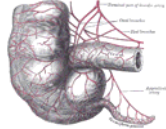


Inflammatory bowel disease as a complex genetic disease.



Stephen L. Guthery, MD, MSc
 Division of Pediatric Gastroenterology and Nutrition
 Department of Pediatrics
 University of Utah
 Primary Children's Medical Center

Objectives

- Understand how a complex genetic condition is different from a Mendelian condition.
- Understand importance of linkage vs. association.
- Understand the concept of an odds ratio.
- Understand the potential clinical application of genomics.

Concepts

1. The single nucleotide polymorphism

Single nucleotide polymorphism: a single base pair change in the genome

A change in DNA sequence.

Heritable

~10 million in genome

TTGCAGCTCTCC
 TTGCAGCTCTCC
 TTGCAGCTCTCC
 ATGCAGCTCTCG
 ATGCAGCTCTCG
 ATGCTGCTCTCG
 ATGCTGCTCTCG
 ATGCAGCTCTCG

A/T 3/8=0.375

A/T 2/8=0.25

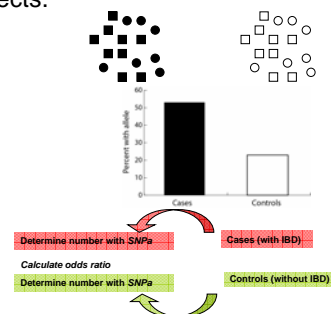
G/C 3/8=0.375



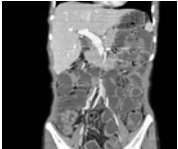
Concepts

1. The single nucleotide polymorphism
2. The genetic association study.


Genetic case-control studies measure genetic differences in diseased and healthy subjects.



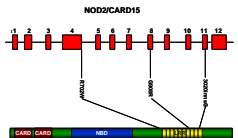
A. What is inflammatory bowel disease



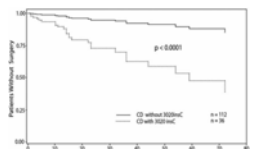
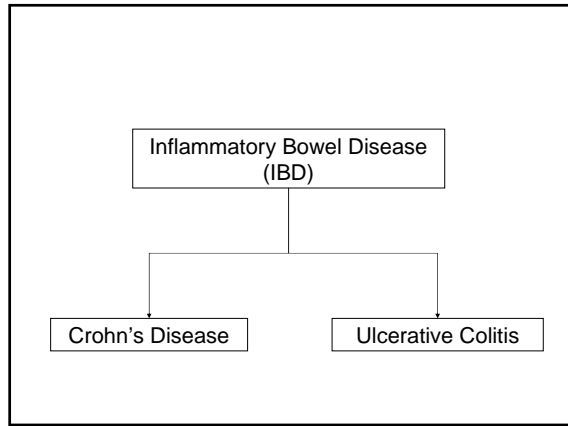
B. Is it a complex genetic disorder?



C. Are there genes that cause it?



D. Can genomics be applied clinically?

IBD is a chronic inflammatory disorder of the GI tract

It is not irritable bowel syndrome (IBS).

Chronic idiopathic inflammatory disorder of the GI tract.

H₀: IBD is an inappropriate inflammatory response to an environmental agent in genetically susceptible individuals.

Epidemiology of IBD, Crohn's disease and ulcerative colitis.

Incidence: 7/100,000 children under age of 18 (Kugathagan et al, *J peds* 2001)

Crohn's: 4.6/100,000/year

UC: 2.1/100,000/year

Approximately 5,300 children hospitalized in 1997 in the US (Guthery et al, *J Peds* 2003)

Approximately 1,000,000 in the US have the disorder.

Disorder (0-18 years of age approx.)	Incidence (per 100,000/year)
Leukemia (All types)	3.9
CNS tumors	3.0
Cystic fibrosis	40
Type I Diabetes	16
Inflammatory Bowel Disease	7

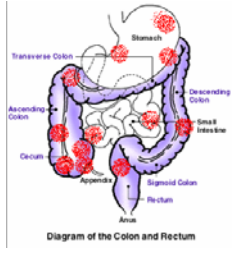
SEER Pediatric Monograph <http://seer.cancer.gov/publications/childhood/CDC>
<http://www.cdc.gov/diabetes/pubs/factsheets/search.htm>
 Cystic fibrosis foundation registry report 2002
 Kugathasan et al. *J. Peds.* 2004.

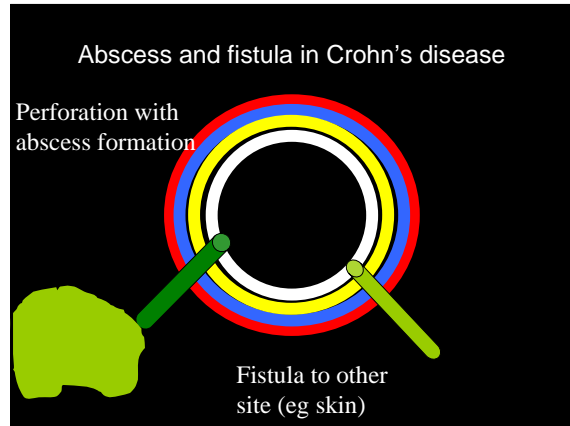
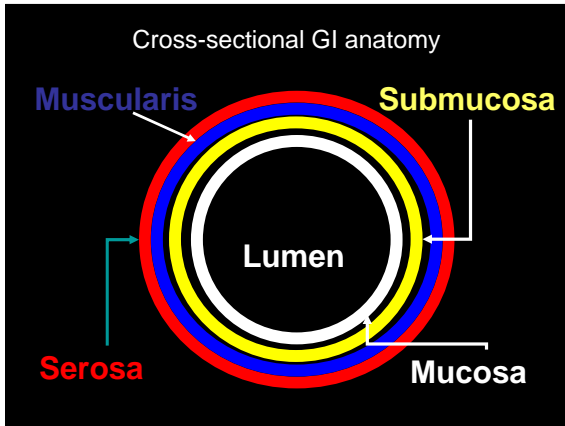
Crohn's disease is discontinuous and global.

Involves any part of the GI tract mouth to anus.

Inflammation is patchy, non-continuous (hence "Regional Enteritis")

May involve all layers of GI tract.





Extraintestinal manifestations of IBD (~6%)

Normal bile ducts

Inflammation and scar tissue Biliary ducts

Uveitis 1-2%

Pyoderma gangrenosum 1%

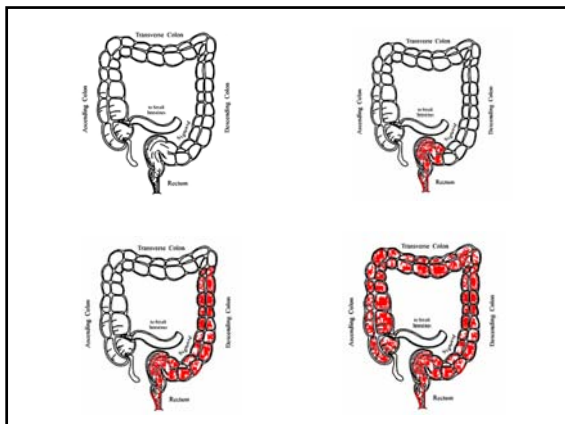
Others:
Erythema nodosum
Arthritis

Primary Sclerosing cholangitis ~3% of men
Copyright ©2001-2006 Mayo Foundation for Medical Education and Research. Reproduced with permission.
Bernstein et al. Am J Gastroenterol. 2001

Ulcerative colitis is a geographically continuous disease of the colon.

Involves the colon continuous, distal > proximal.

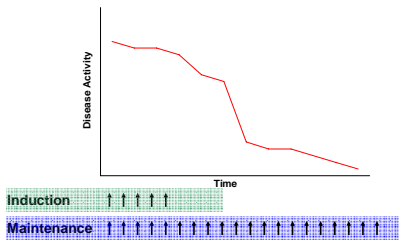
It continuously distributed.



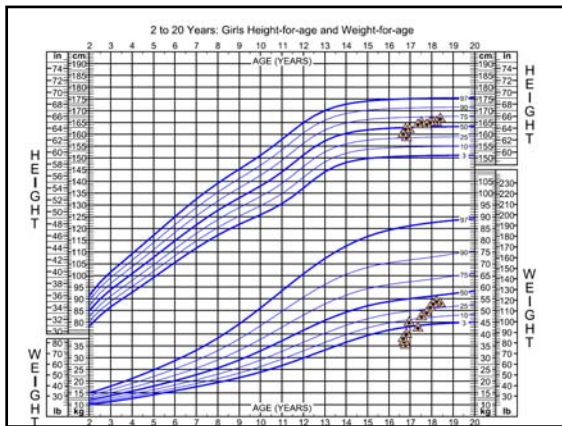
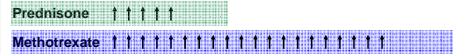
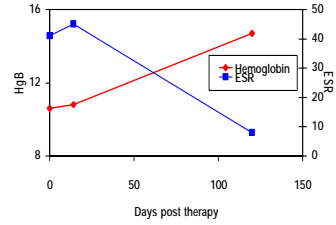
UC VS. CROHN'S: Summary

	UC	Crohn's
Weight loss	Occasional	Common
Linear growth failure	Occasional	Common
Pubertal delay	Occasional	Common
Fistulae	Rare	Common
Bowel obstruction	No	Yes
Distribution of disease	Continuous	"skip lesions"
GI disease outside colon	No	Yes

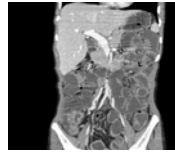
Therapy for Crohn's disease is divided into induction and remission.



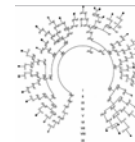
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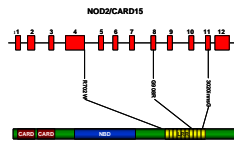
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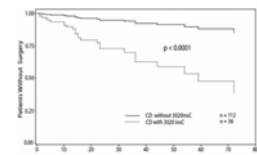
B. Is it a complex genetic disorder?



C. Are there genes that cause it?



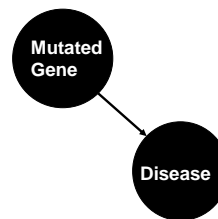
D. Can genomics be applied clinically?



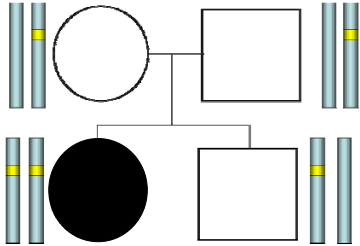
What is the evidence that IBD is a complex genetic disorder?

There is no apparent Mendelian pattern of inheritance.

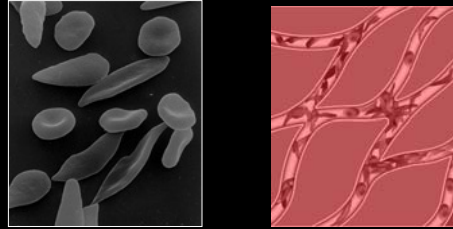
Gene-disease Relationship: Single-gene Diseases



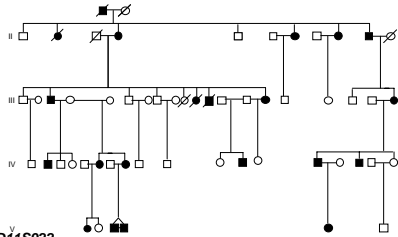
Autosomal recessive pedigree



Sickle cell anemia results from a mutation in the β -globin gene.



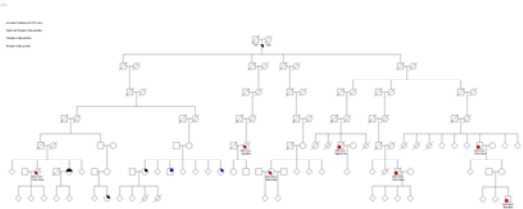
Autosomal dominant condition



D11S922
LOD Score=5.31

Courtesy of Mike Bamshad, MD

IBD has low penetrance.

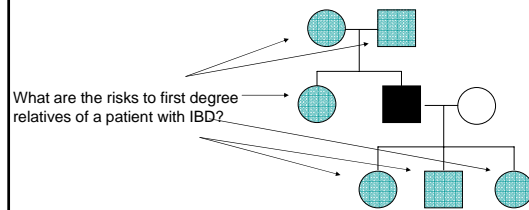


What is the evidence that IBD is a complex genetic disorder?

There is no apparent Mendelian pattern of inheritance.

There is familial aggregation.

Crohn's disease clusters in families.



Analysis of UPDB demonstrates an increased risk for IBD among first degree relatives.

	Relative Risk (95% CI)	
	Possible cases	Probable cases.
Crohn's disease	4.5(1.9-10.8)	4.6 (1.1-18.2)
Ulcerative colitis	9.3 (3.7-23.6)	11.1 (3.6-34.3)
IBD	4.9 (3.0-8.2)	6.8 (2.9-16.0)

What is the evidence that IBD is a complex genetic disorder?

There is no apparent Mendelian pattern of inheritance.

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Heterogeneity.

Heterogeneity in inflammatory bowel disease

Disease/clinical

genetic (genetic and non-genetic factors)

locus (mutations in different loci)

allelic (different mutations in the same gene)

Inflammatory Bowel Disease (IBD)

Crohn's Disease

Ulcerative Colitis

Inflammatory Bowel Disease (IBD)

Crohn's Disease

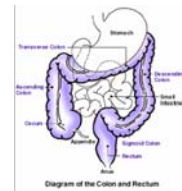
Indeterminate Colitis

Ulcerative Colitis

Subtypes of Crohn's disease: the Vienna classification Gasche *Inflamm*

Bowel Dis 2000

Age at diagnosis	A1, <40 years
	A2, >40 years
Location	L1, Terminal ileum
	L2, Colon
	L3, Ileocolon
	L4, Upper gastrointestinal
Behavior	B1, non-stricturing non-penetrating
	B2, Stricturing
	B3, Penetrating



24 subtypes

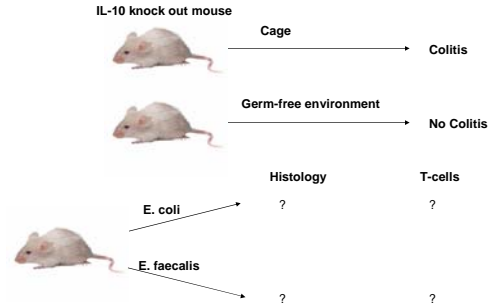
Heterogeneity in inflammatory bowel disease

Disease

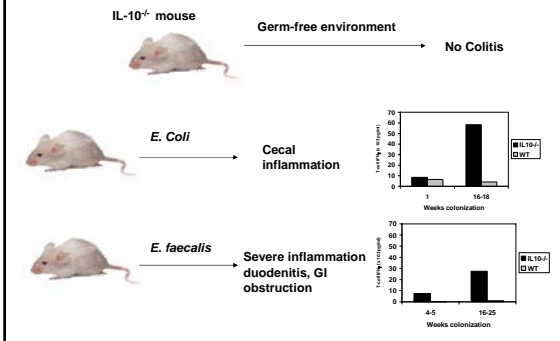
Genetic (genetic and non-genetic factors)

Environmental factors increases risk of IBD in an animal model of IBD

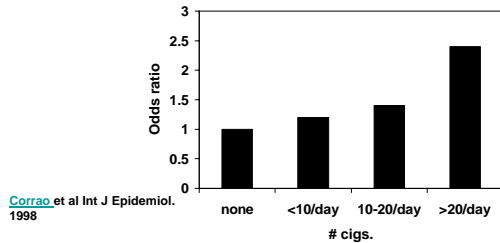
(© Kim et al Gastro, 2005)



Commensal bacteria determine phenotype in IL-10^{-/-} mice.



Smoking is a risk factor for Crohn disease



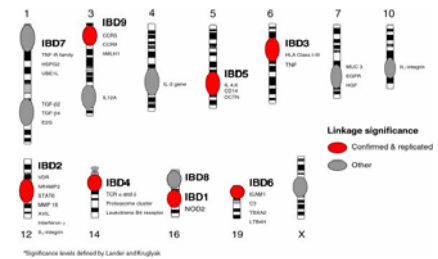
Heterogeneity in inflammatory bowel disease

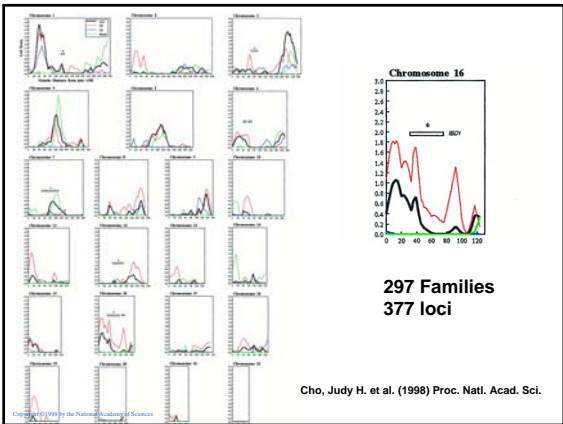
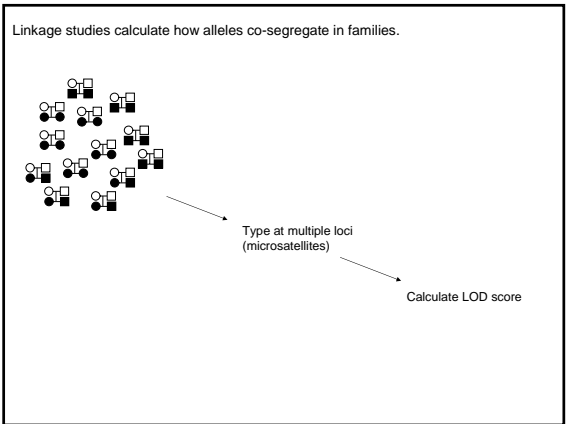
Disease

genetic (genetic and non-genetic factors)

locus (mutations in different loci)

Linkage studies demonstrate multiple IBD susceptibility loci.





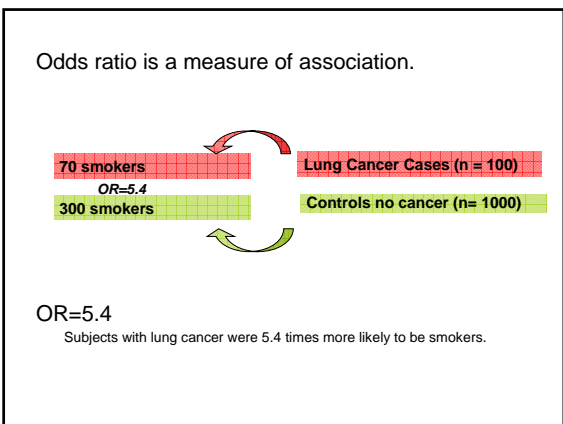
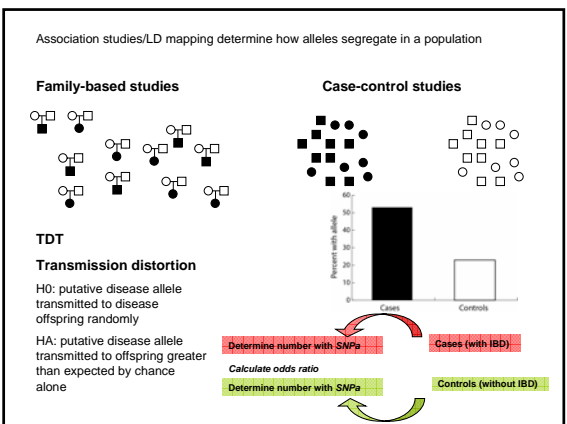
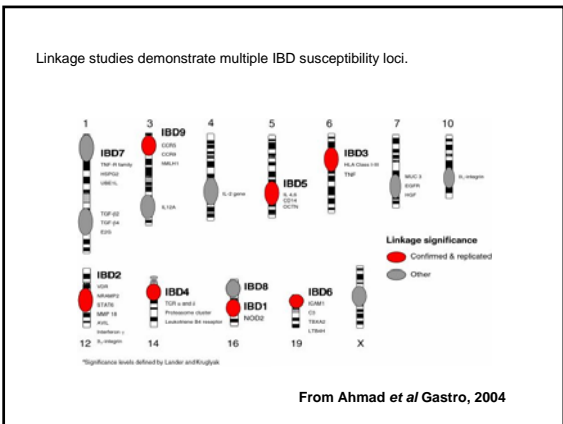
Heterogeneity in inflammatory bowel disease

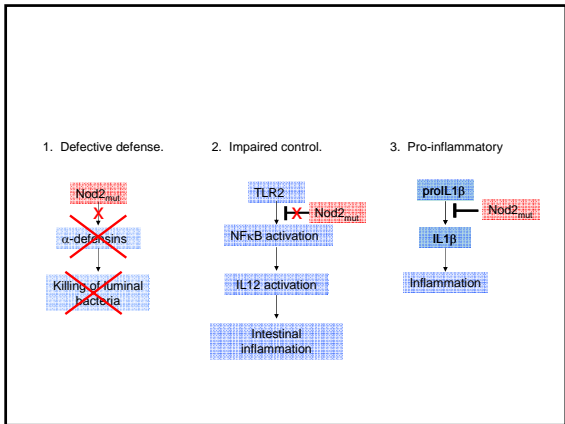
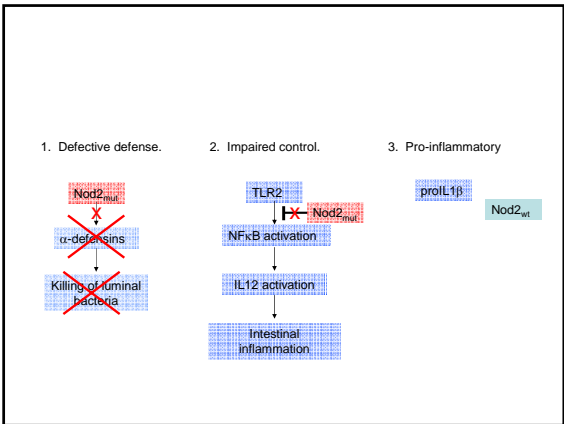
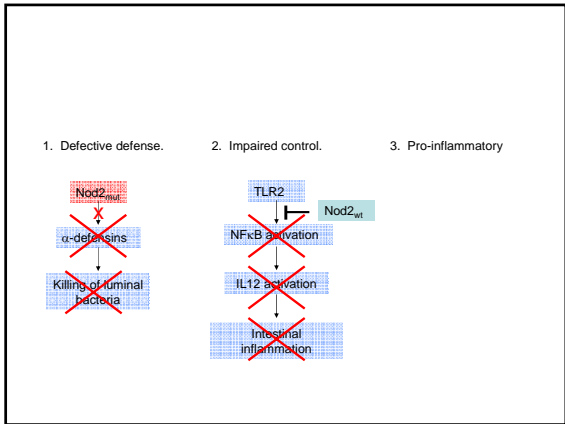
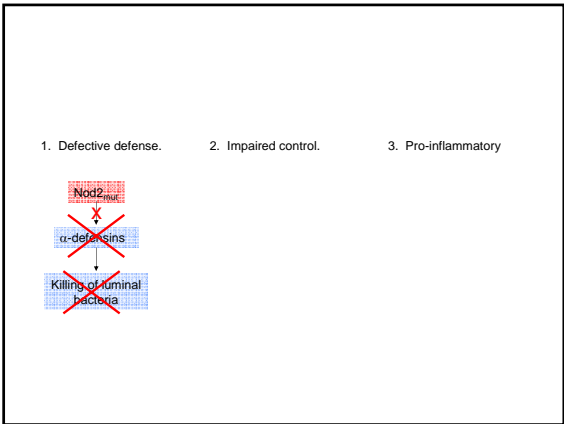
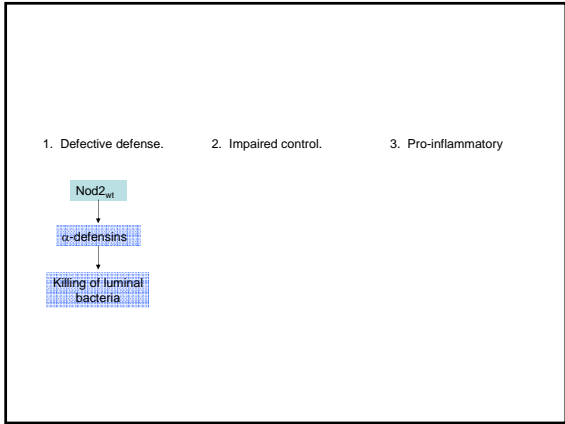
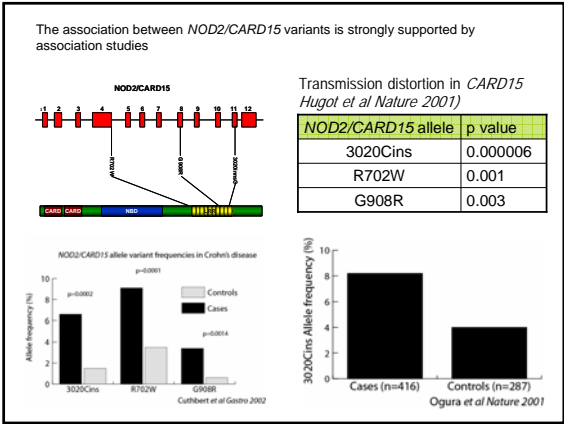
Disease

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locus (mutations in different loci)

allelic (different mutations in the same gene)





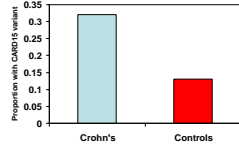
Mutations in *NOD2/CARD15* are neither necessary nor sufficient to cause disease

Majority of Crohn's patients do not have mutation in *NOD2/CARD15* gene.

Genotyping is not used for clinical purposes (yet)

Mutation in other gene variants likely contribute to disease.

Environmental clearly plays a role



Economou *et al Am J Gastro* 2004

Heterogeneity in inflammatory bowel disease

Disease

genetic (genetic and non-genetic factors)

locus (mutations in different loci)

allelic (different mutations in the same gene)

What is the evidence that IBD is a complex genetic disorder?

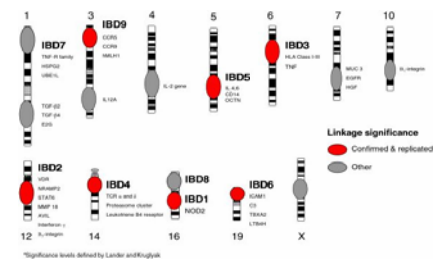
There is no apparent Mendelian pattern of inheritance.

There is familial aggregation.

Heterogeneity.

Small contribution of SOME loci to overall risk.

Linkage studies demonstrate multiple IBD susceptibility loci.



From Ahmad *et al Gastro*, 2004

Whole genome association study

1. Find some cases.
2. Find some controls.
3. Genotype at 100,000-500,000 SNPs
4. Identify frequency differences.
5. Apply correction for multiple comparison
6. Confirm in another dataset

Allele frequency differences across ~63,000 SNPs

SNP	Frequency in Cases	Frequency in Controls	p value	FDR p value	Bonferroni p value
1774	0.8	0.07	4×10^{-11}	4×10^{-8}	2×10^{-6}
61196	0.75	0.08	2×10^{-9}	7×10^{-7}	0.003
4324	0.725	0.97	0.003	0.04	1
5461	0.2	0.53	0.004	0.05	1
18375	0.28	0.05	0.01	0.12	1
13228	0.85	1	0.03	0.19	1
25846	0.85	1	0.03	0.19	1
17675	0.65	0.87	0.05	0.24	1

A genome-wide association study identifies IL23R as an Inflammatory Bowel Disease Gene

Duerr et al. Science Oct 2006

547 Cases of Crohn's disease

548 Controls

308,332 SNPs

A genome-wide association study identifies IL23R as an Inflammatory Bowel Disease Gene

Duerr et al. Science Oct 2006

rs2066843 (adjp value= 8.8×10^{-4})
rs2076756 (adjp value= 1.6×10^{-4})

CARD15

rs11209026 (adjp value= 1.6×10^{-3})

IL23R

Experimental evidence suggests IL-23 pathway is involved in IBD

IL-23 required for murine colitis

Overexpression of IL-23 results in severe inflammation in mice.

IL-17 present in mucosa of patients with IBD.

What is the evidence that IBD is a complex genetic disorder?

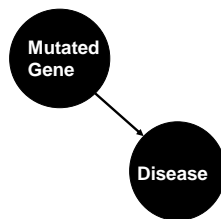
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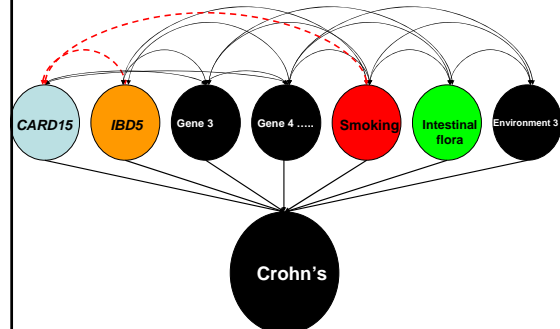
Gene-disease Relationship: Single-gene Diseases



Gene-trait Relationship: Crohn's disease

"Genetics loads the gun, environment pulls the trigger"

-Judith Stearns.



Questions that come up in the clinic

I've heard IBD is genetic, what is the risk to my family members?

Analysis of UPDB demonstrates an increased risk for IBD among first degree relatives.

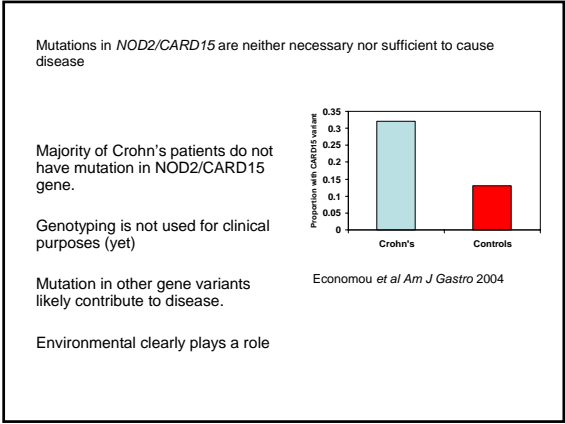
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IBD	4.9 (3.0-8.2)	6.8 (2.9-16.0)

Crohn's disease prevalence=81/100,000
 Ulcerative colitis prevalence=57/100,000

Questions that come up in the clinic

I've heard IBD is genetic, what is the risk to my family members?

Is genotyping helpful for diagnosis?



Questions that come up in the clinic

I've heard IBD is genetic, what is the risk to my family members?

Is genotyping helpful for diagnosis?

Is genotyping helpful for prognosis?

