Integration of host genomics into infectious risk in AML patients: challenges and opportunities

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ICAAC 2014

Conflict of Interests and Speaker Background

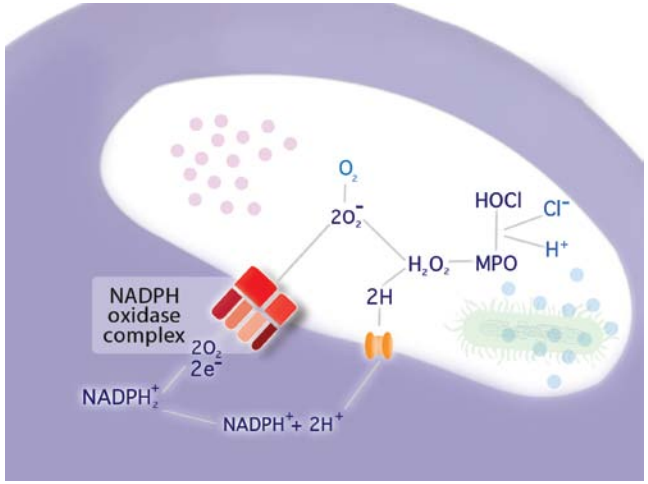
- No conflicts of interest to declare
- Speaker is infectious diseases practitioner at MD Anderson Cancer Center, Houston, TX
  - Major research focus is bacterial genomics
  - Interested in understanding how to leverage host genomics to better prevent and treat infections in cancer patients

Overview of Talk

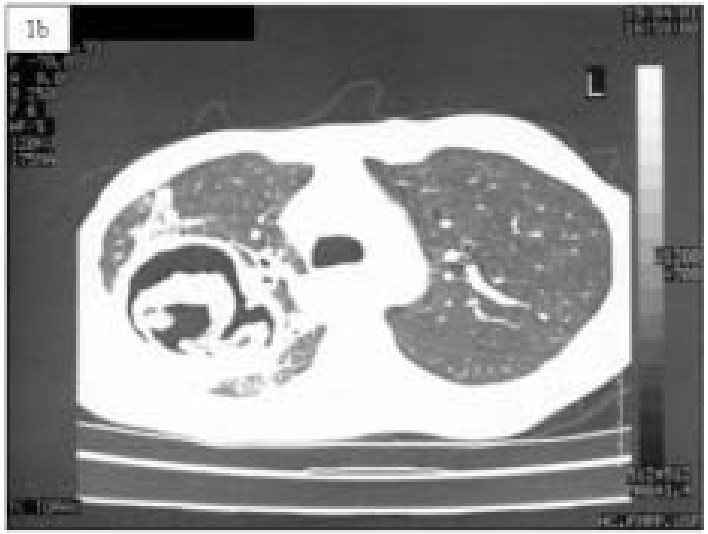
- Why is there an interest in incorporating genomics into risk of infection in cancer patients?
  - Particularly now
  - Particularly for fungal infections
- Review known genetic predispositions to fungal infections with emphasis on cancer patients
- Summarize promises and difficulties of the genomic approach to fungal infection predisposition

Rare Diseases Show that There Can Be Strong Genetic Component to Fungal Infection Susceptibility

Chronic granulomatous disease



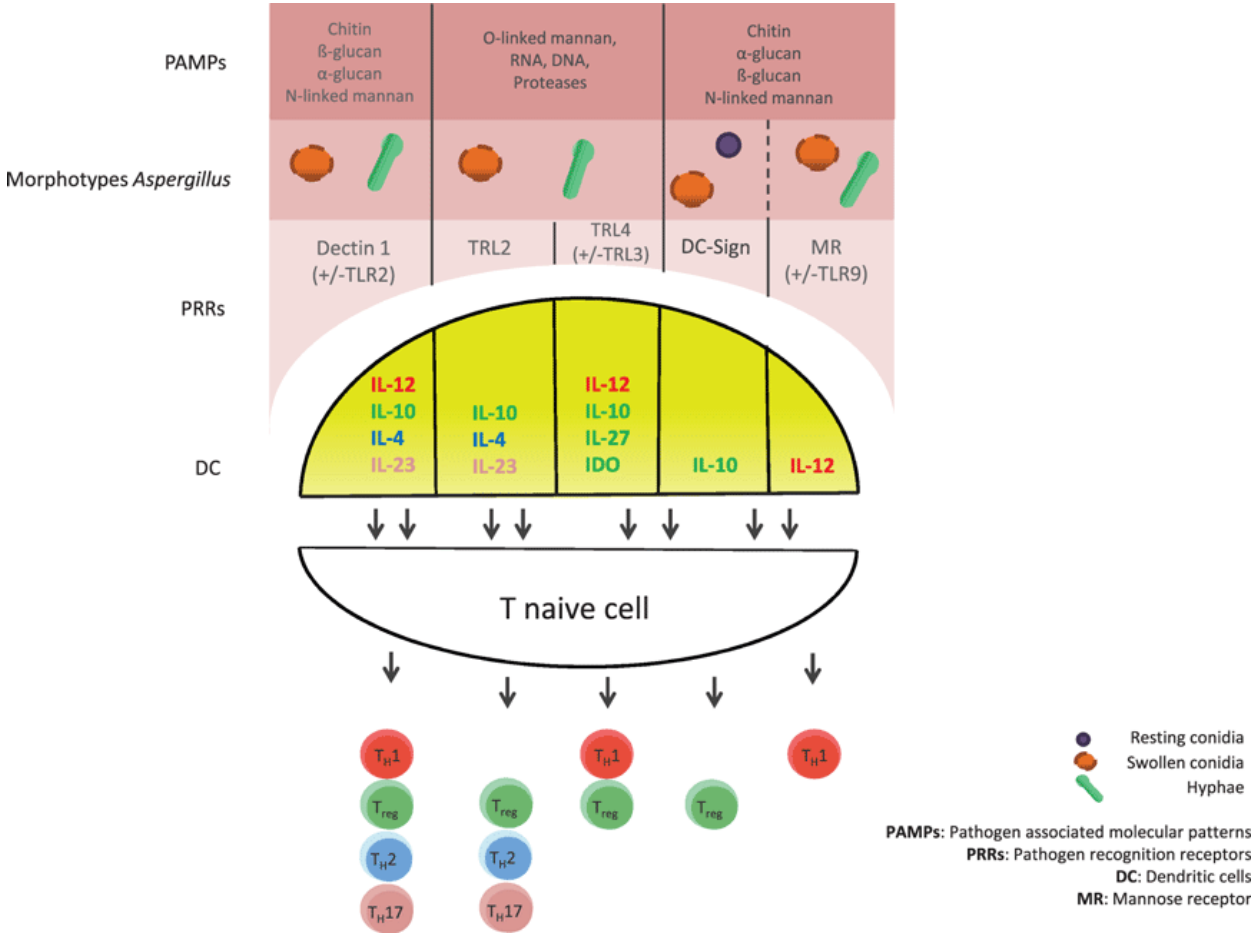
Invasive aspergillosis



Other examples:

- Chronic mucocutaneous candidasis
- Hyper IgE syndrome

Innate Immune System is Critical to Anti-Mold Defense



Mycoses
Volume 56, Issue 4, pages 403-413, 14 FEB 2013 DOI: 10.1111/myc.12052
http://onlinelibrary.wiley.com/doi/10.1111/myc.12052/full#f2

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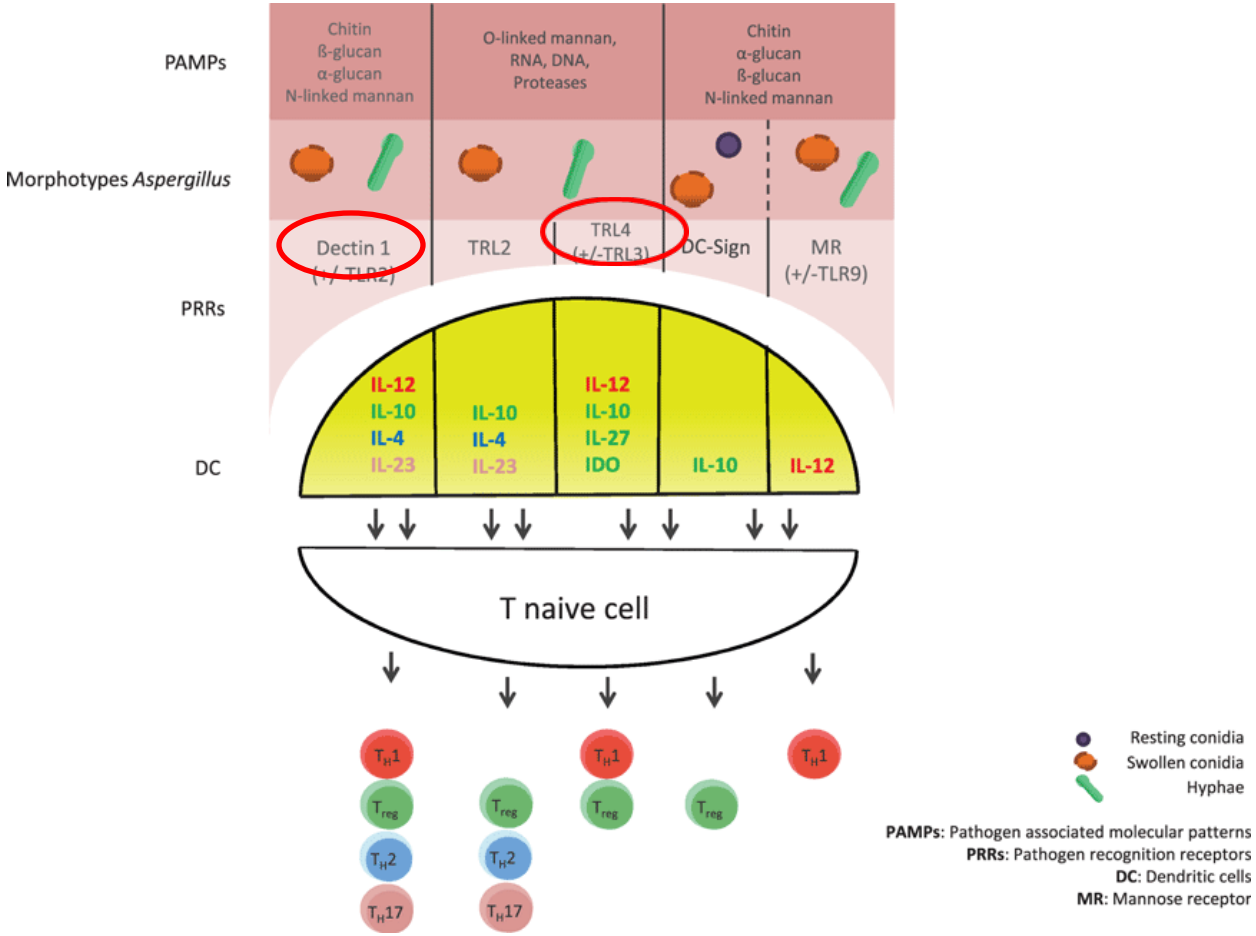

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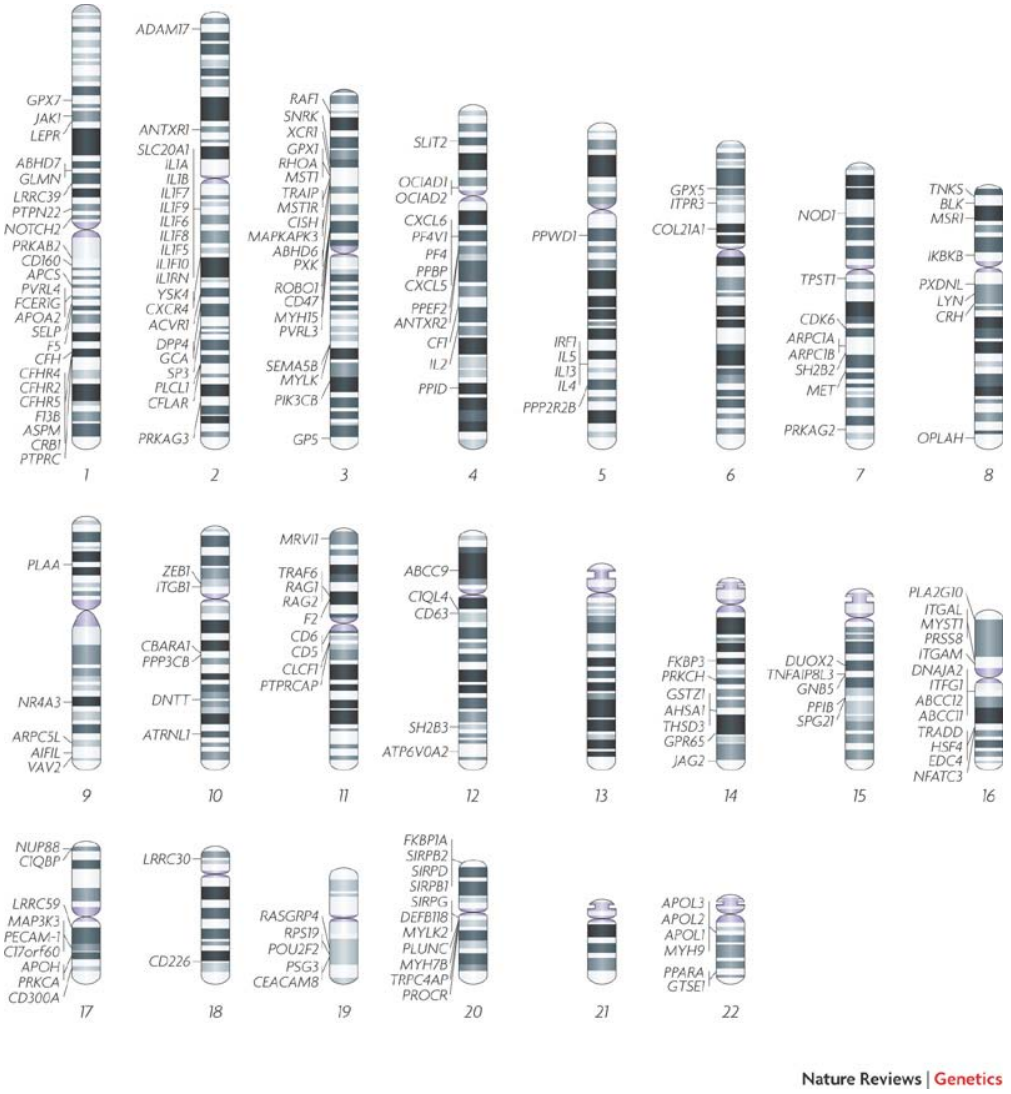
Infection is a Major Driver of Diversity of the Human Genome

Examples of immunity related genes under positive selection for variance



Barriero LB et al., Nature Genetics 2010;11:17-30

Clinical Aspects of Mold Infections That Drive Enthusiasm for Identifying Genetic Risk

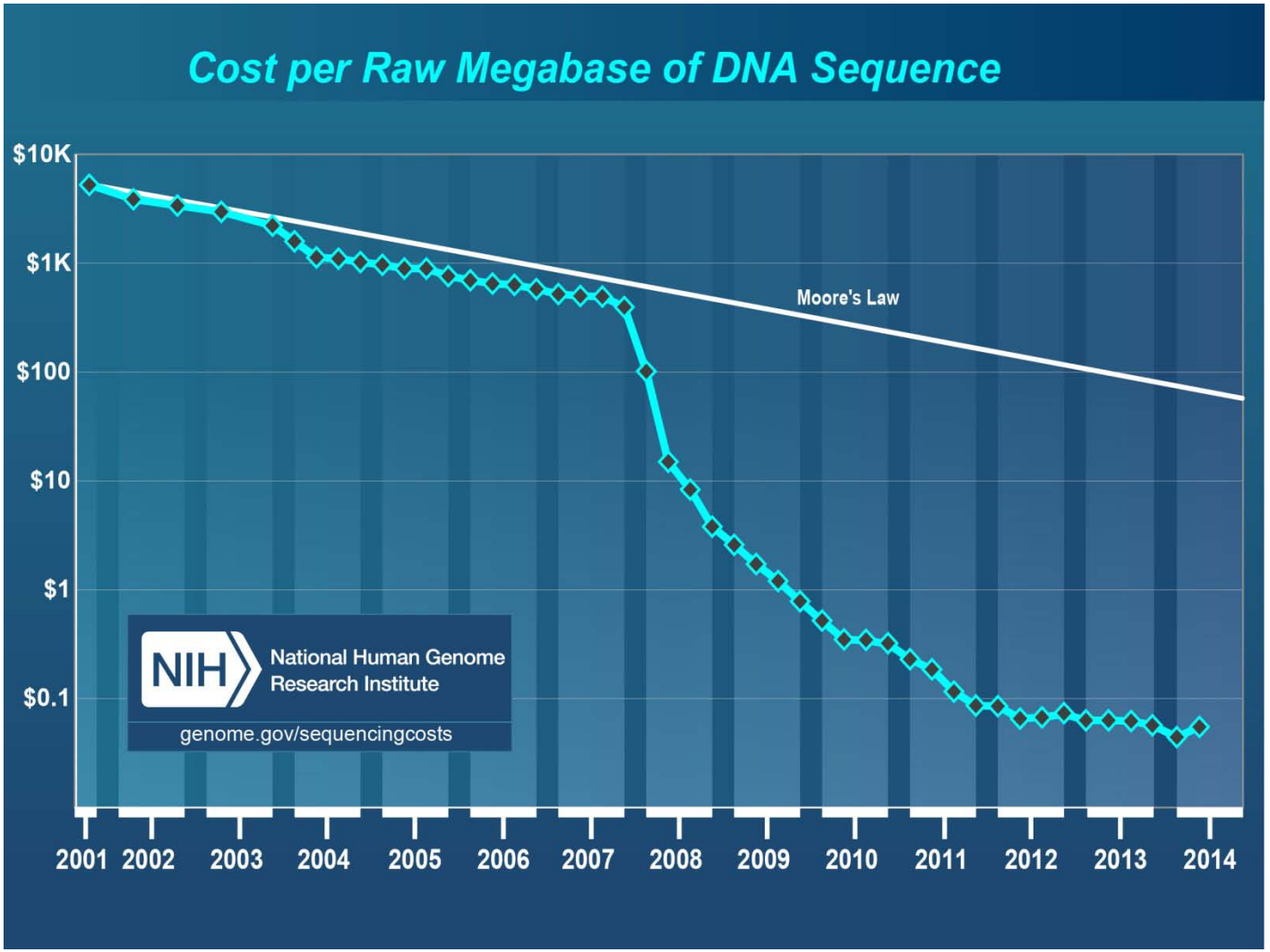
- Affects around 10% of at-risk patients
  - If incidence was very low or very high then prediction much less useful
  - 8% IFI rate in fluconazole arm of 2007 AML posaconazole prophylaxis study (Cornely et al., NEJM)
  - Highly lethal and expensive to treat
- Effective prophylaxis exists
  - Expense, drug-interactions, resistance, side effects limit enthusiasm for universal prophylaxis
- Invasive fungal infection not currently positively predictable with clinical scoring system

The Particular Problem of Anti-Fungal Prophylaxis in the AML Patient

- Newer generation azoles are preferred agents for prophylaxis in the AML patient
  - Higher rates of mold infections in patients receiving echinocandins as prophylaxis
- At MDA, a large percentage of AML patients are treated with novel, oral, targeted therapy
  - E.g. FLT3 inhibitors
- Great hesitancy (or even protocol violation) to give azoles to these patients
  - A better understanding of who really needs effective anti-mold prophylaxis is needed

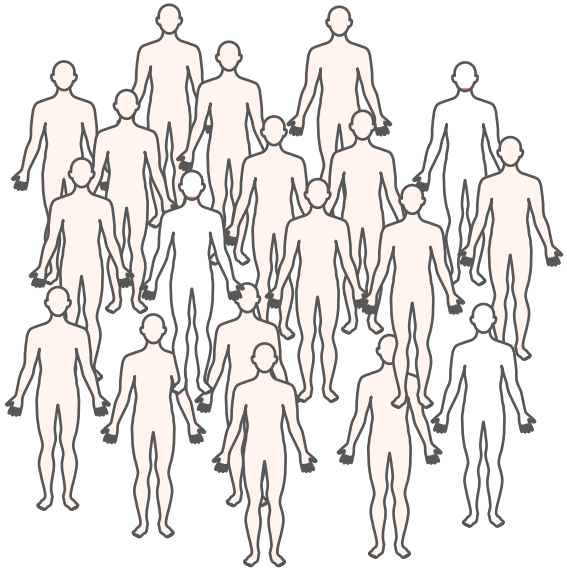
MZ Gomez et al., Antimicrob Agents Chemother 2014;58:2775-80.

Rapid Reduction in Sequencing Costs Makes Genomic Approach Feasible



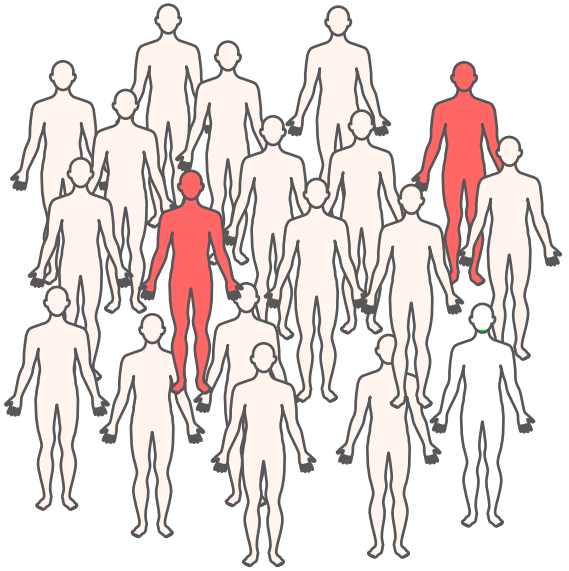
Underlying Theory of IFI Genetic Susceptibility in AML Patients

Group of AML patients that have no clear genetic predisposition to fungal infection



Intense immunosuppression

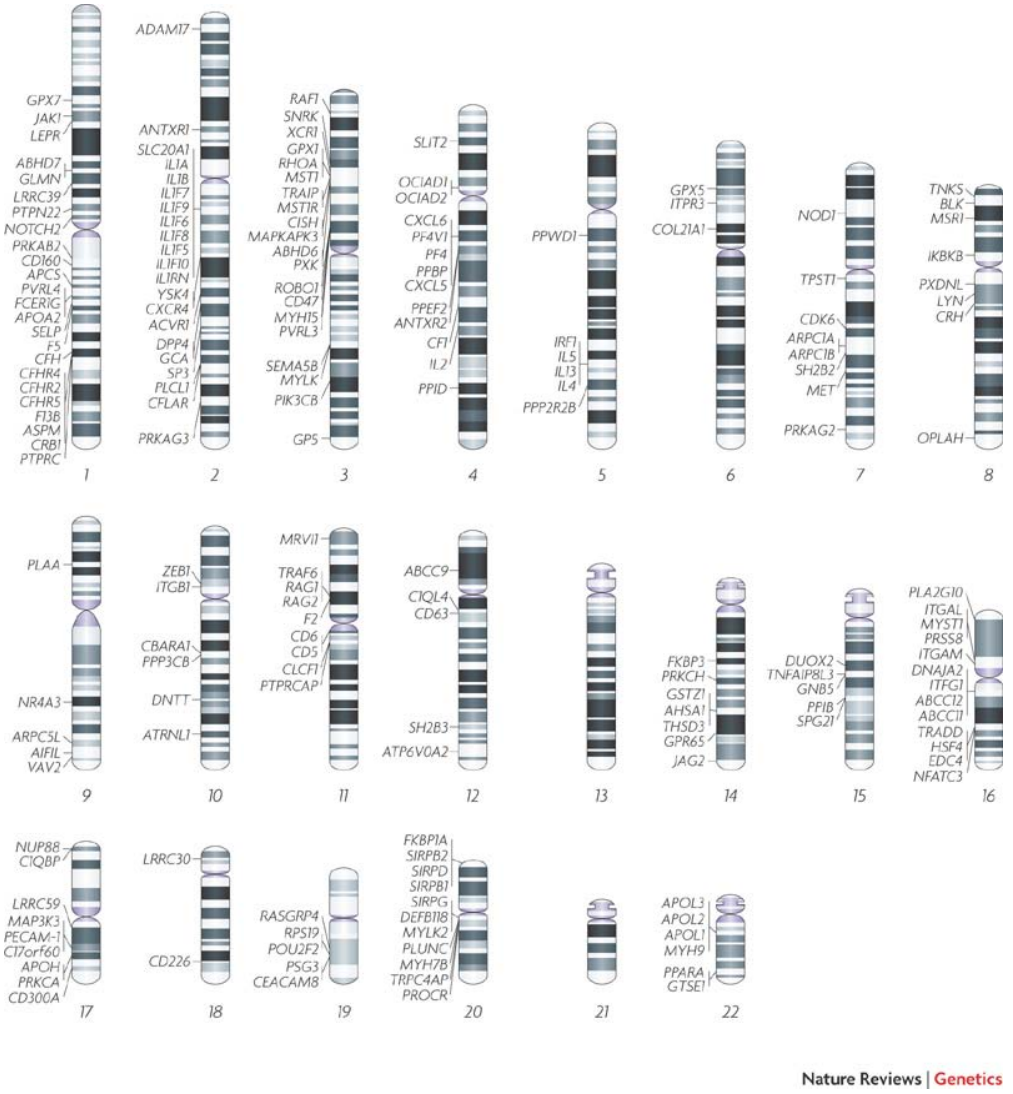
Development of IFI is driven at least in part by genetic variation



The Diversity of Innate Immune Function May Impart IFI Susceptibility

Unlikely that invasive mold infections are major evolutionary drivers of diversity

However, pathways of mold control are shared with pathogens driving diversity
- Gram-negative infections, etc.



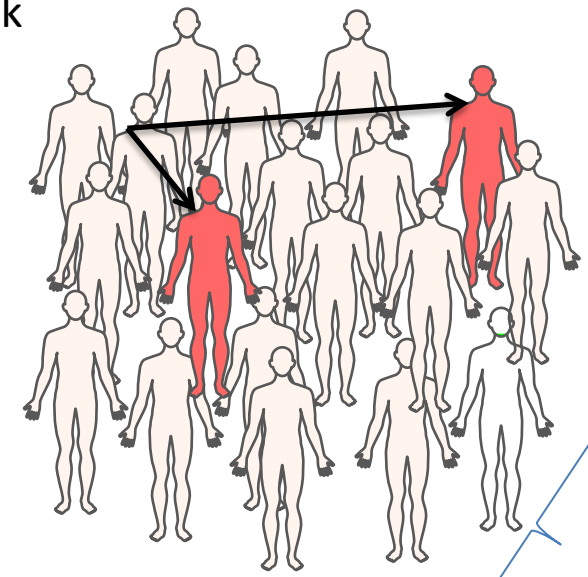
Nature Reviews | Genetics

Barriero LB et al., Nature Genetics 2010;11:17-30

Genetic Identification of IFI Predisposition Could Be Used to Risk-Stratify Patients

Effective, targeted anti-mold prophylaxis for at high risk patients

- Active compliance programs
- Therapeutic drug monitoring



- Anti-candida therapy for low-risk patients?
- Only start anti-mold therapy when:
  - Clinical suspicion for infection based on non-invasive testing?

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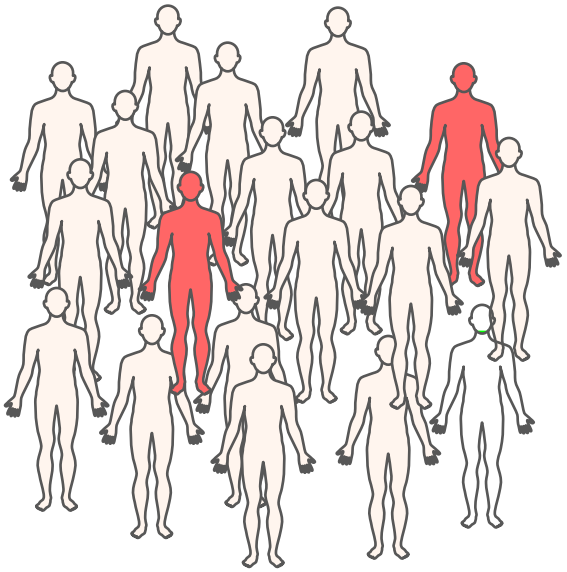
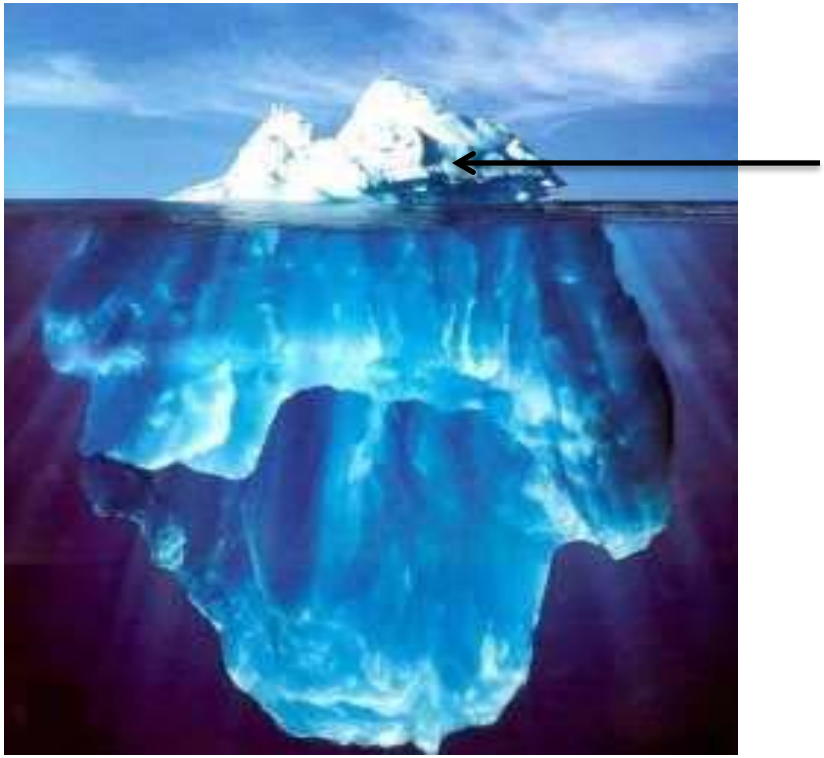


Personalized medicine!

What Does a Genomic Approach Have to Offer?



Maybe what we know about genetic predisposition to fungal infections in 2014 is only a fraction of the "truth"

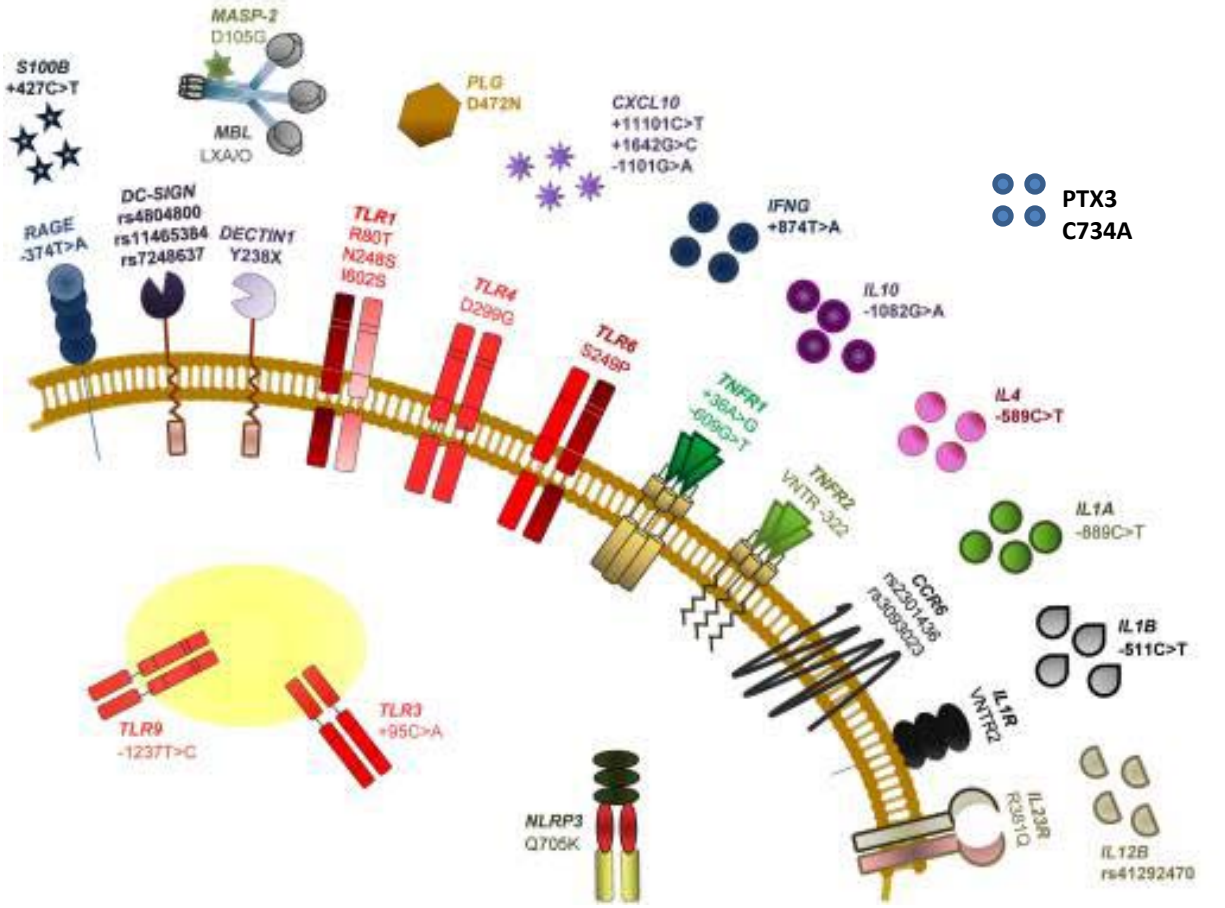
- Variation in innate immune system
- Variation in pharmacokinetic handling of:
  - Chemotherapy
  - Anti-fungal prophylaxis
- Variation in endogenous microbes capable of limiting mold growth
- Variation in genes that we don't even suspect of being involved in control of mold infections!

Only via a genomic approach can we approach this subject in a unbiased, data driven manner

Caution Regarding Genetic Association Studies in 2014

- There are > 12 million variations between the genomes of two non-related people
- Our ability to accurately find, record, and study these variations remain limited
- Excellent review of how to read genome-wide association studies for the clinician
  - J Attia et al., JAMA, 2009;301 (series of 3 articles)
- Humbling look at the current limitation of sequencing on clinical care
  - FE Dewey et al., JAMA, 2014:1035-1044

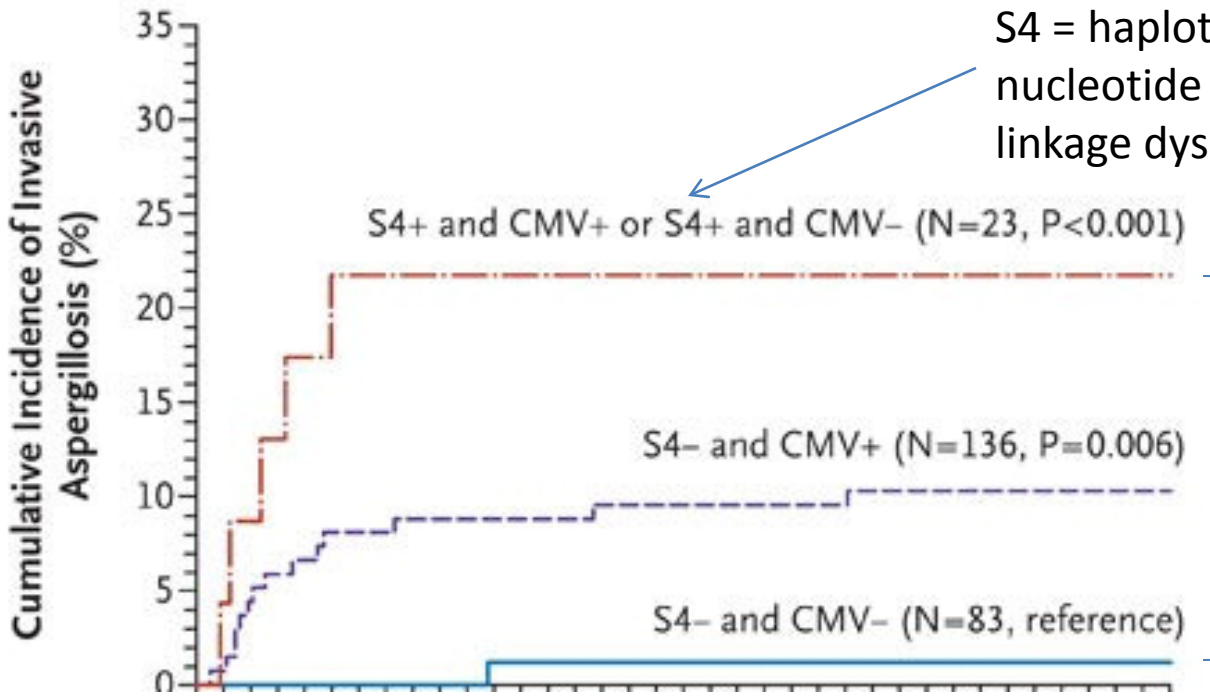
Several Genetic Polymorphisms Have Been Linked to Invasive Aspergillosis



Generally studied in isolation

Slide modified from A Carvalho et al., Front Immun 2012;3:1-8.
Excellent recent review: JF Camargo et al., Clin Infect Dis 2014;15:569-77.

Relationship of Donor TLR4 Alleles and Invasive Aspergillosis in HSCT Recipients



S4 = haplotype of TLR4 single nucleotide polymorphisms in linkage dysequilibrium

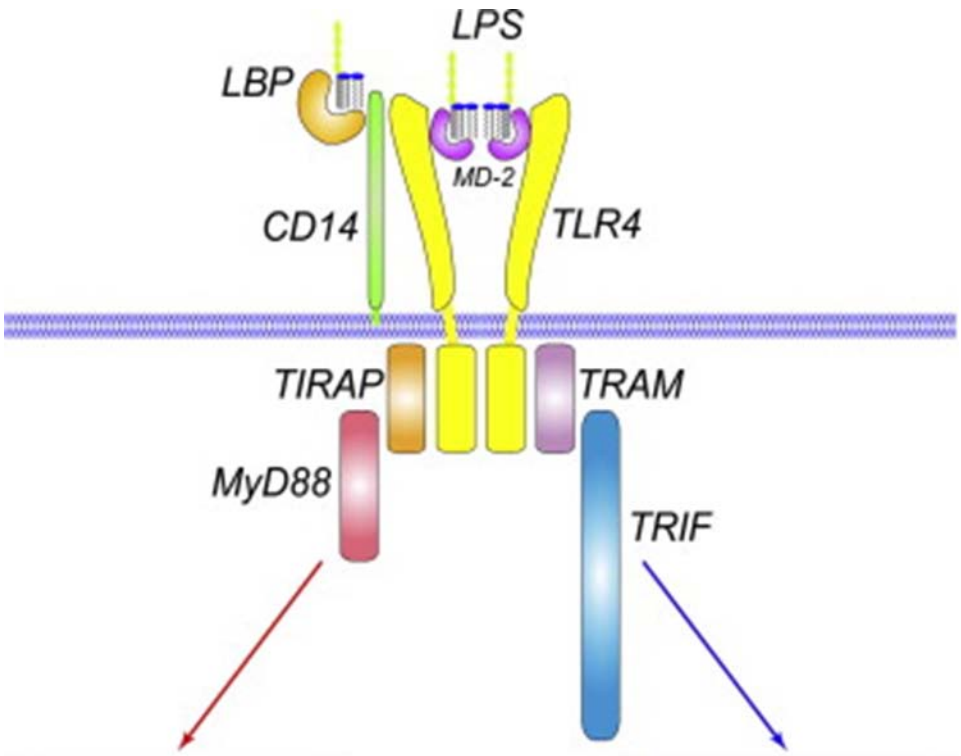
Adjusted hazard ratio 6.16 in discovery study and 2.49 in validation study

PY Bochud et al, NEJM, 2008:359:1766-77

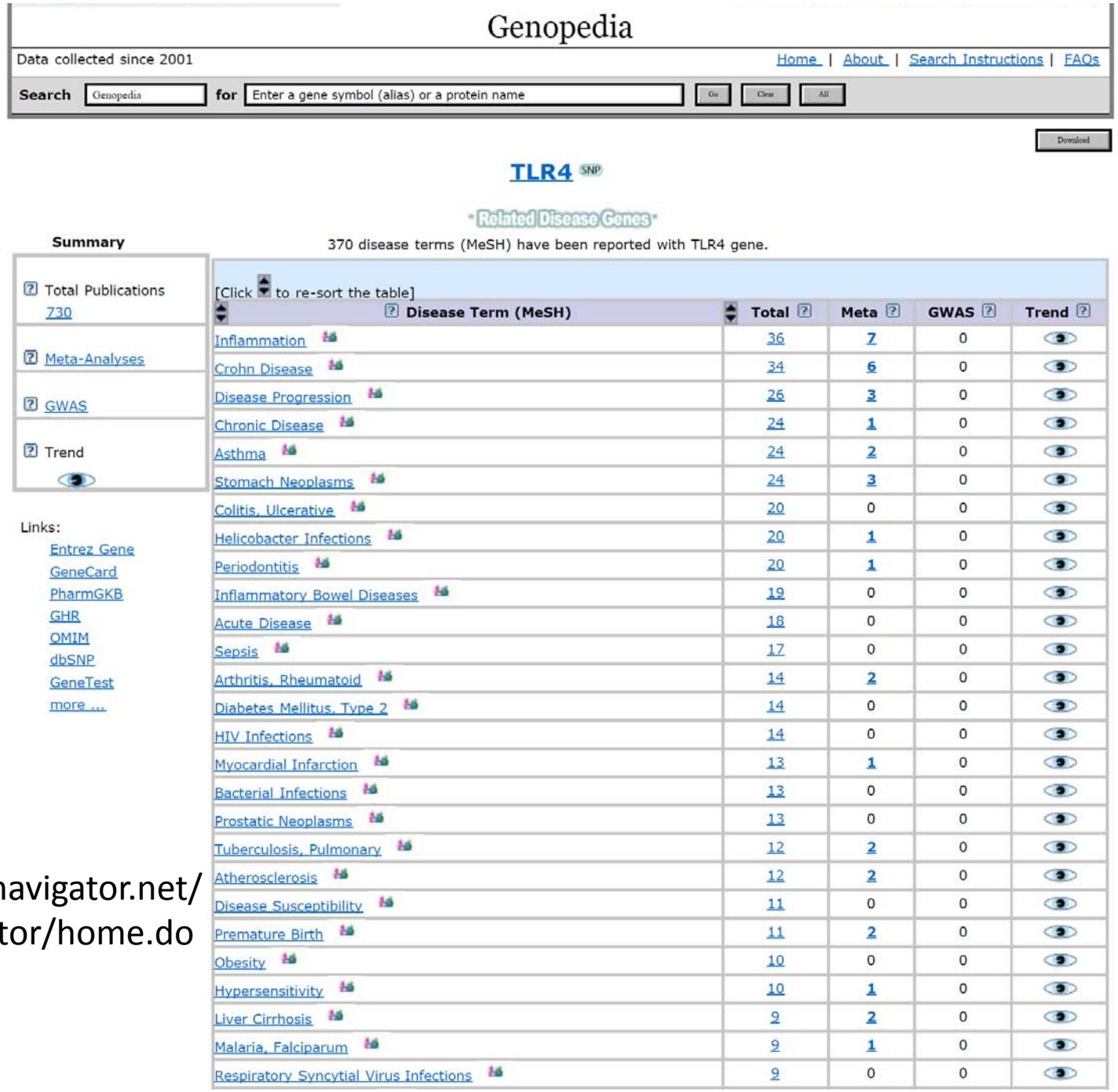
About 250 patients total in the study

What Do We Know about TLR4 and the SNPs Identified?

TLR4 is key receptor for lipopolysaccharide from Gram-negative bacteria



- TLR4 also recognizes *Aspergillus* mannan
- S4 haplotype present in about 12% of Americans
- Some studies show S4 haploptye results in decreased responsiveness to LPS
- Numerous associations between S4 haplotype and a variety of diseases



Genopedia

Data collected since 2001

Home | About | Search Instructions | FAQs

Search Genopedia for Enter a gene symbol (alias) or a protein name Go Clear All

Download

TLR4 SNP

Related Disease Genes

Summary

Total Publications 730

Meta-Analyses

GWAS

Trend

Links:

Entrez Gene
GeneCard
PharmGKB
GHR
OMIM
dbSNP
GeneTest
more ...

370 disease terms (MeSH) have been reported with TLR4 gene.

[Click to re-sort the table]

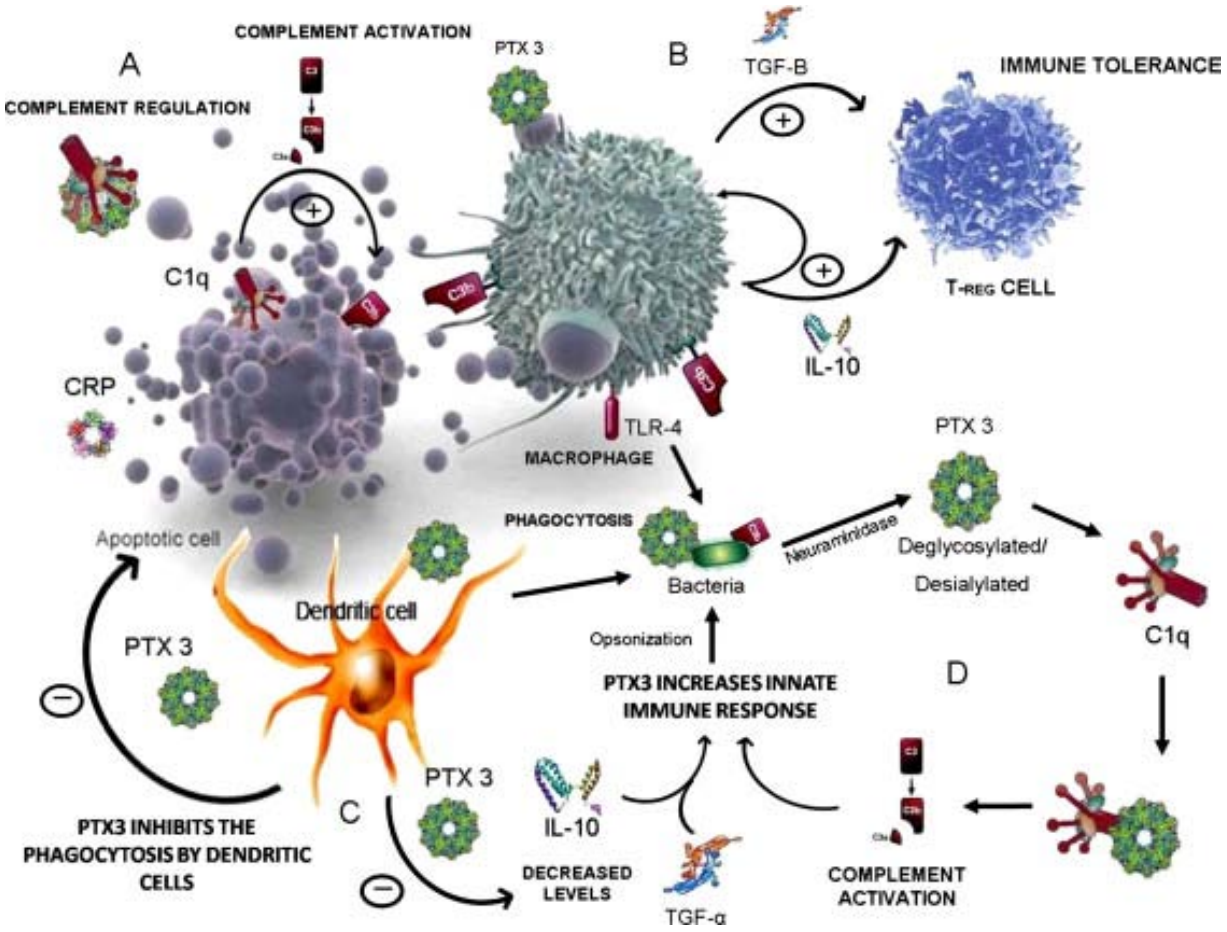
Disease Term (MeSH)	Total	Meta	GWAS	Trend
Inflammation	36	7	0	
Crohn Disease	34	6	0	
Disease Progression	26	3	0	
Chronic Disease	24	1	0	
Asthma	24	2	0	
Stomach Neoplasms	24	3	0	
Colitis, Ulcerative	20	0	0	
Helicobacter Infections	20	1	0	
Periodontitis	20	1	0	
Inflammatory Bowel Diseases	19	0	0	
Acute Disease	18	0	0	
Sepsis	17	0	0	
Arthritis, Rheumatoid	14	2	0	
Diabetes Mellitus, Type 2	14	0	0	
HIV Infections	14	0	0	
Myocardial Infarction	13	1	0	
Bacterial Infections	13	0	0	
Prostatic Neoplasms	13	0	0	
Tuberculosis, Pulmonary	12	2	0	
Atherosclerosis	12	2	0	
Disease Susceptibility	11	0	0	
Premature Birth	11	2	0	
Obesity	10	0	0	
Hypersensitivity	10	1	0	
Liver Cirrhosis	9	2	0	
Malaria, Falciparum	9	1	0	
Respiratory Syncytial Virus Infections	9	0	0	

http://hugenavigator.net/HuGENavigator/home.do

Caution When Looking at Genetic Association with Fungal Infection

- Association ≠ Causality
  - Many polymorphisms and other genetic variation are linked
    - What is found may only be a marker
- Causality ≠ Mechanism
  - Even if a genetic polymorphism does cause increased susceptibility to infection, the mechanism may be obscure
    - E.g. TLR4 polymorphisms may predispose to delayed immune reconstitution rather than having a direct anti-fungal effect
    - Polymorphisms in chemotherapy metabolism may predispose through effect on drug rather than directly on fungus

Pentraxin 3 is Acute Phase Reactant with Diverse Physiologic Roles



OD Ortega Hernandez et al., Semin Arthritis Rheum 2009

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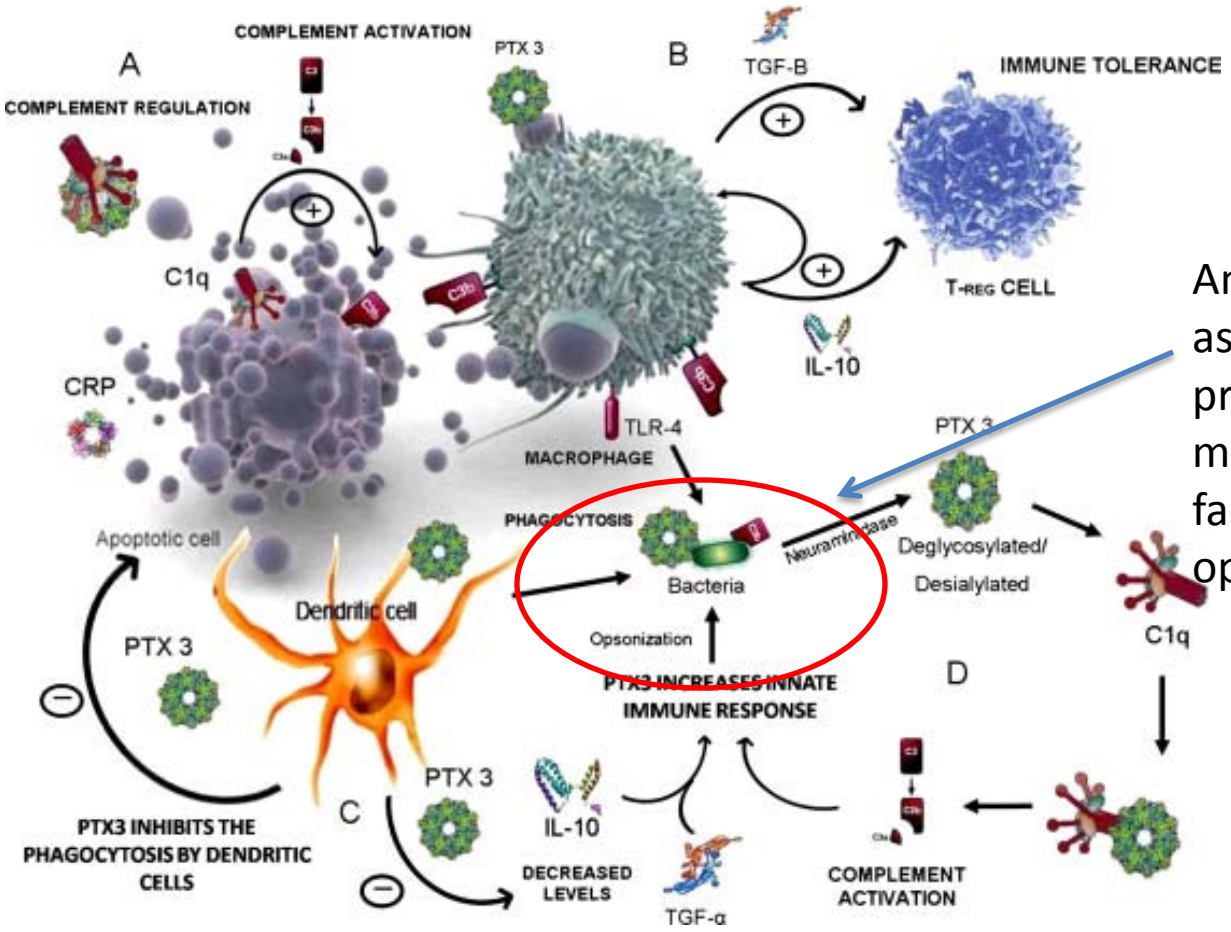
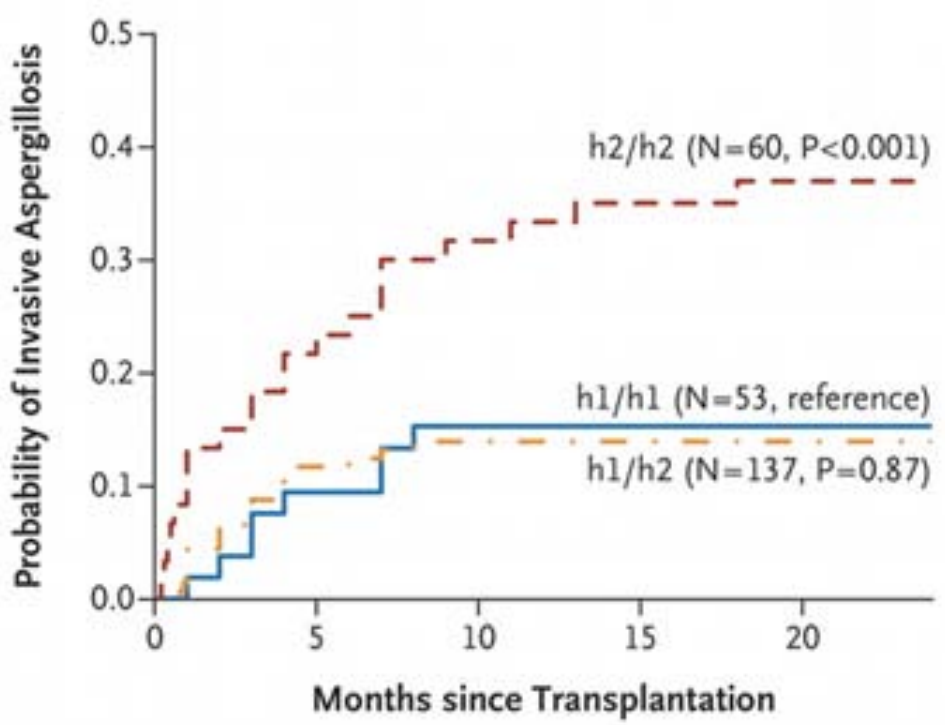


Anti-fungal aspects of PTX3 presumably mediated by facilitating opsonization

OD Ortega Hernandez et al., Semin Arthritis Rheum 2009

Association of PTX3 SNPs with IA in HSCT Patients

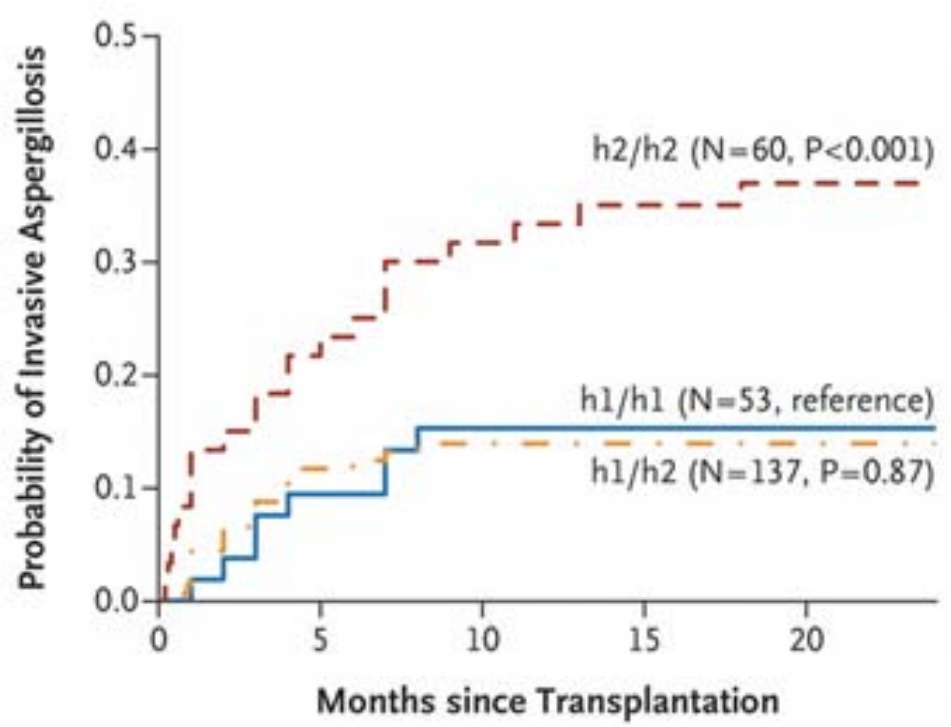


Hazard ratio = 3.08

About 250 patients total in the study

C Cunha et al, NEJM 2014;370:421-31.

Association of PTX3 SNPs with IA in HSCT Patients



Hazard ratio = 3.08

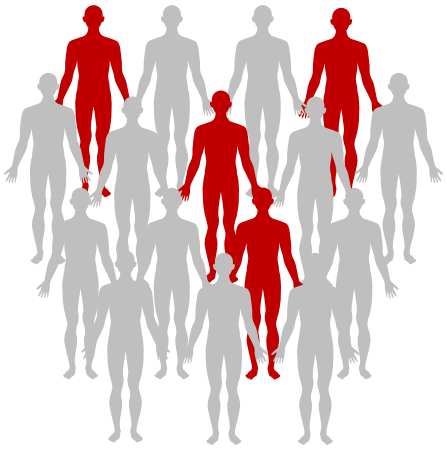
Neutrophils with h2/h2 genotype were defective in phagocytosing *Aspergillus*

C Cunha et al, NEJM 2014;370:421-31.

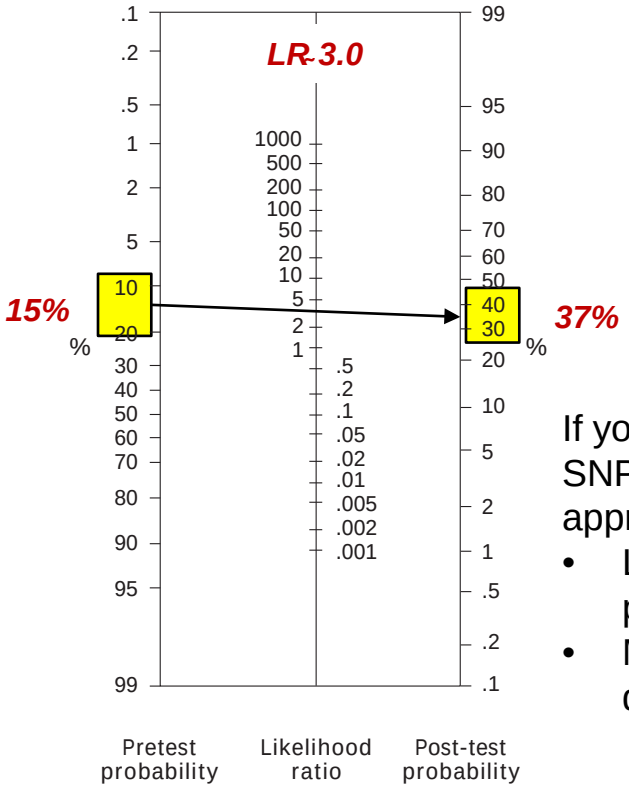
How Does the Current Genetic Data Influence the Clinical Approach to the At Risk Patient?

High risk stem cell transplant population

Homozygous haplotype h2/h2 PTX3 (24%)
(1 in 4 donors)



Cumulative incidence, 24 months

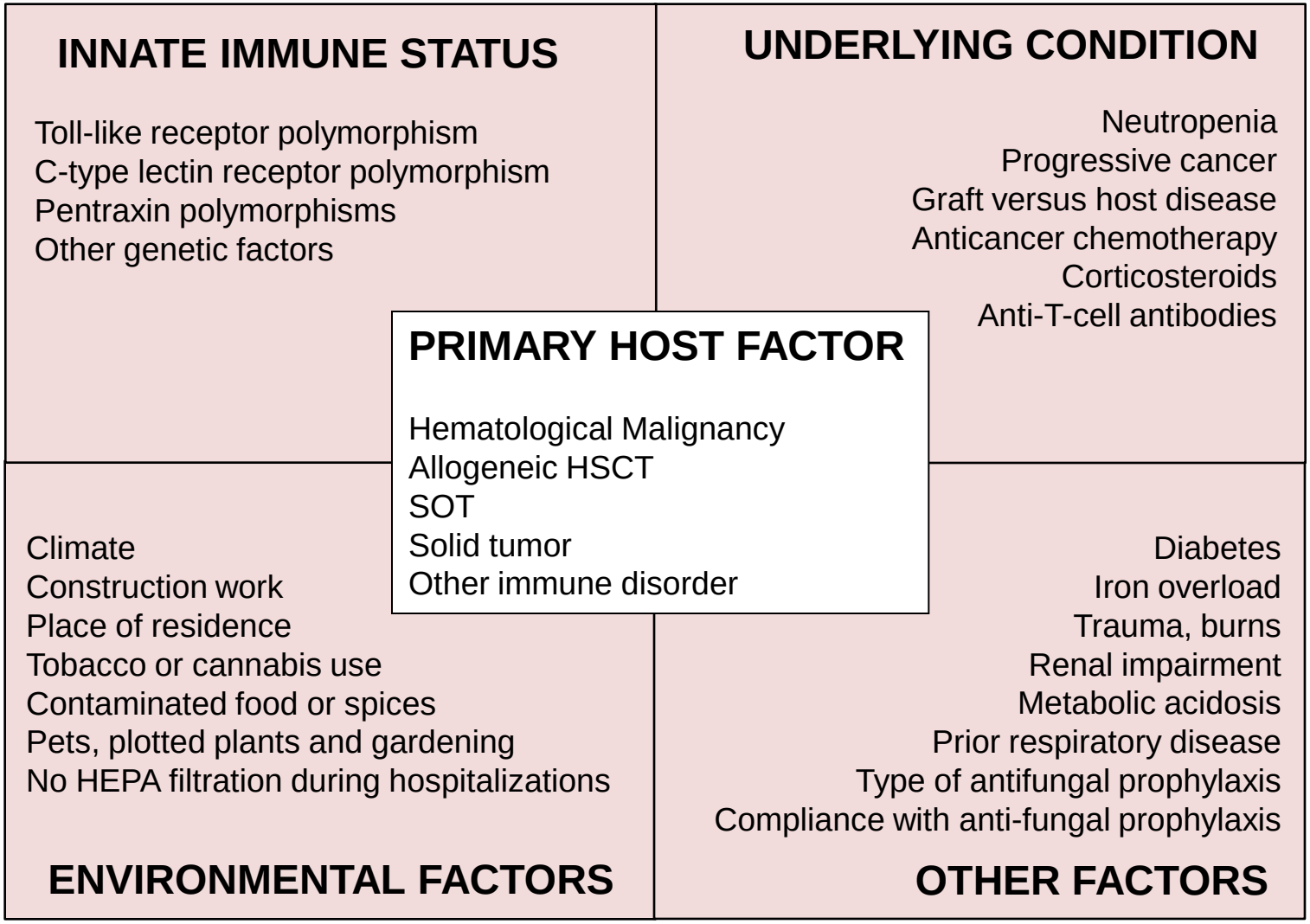


If you knew that your patient had PTX3 SNPs, would you change your approach to that patient?

- Less tolerance for non-azole based prophylaxis?
- More intensive monitoring for IFI development?

Cuhna et al. New Eng J Med 2014;370:421-432.

Host Genetics are Only a Part of the Risk of Developing Invasive Aspergillosis

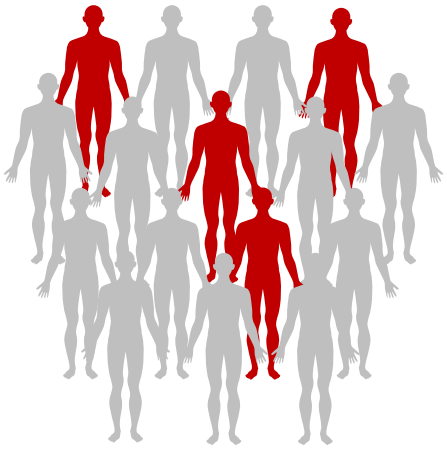


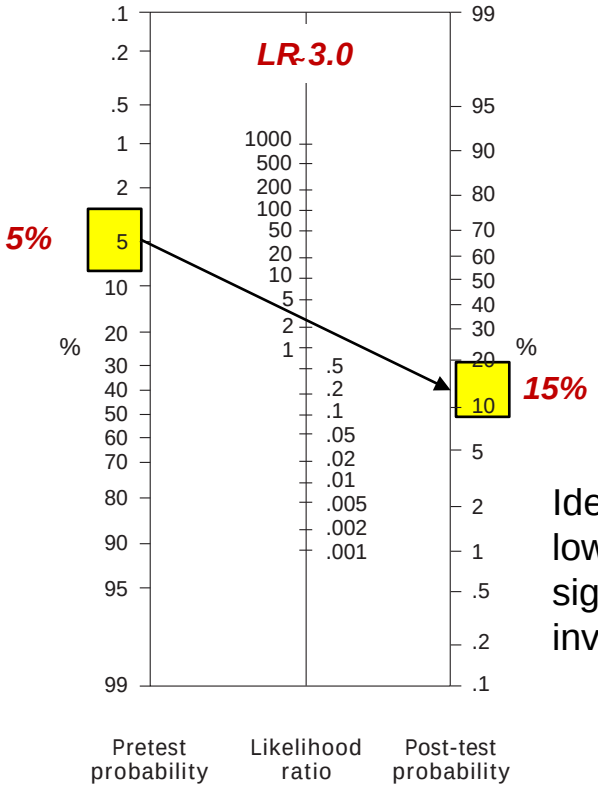
Adapated from Russell Lewis and Herbrecht et al. Ann NY Acad Sci 2012;1272:23-30.

Genetic Data Need to be Incorporated Into, Not Replace, Existing Understanding of Fungal Infection Risk

Lower risk leukemia population

Homozygous haplotype h2/h2 PTX3 (24%)
(1 in 4 donors)





Identifying PTX3 polymorphisms in a lower risk patient results in a significantly lower predicted rate of invasive aspergillosis

Cuhna et al. New Eng J Med 2014;370:421-432.

What Are the Major Issues Currently Facing Fungal Infection Genetic Association Studies?

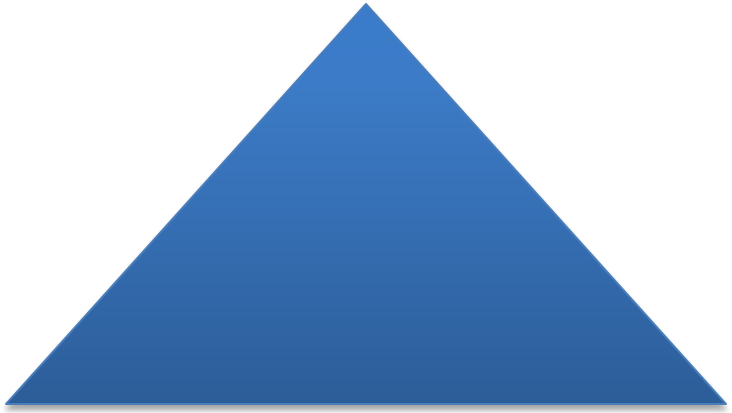
- How sure are we about the diagnosis?
  - Both negatively and positively
  - Majority of cases are “probable” IA
  - Autopsies are rarely done
- Sample sizes are small and either single or a few centers
  - Most well-powered genetic association studies (e.g. cardiovascular risk) involved thousands of patients from dozens of institutions

Can We Leverage Cancer Genetics to Address Fungal Infection Susceptibility?

- Ongoing intense interest in cancer community to sequence cancer genomes
  - Same data can be utilized to ask questions about infectious diseases susceptibility
  - Obvious caveat:
    - Must have infectious diseases related clinical data to correlated with the genomic data
    - Not readily available with Cancer Genome Atlas datasets

AML, APPOLO, and Infectious Risk Predisposition

Whole exome sequencing data from
500+ AML patients



Collection of clinical co-morbidity and risk factor data

Standardized assessment for development of mold infections

Development of testable hypotheses regarding genetic risk predisposition to invasive mold infections in AML patients including the transition of HSCT

How Can We Improve Genetic Studies of Predisposition to Fungal Infections in Cancer Patients?

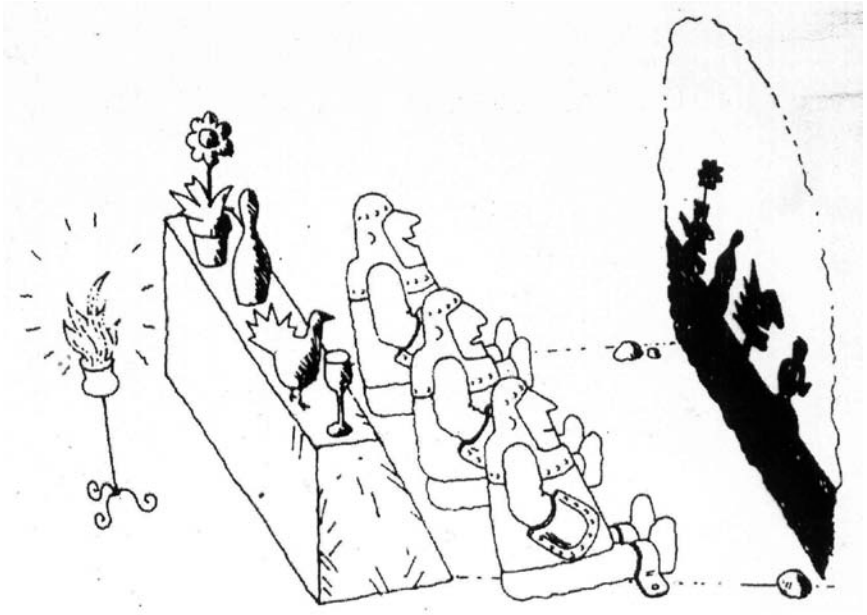
- Improved diagnostics imperative
- Larger, multi-center studies needed
- Cooperation between experienced geneticists, researchers, and clinicians in trial design and implementation
  - Need to carefully account for non-genetic factors
- Genome wide approaches need to be optimized
  - Improved detection of genetic polymorphisms using next-generation sequencing techniques

Summary

- Although much has been learned about genetic susceptibility to fungal infection in cancer patients, I believe there is more that remains unlearned!
- Getting to this unlearned information and making it clinically impactful is the real challenge:
  - Better diagnostics
  - Increased cooperation
  - Integration of genetics into clinical algorithms to demonstrate impact

For My Learned Greek Colleague

- When I take care of leukemic or HSCT patients, I feel like I am looking at shadows



- I am hopeful that genetics (not by itself) will help us start to turn towards the light