The Genetics of Inflammatory Bowel Disease

Why has it not hit the clinic?

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What can genetics offer the clinician looking after someone with CD?

For the patient:

- Predicting disease behavior - location, complications
- Stratifying treatment

For the family

- Identifying those at risk
- surveillance
- Symptom anticipation/ early intervention

How “genetic”is IBD?

- Sibling risk
  - 2-14% of probands have a family history
  - sibs have a 15-42-fold risk of developing the disease

- Twin studies
  - Monozygotic vs Dizygotic twins
  - MZ rate - 30% concordance; DZ rate: 3.6%

- Concept of heritability
  - what percentage of the liability towards developing CD lies in the genes (as opposed to environmental factors) - 0.7

Some statistics relating to the human genome

- 46 strands of DNA – the “diploid” genome
- The 23 strands comprised of 3,000,000,000 bases of DNA
- 21,000 genes (comprises 2% of our genome)
- Humans are 99% identical at the sequence level

How do we identify these genetic factors
Defining risk elements using molecular genetics

Linkage

- Tracing risk variants in families with clustering of the disease
- Not applicable to all families with CD
- Selects for families with variants with large effect

Association

- Looks across populations for sharing of variants in the genomes indicating that those variants (or variants physically near them on the chromosome) confer susceptibility to CD
- 140 loci now identified

NOD2 - the poster-child of complex disease genetics

- Gene involved in innate immunity regulation
- Like all genes - possesses many variants
- A small number alter its function
- Possession of one or two copies of these variants inflates the risk of developing CD - 4-fold (one copy) or 20-40-fold (two copies)
- These variants have been discovered by tracing these variants in susceptible families - linkage

Pausing to think about risk variants at the individual level

Why isn't NOD2 useful for personalised risk prediction?

The variants are:

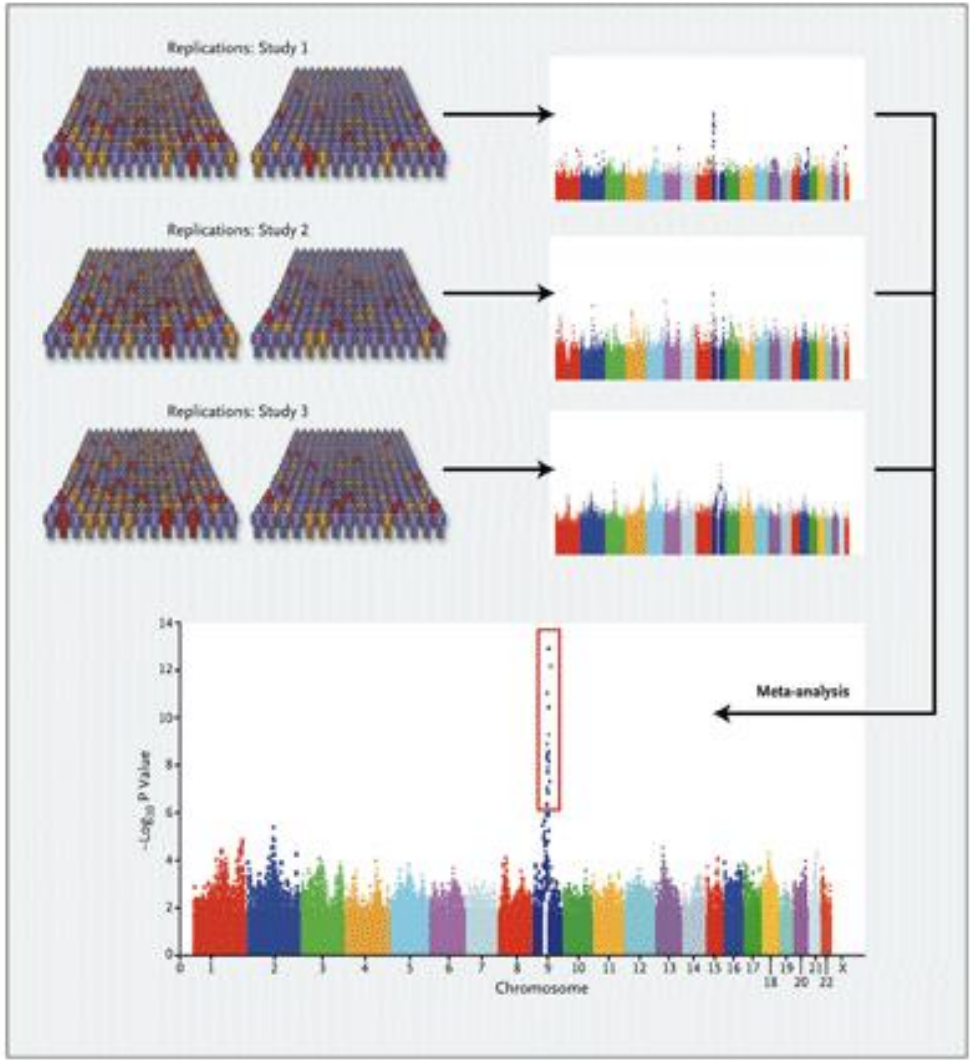
1. Rare (depending on ethnicity present in 0.01% - 7% of the population)
2. Confer impressive increases in risk for a relatively rare disease

The incidence of CD is ~1% - therefore…….

a person with: one copy of a NOD2 risk variant is at 4% risk of CD

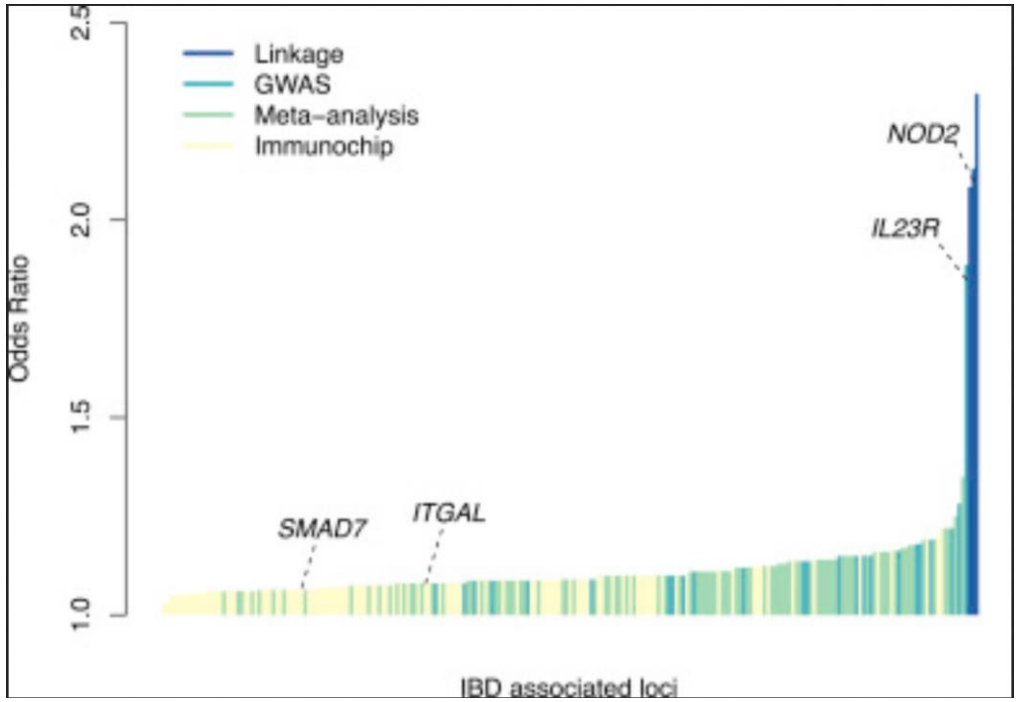
two copies (very rare individuals): 20-40% risk

Genome Wide Association Analysis
A Genetic Case-Control Study



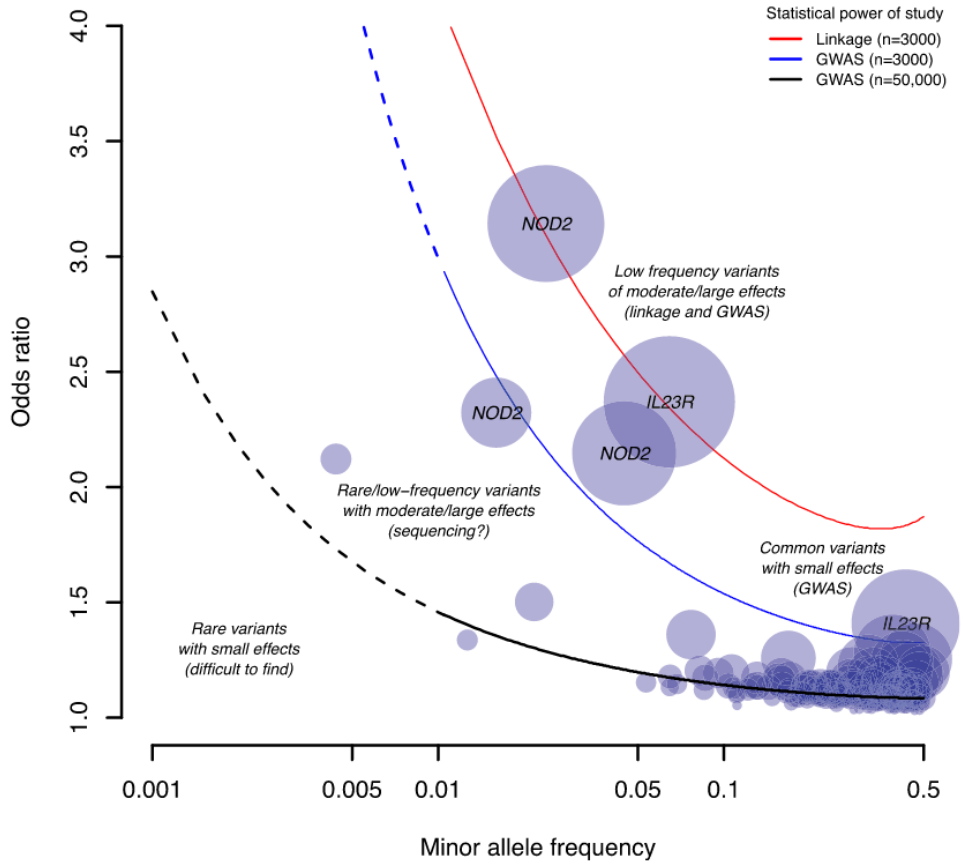
N Engl J Med 2010;363:166-76.

The long tail - large numbers of weakly acting variants contribute to susceptibility to CD



de Lange and Barratt J Autoimmunity 64: 91-100

Rare and Common; Strong and Weak
The genetic variants that predispose to CD



J.Z. Liu, C.A. Anderson Best Practice & Research Clinical Gastroenterology 28 (2014) 373–386

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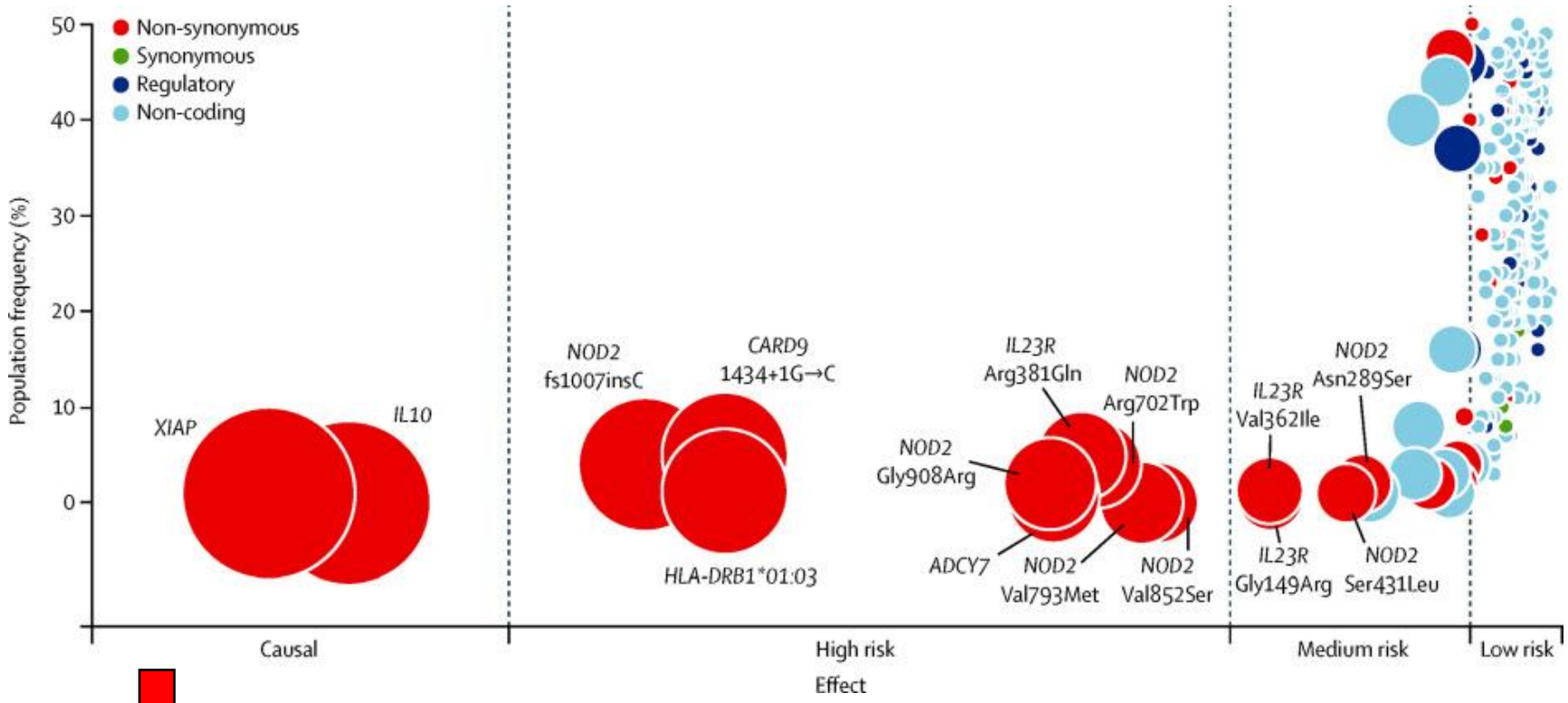
Aggregating the Genetic Burden - a way forward to measure susceptibility to the development of CD



Aggregation of all contributory variants into a risk score for individual patients.
These scores could be used clinically like any other risk factor.

Lancet: Gastro Hepatol (2017)

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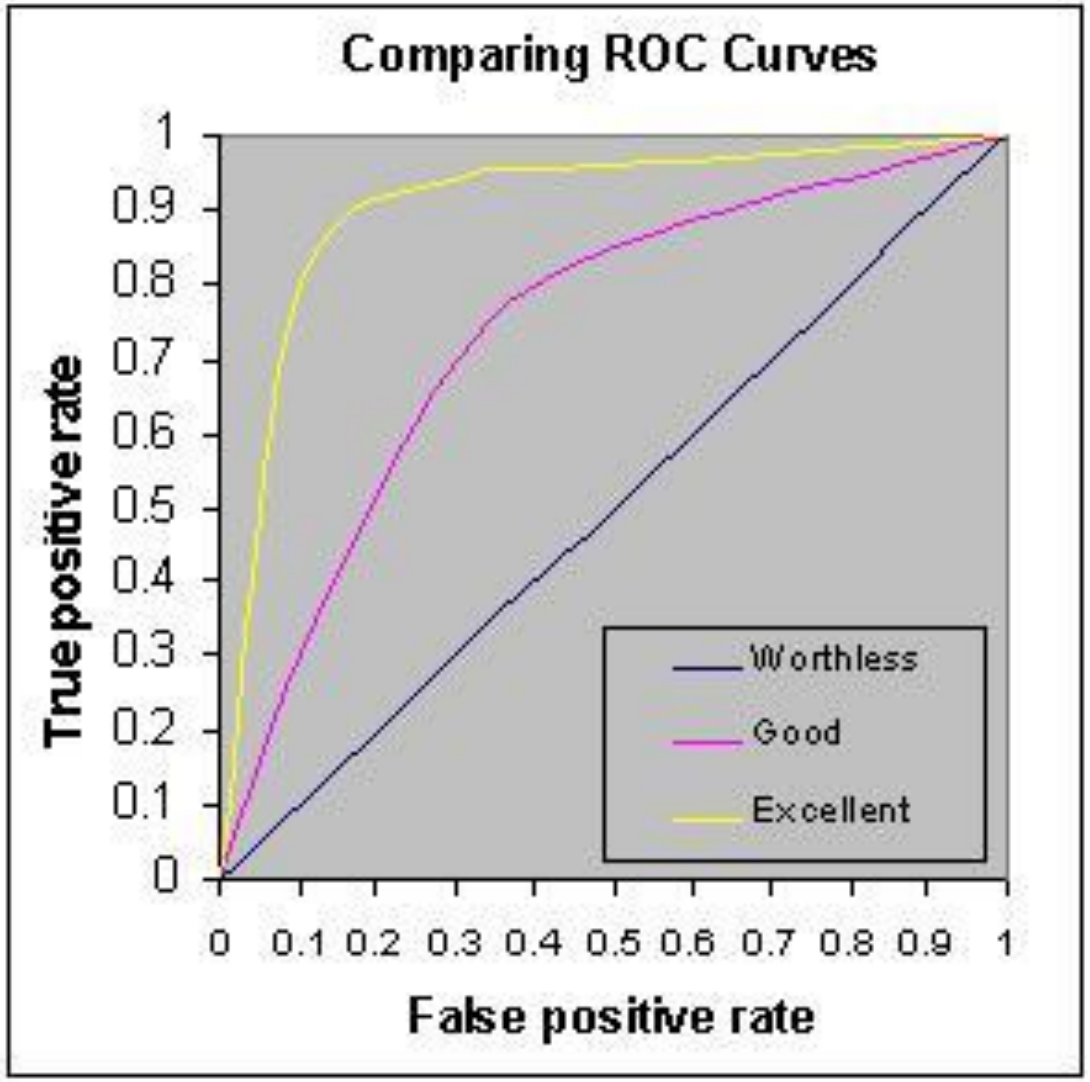
Genetic risk prediction - a hard space for a "rare disease"

- Receiver operating curves

- For IBD area under the curve estimates for the best predictive risk scores = 0.67



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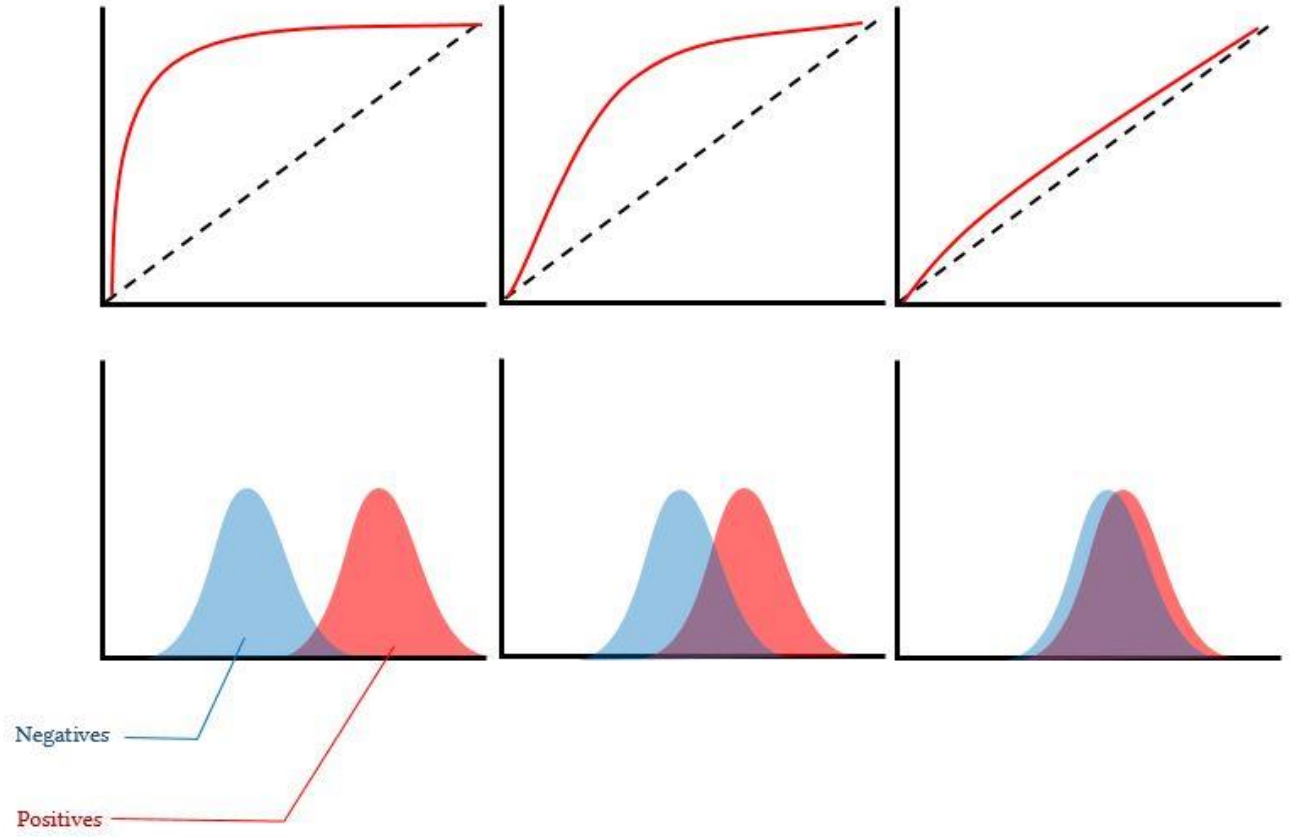
ROC - put another way

ROC curve

Distributions



Summary

- Genetics has taught us a huge amount about the pathogenesis of IBD
- Many genes are conclusively implicated in its causation
- Infant or early childhood onset IBD the sweet spot for genetic diagnosis
- Over half of the genetic susceptibility remains to be discovered
- The use of genetic risk factors for individuals is very limited
- Predictive risk scores will be of limited utility due to the condition's relative rarity