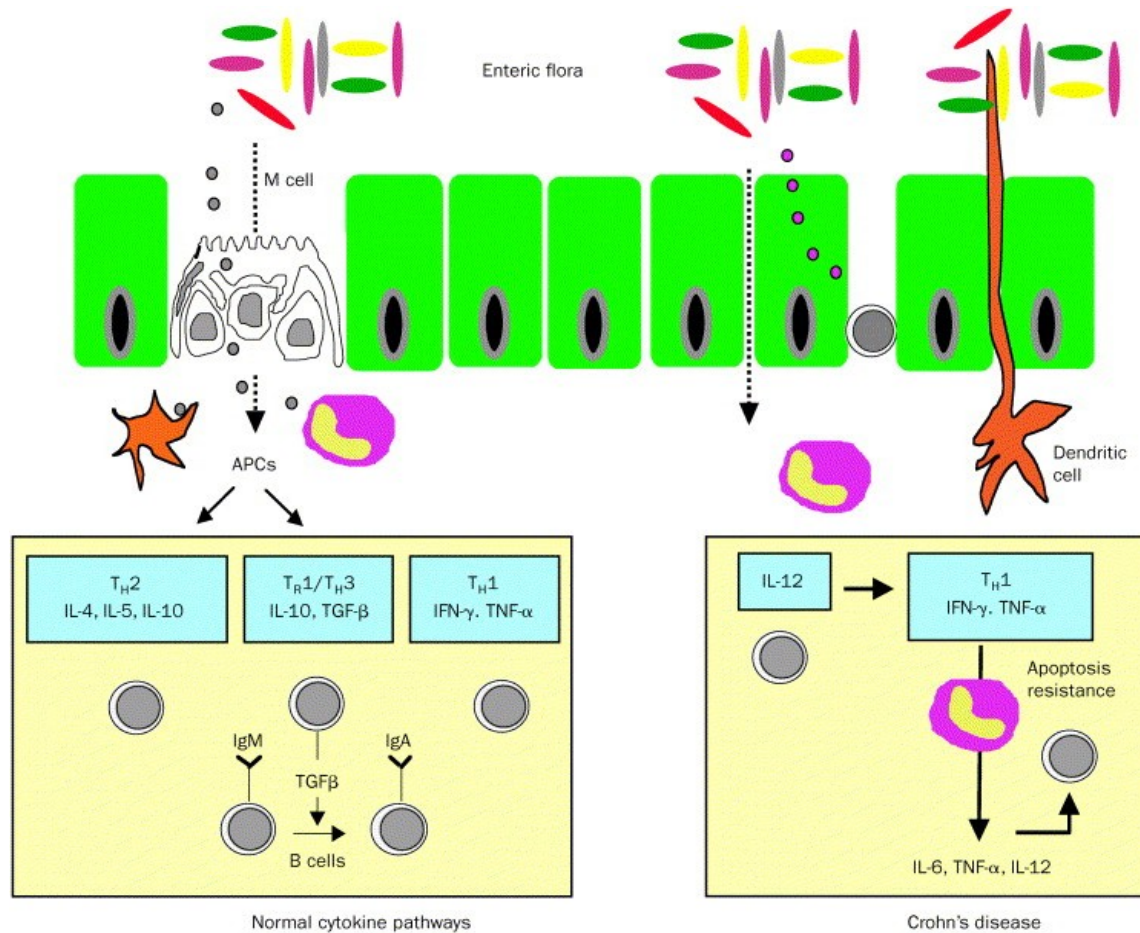




What causes Crohn's?

- Genetic predisposition, environmental factors and immune-mediated tissue injury
- Abnormal mucosal immune reaction regulated by T-lymphocytes to certain enteric bacteria present in the intestines
- Epithelial cells sense bacteria type. TH1 for dangerous, TH2 & TH3 for acceptable
- With Crohn's, only TH1 cytokines such as TNF are used
- Apoptosis resistance → Unrestrained TH1 generates activated matrix metalloproteinases causing tissue destruction

Normal vs. Crohn's Pathway





Symptoms

- Abdominal pain, Diarrhea, Fever, Weight loss, Bleeding
- Complications due to symptoms:
 - Strictures → obstruction
 - Fistulas
 - Anemia
 - Perforation
- “Flare-ups” followed by periods of being healthy
- Perforating vs. Non-perforating
 - Abscesses/free perforation vs. blockage/bleeding



Diagnosis

- Physical examination of abdomen
- Barium Small Bowel Follow-through
- Colonoscopy
- Endoscopy
- Blood work:
 - Albumin, c-reactive protein, sedimentation rate, white count, hemoglobin



Treatment

- Aminosalicylates (5-ASAs)
- Immunosuppressives: specific
- Corticosteroids: nonspecific
- Anti-TNF: tumor necrosis factor
- Surgery: bowel resection, anastamosis
- Diet: Low fiber, low residue, Low lactose
- No cure ... yet! Genetic research is getting us closer

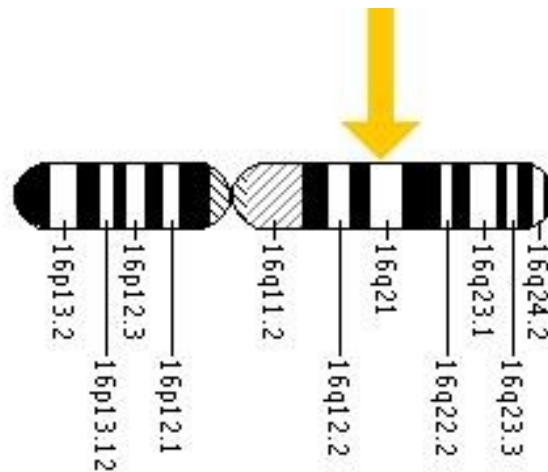


THE GENES: NOD2

- Located on Chromosome 16
- Makes a protein called nucleotide-binding oligomerization domain containing 2: involved in immune response and epithelial cells in lining
- NOD2 creates nuclear factor-kappa-B attack “bad” bacteria
- 30+ NOD2 variations are associated with Crohn's (protein is slightly shorter, one amino acid missing)

More NOD2

- Studies suggest changes in NOD2 allow bad bacteria to invade the lining
- An abnormal immune response to this bacteria could cause inflammation



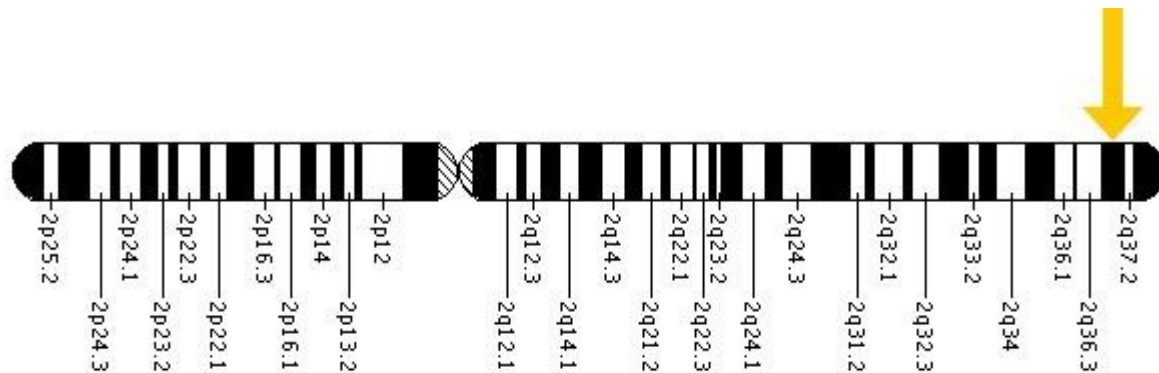


THE GENES: ATG16L1

- Located on Chromosome 2
- Makes a protein called ATG16 autophagy related 16-like 1
 - A family of proteins responsible for autophagy – destroying old cell parts and proteins
 - Important in cell death and immune destruction of viruses and bacteria

More on ATG16L1

- One variation associated with CD:
replacement of the amino acid threonine
with alanine
- If worn-out cell parts in bacteria that
should be destroyed stay, it could cause
abnormal immune response



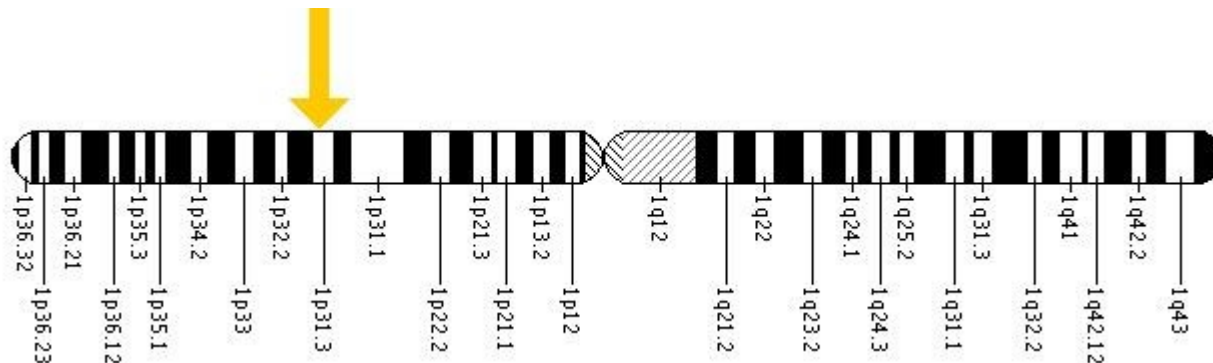


THE GENES: IL23R

- Located on chromosome 1
- a protein called the interleukin 23 receptor on surface of immune cells
 - T-Cells, Natural Killer cells, Dendritic
- Protein protrudes out of cell and binds with interleukin 23 (cytokine, immune regulator), this causes inflammation
- Many variations of IL23R associated

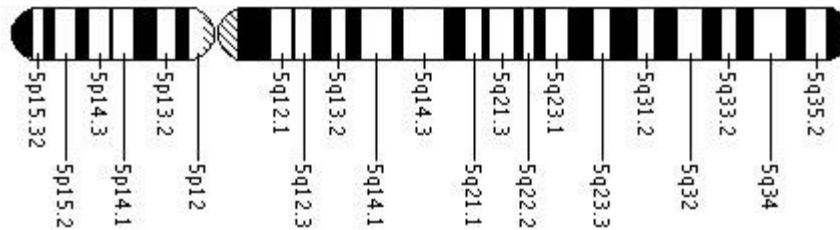
More on IL23R

- One change appears to *reduce* the likelihood of developing Crohn's
 - replacing the amino acid arginine with glutamine
 - Unclear how this works, but receptor's ability to trigger inflammation in intestinal walls shows its connection

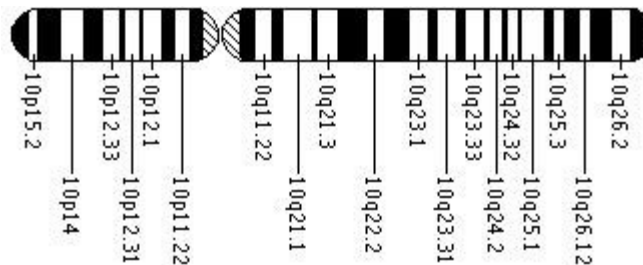


Chromosomes 5 & 10

- IBD Locus on long arm of 5 (5q31)
- “Gene desert” on short arm (5p13.1), nearby gene PTGER4
 - T-cell signaling and skin immune response



- Gene desert on 10 (10q21.1), may affect nearby gene ERG2: immune response





Implications

- Current medications treat only the symptoms and involve a great deal of trial and error
- Genetic research has the potential to improve therapy as well as provide early detection and a cure



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