BRIGHAM AND WOMEN'S HOSPITAL
| The Lung Center |

SEVERE ASTHMA PROGRAM

PARTNERS ASTHMA CENTER

Update on Severe Asthma 2023

The Genetics of Severe Asthma

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Declaration of Financial Interest

- Genetics Section Editor for UpToDate, Inc.

- Spouse consultant for CRO as blinded interpreter of clinical trial data in hematology (unrelated)

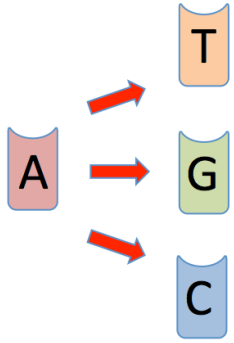
Outline

- How genes cause disease?
- Is Severe Asthma Genetic?
- Common genetic variation in severe asthma
- Rare genetic variation in severe asthma
- Clinical approach to the genetics of severe asthma

How genes cause disease

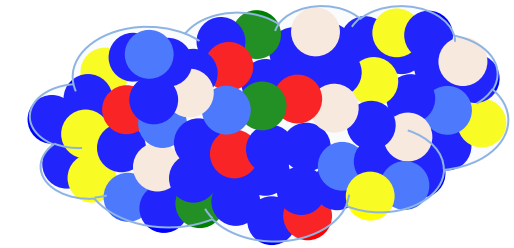
How genes cause disease

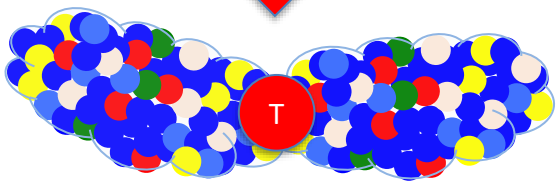
Genetic variation is a change in DNA sequence



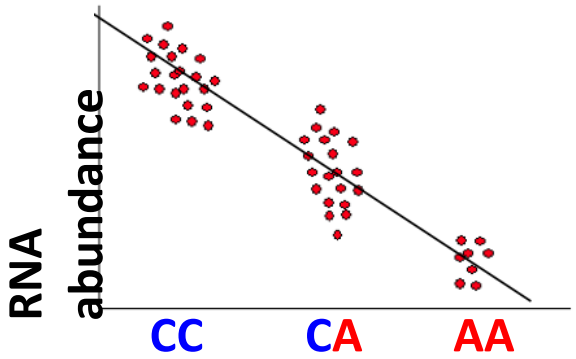
DNA codes for proteins that confer cellular functions

Structure & Function



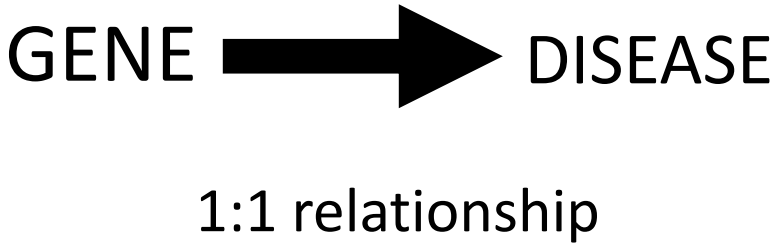


<u>Regulatory variants</u> alter function by altering gene <u>abundance</u>



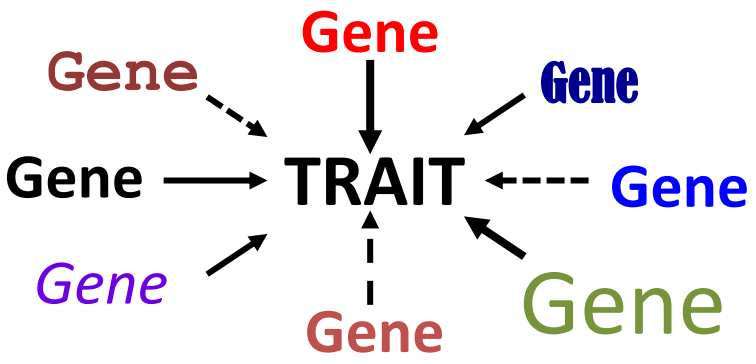
<u>Coding variants</u> cause dysfunction by altering protein <u>structure</u>

Rare Monogenic Disease vs. Common Polygenic Disease

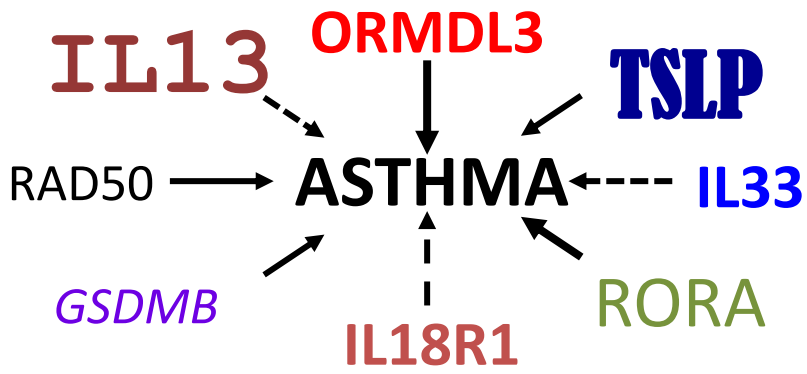


1:1 relationship

Monogenic /
Mendelian Disease



Polygenic /
Complex Disease



Asthma / Atopy
>60 loci

Is Severe Asthma Genetic?

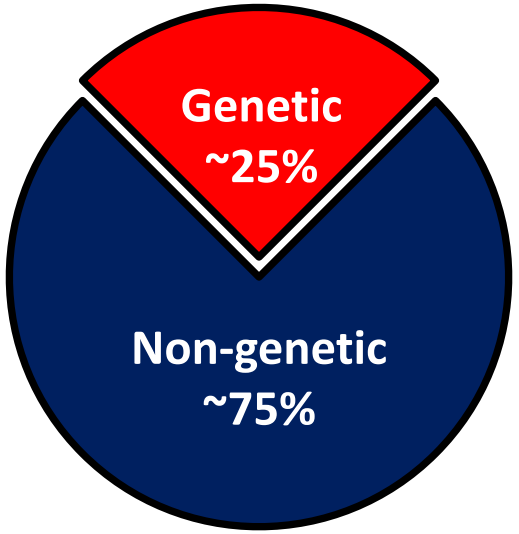
The heritability of severe asthma

Danish Twin Registry:[1] 256 twin pairs

- heritability of **symptom severity 24%**
- **Medication-based score: 2%**

EGEA Mixed case-control / family-based study:[2] 944 subjects

- strong within-family correlation for **symptom severity [ICC = 0.23]**
- **Not for inhaled corticosteroids [ICC = -0.15].**

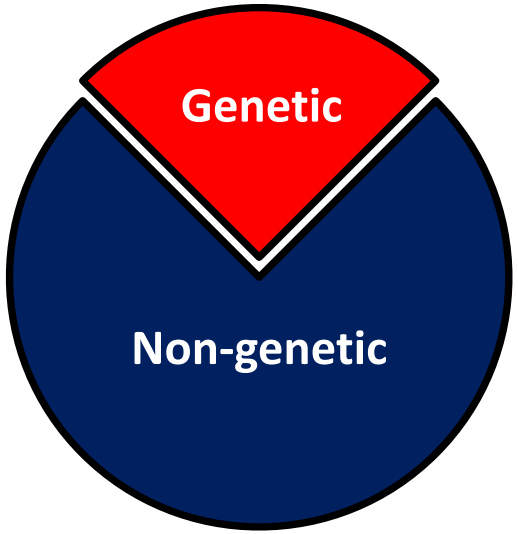


CAMP Whole Genome Prediction study:[3] 832 asthmatics

- Heritability > 50% observed for IgE levels (r^2 = 0.53), FEV1 (0.83); BDR (0.67)
- **Not observed for steroid responsiveness**, airways hyper-responsiveness, or eosinophil count

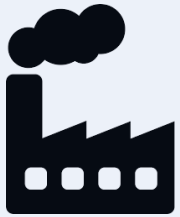
1. Thomsen SF et al. Clin Respir J. 2012; 6:228-37. (PMID: 22081985)
2. Pin I et al. Am J Respir Crit Care Med. 2002; 165:185-9. (PMID: 11790652)
3. McGeachie MJ et al. Immun Inflamm Dis. 2016; 4:487-496. (PMID: 27980782)

The non-genetic contributors to severe asthma



Environmental

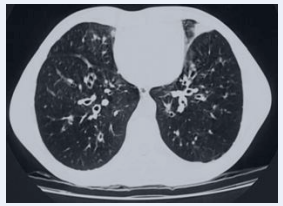
Allergens



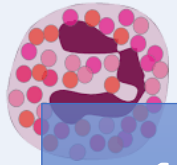
Air pollution

IL1RL1/IL18R1
IgE levels and asthma severity

Medical Co-morbidity



Bronchiectasis / ABPA



EGPA

Nasal polyps

Obesity

16p11.2
asthma susceptibility

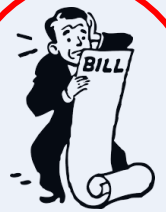
GERD

Behavioral

Cigarette Smoking

CHRNA5
Nicotine addiction and lung function

Psychosocial



Stress

SES

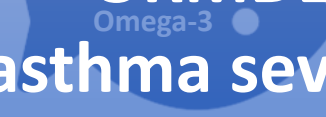
Healthcare Access

ADCYAP1R1
stress, asthma, BDR

Nutritional

Vitamin Insufficiency

ORMDL3
asthma severity & susceptibility

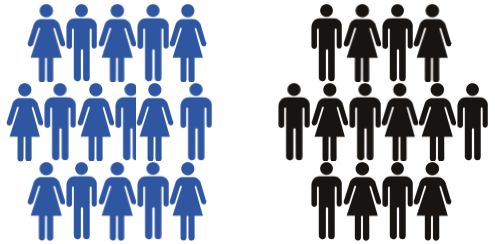


habits

Common variants

Genome-Wide Association Studies

Recruit cohort & phenotype



Cases (n = 994)

Controls (n = 1,243)

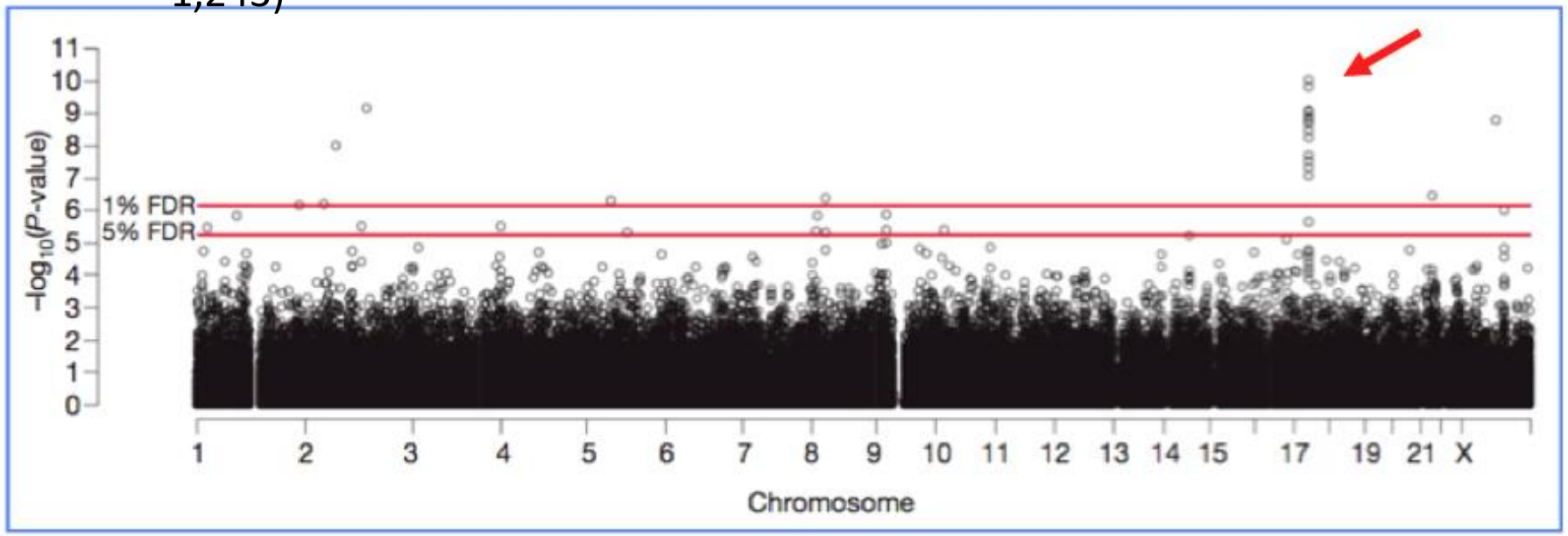
Genotyping Microarrays

317,447 polymorphisms

Individual Variant Association Testing

	Cases	Controls
A	62%	52%
C	38%	48%

Logistic regression
Rigorous analysis

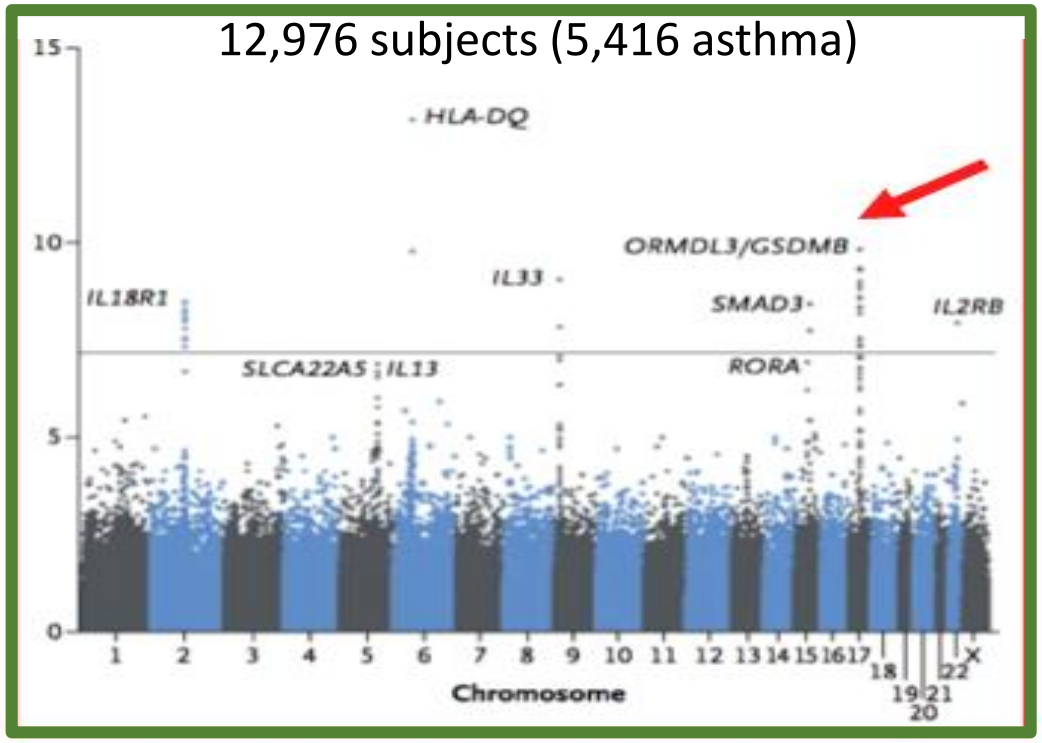


Moffatt MF et al. Nature. 2007 448:470-473.

Asthma GWAS

EVE (North America)

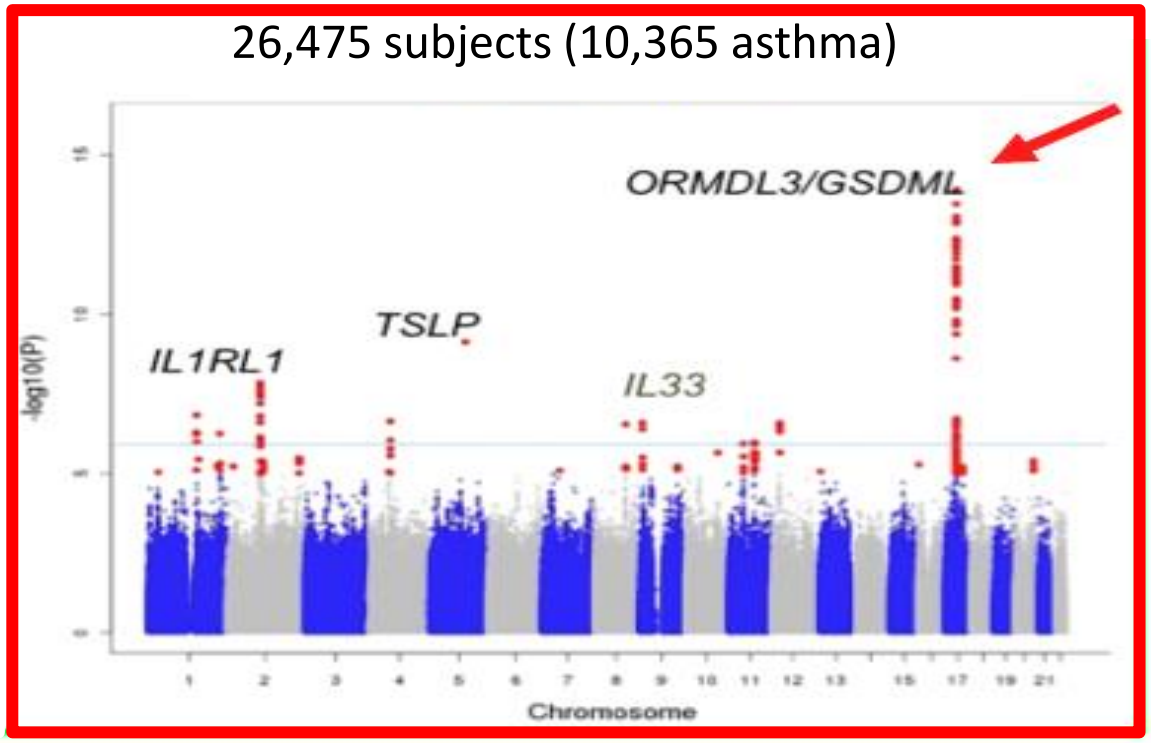
12,976 subjects (5,416 asthma)



Torgenson et al. Nature Genetics 2011

GABRIEL (Europe)

26,475 subjects (10,365 asthma)

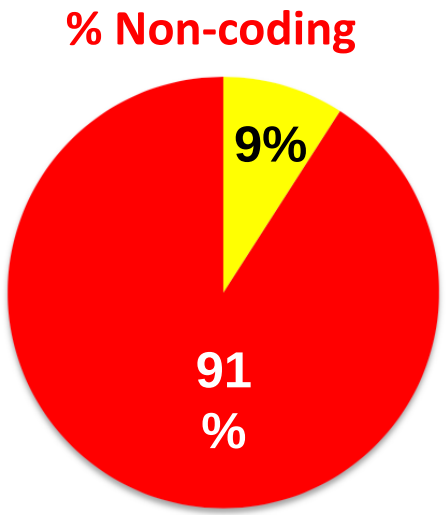


Moffatt et al. New Engl J Med 2010

$1.2x10^{-14}$	**17q21 (ORMDL3/GSDML)**	**$6.4x10^{-23}$**
$1.4x10^{-8}$	IL1RL1/IL18R1 (chr. 2)	$3.4x10^{-9}$
$7.3x10^{-10}$	TSLP (chr. 5)	7.5^{-8}
$2.5x10^{-7}$	IL33 (chr. 9)	$9.2x10^{-10}$

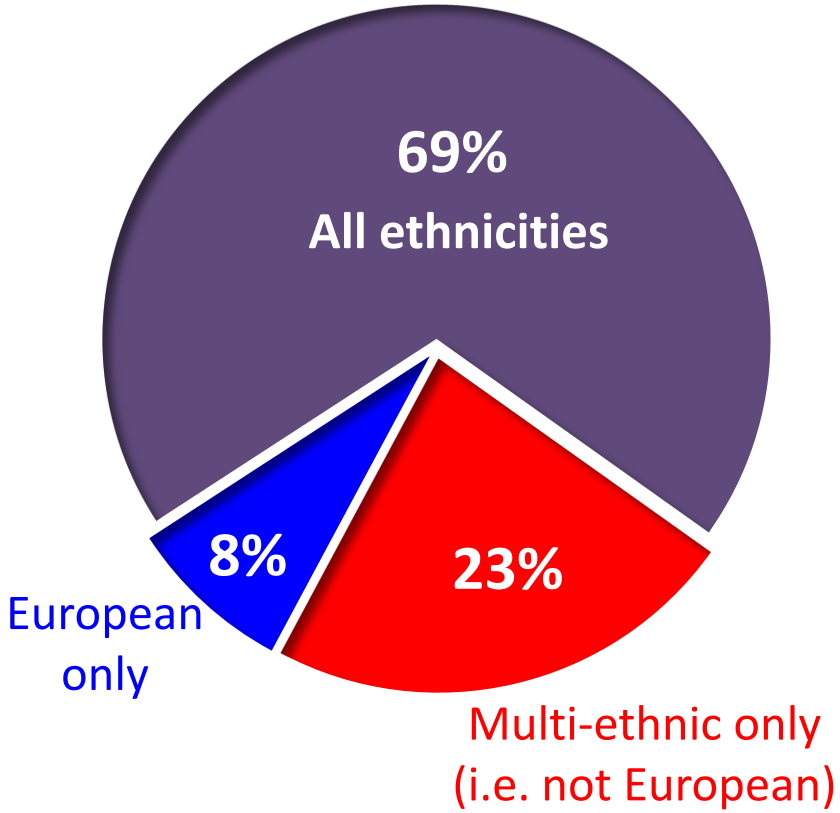
Most consistently replicated asthma genes

Antigen presentation	HLA-B, HLA-DPA1, HLA-DQA1, HLA-DQB1, MICA
Cell-cell adhesion	AIF1, CAMK4, CCR7, ETS1, LPP, NDFIP1
Cytokines, cytokine signaling	IL13, IL18R1, IL1RL2, IL33, BCL6, FASLG, GATA3, IL6R, STAT6, TNFSF18, TNFSF4, TSLP
T cell development and activation	RORA, RORC, IKZF4, WDR36, BACH2
Activation of NK cells	NCR3
Sphingolipid synthesis, ER stress	ORMDL3
TGF-beta signaling	SMAD3 (Dominant-negative inhibitor of TGF beta) LRRC32 (Regulator of TGF-beta bioavailability) WNT11 (TGF-beta mediated actin expression) GSDMB (influences TGF-beta expression)
Miscellaneous Functions	
Synthesis-Dependent Strand Annealing	RAD50, RAD51B, RMI2
Cytoskeletal organization	DIAPH1
Endocytosis	AP5B1
Hormone transduction	ITPR3
IgE receptor	FCER1G
Mitochondrial protein / oxphos	NDUFS2
Mycobacterial immunity	TLR1
PD-1 signaling	CD247
Amino acid metabolism	SUOX
Anti-transcriptional repression	SMARCE1
D-2-hydroxyglutarate metabolism	D2HGDH
Function unclear	C5orf56, KIRREL3, LINC00299, MIR5708, ZBTB10, ZNF



Similar genetic architecture across ancestry groups

Shared Genetic Loci



Demenais et al. Nat Genet 2018

Rare variants in IL33 protect from asthma

Eosinophil level

Cohort	Effect Estimate	p-value	N Individuals
Iceland	-0.21 (-0.27, -0.16)	2.5×10^{-16}	103,104
Netherlands	-0.48 (-0.93, -0.03)	0.04	1,370

Asthma

Cohort	Odds Ratio	p-value	N Cases	N Controls
Iceland	0.36 (0.21, 0.61)	1.2×10^{-4}	3,512	298,026
Netherlands	1.08 (0.36, 3.21)	0.89	351	2,830
Germany	0.89 (0.14, 5.48)	0.90	284	252
Denmark-1	0.72 (0.29, 1.79)	0.48	1,121	1,004
Denmark-2	0.24 (0.06,0.94)	0.04	1,197	865
Combined	**0.47 (0.32, 0.70)**	**1.8×10^{-4}**	**6,465**	**302,977**

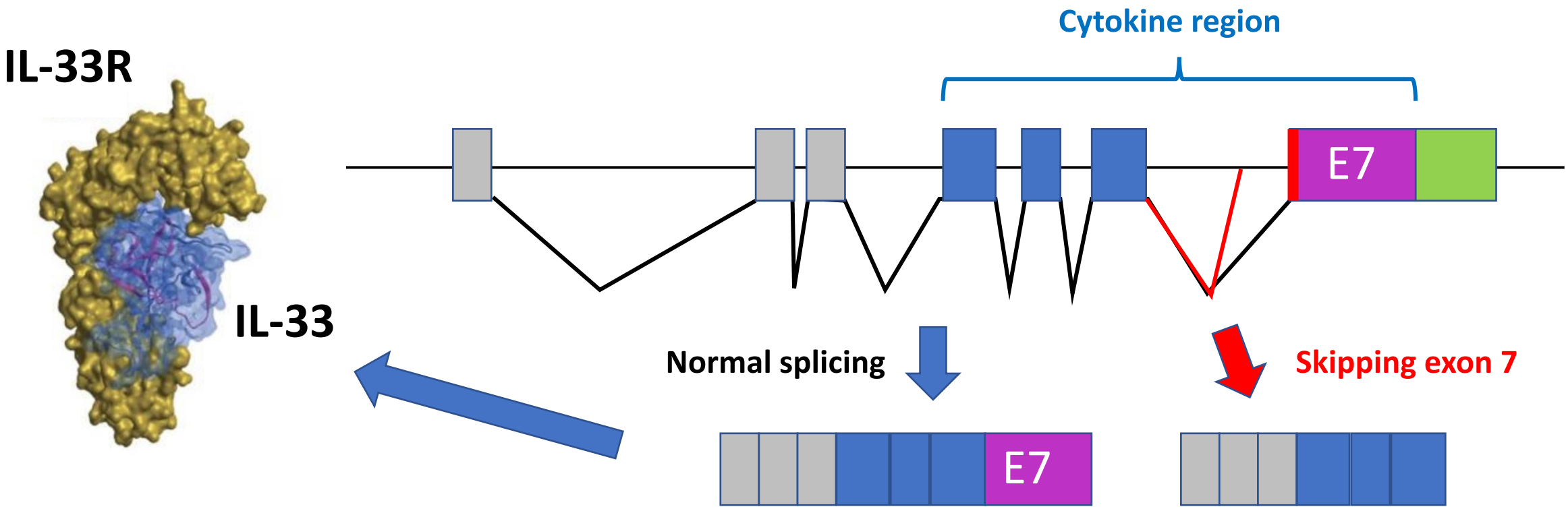
A rare variant .40-0.70% frequency in general population

Associated with reduced eosinophil levels

Associated with a reduced asthma risk by at ~ 50% (95% CI 32 – 70%)

Smith et al. PLoS Genet. 2017; 13:e1006659

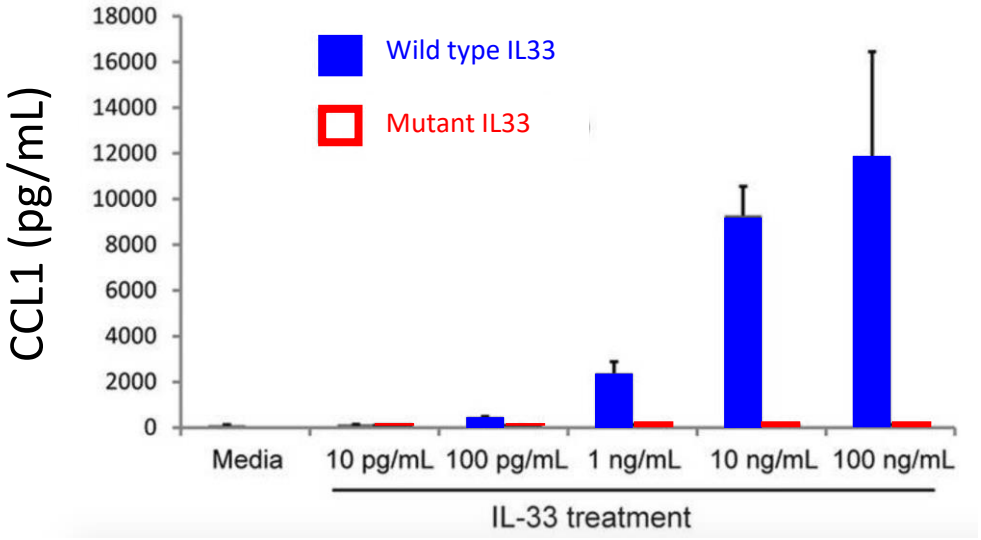
Asthma-protective IL33 loss-of-function variant



Smith et al. PLoS Genet. 2017; 13:e1006659

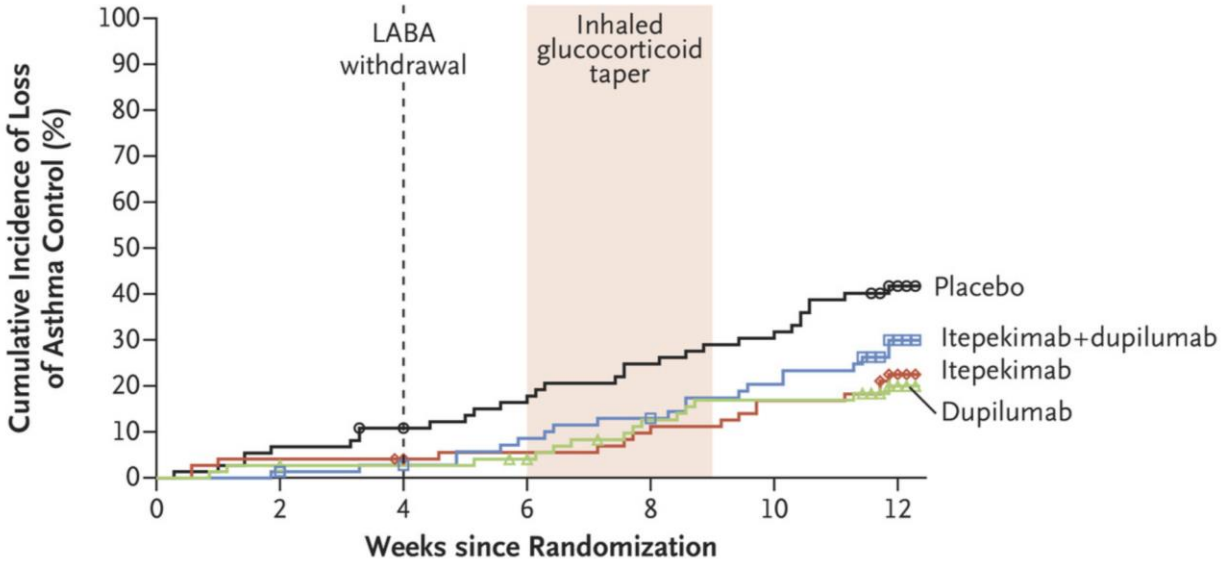
Asthma-protective IL33 loss-of-function variant

Mutation confers reduced gene function



Smith et al. PLoS Genet. 2017; 13:e1006659

Anti-IL-33 monoclonal antibody (itepekimab) for the treatment of moderate to severe asthma



Wechsler et al. NEJM 2021; 385:1656-1668

Common genetic variation in severe asthma

Challenges of genetic studies of severe asthma

Variability in Phenotype Definition

	ATS/ERS	GINA	BTS	SARP	EPR-3 (kids)	PSACI
High dose ICS alone				Major Criteria		
2nd controller medication				Minor Criteria		This + one of the following:
Step down loss of control				Minor Criteria		
Systemic steroids	>50% of year		Continuous / frequent	Major Criteria >50% of year		
Control of comorbidities						
Airway obstruction				Minor Criteria	Age ≥ 5	
Urgent care visits				Minor Criteria		
Near fatal asthma				Minor Criteria		
Rescue BD use				Minor Criteria		
Symptoms					All kids	

1. Complicates between study comparisons
2. Complicates combining studies (meta-analysis)
3. Misclassification reduces power

Challenges of genetic studies of severe asthma

Reduced Sample Size

At best, 10% of asthma is severe

Unless study is enriched for severe disease, focus on this population
can result in a 90% reduction in case sample size

Could translate to a 70% reduction in power

GWAS of severe asthma

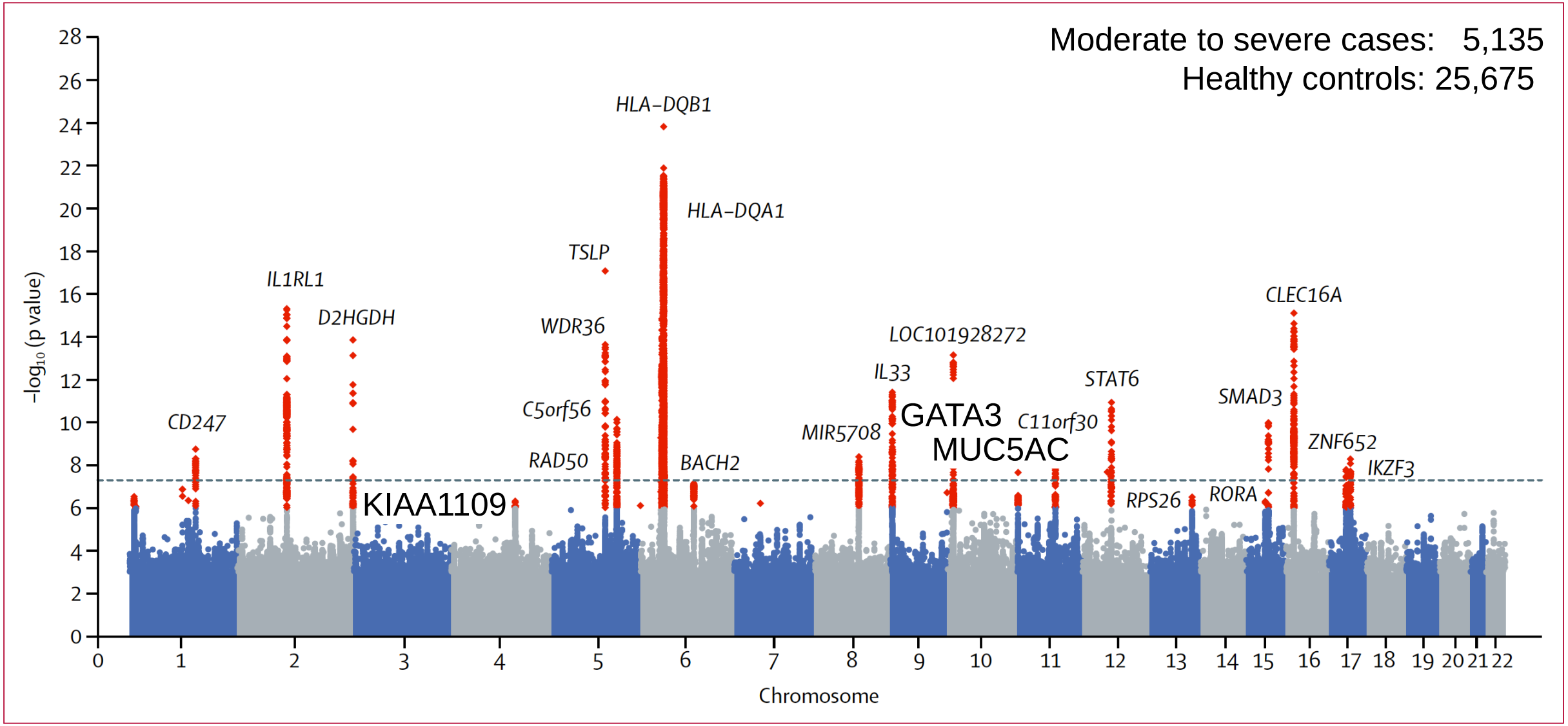
Study	Definition of severity	Sample size (severe / controls)	Notable Genes	Variant	Effect estimate OR (95% CI)	Comments
Li et al.	"severe or difficult-to-treat"	473 / 1892	RAD50IL13 HLADR/DQ	rs2244012 rs1063355	1.64 (1.36-1.97) 0.68 (0.58-0.81)	No SNP achieved genome-wide statistical significance. rs2244012 liked to severity associated identified in Shrine et al
Wan et al.	GINA step 3-5	933 / 3346 231 / 1345	ORMDL3 / GSDMB	rs4794820	0.75 (0.69-0.83)	Most commonly associated with asthma (including cohorts of mild asthma).
Shrine et al.	BTS stages 3–5 (Moderate – severe)	5135/ 25675 5414/ 21471	GATA3 MUC5AC KIAA1109	rs10905284 rs11603634 rs560026225	0.90 (0.88–0.93) 1.09 (1.06–1.12) 1.12 (1.08–1.16)	24 genes significantly associated with moderate-to-severe asthma, 21 were previously associated with asthma in cohorts with mild disease. **MUC5AC** association is the sole finding restricted to more severely affected cohorts.

Li et al. JACI 2010; 125:328-35

Wan et al. Thorax. 2012; 67:762-8

Shrine et al. Lancet Resp Med. 2019; 7:20-34

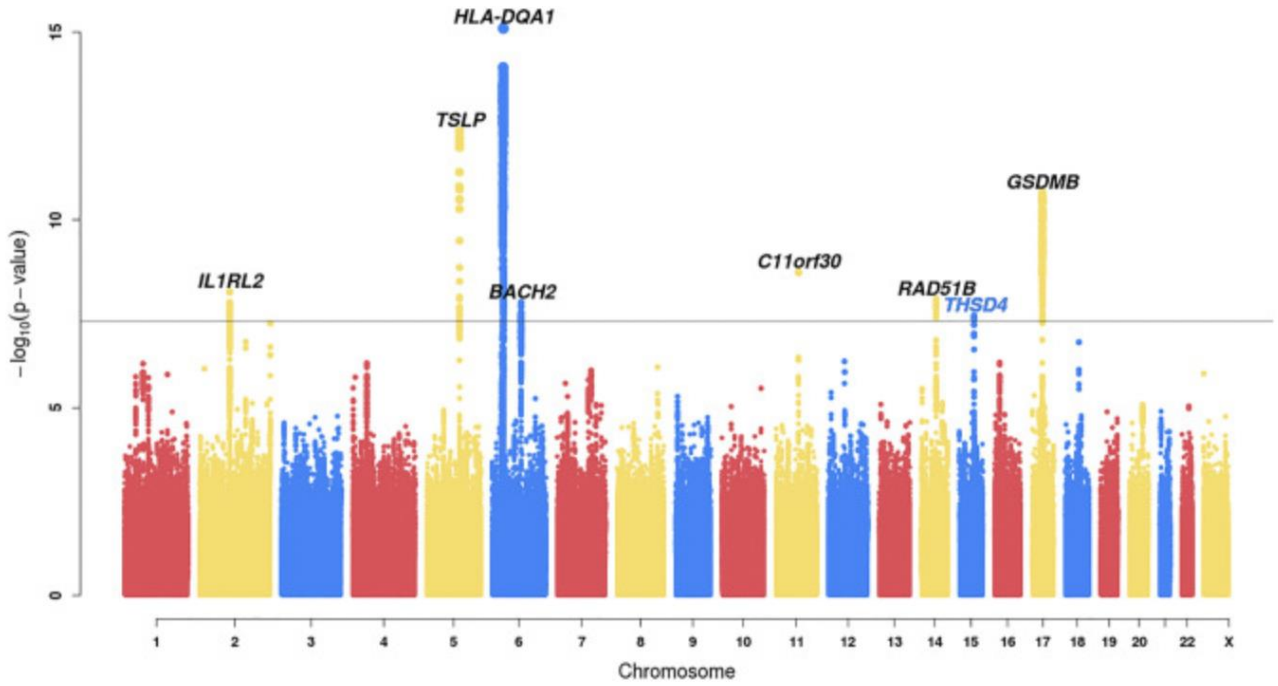
Largest GWAS of severe asthma



Shrine et al. Lancet Resp Med. 2019; 7:20-34

Genome-wide sequencing study

Moderate to severe cases: 3,181
Healthy controls: 3,590



Chang et al. Sci Rep. 2022; 12: 5574.

Rare genetic variation in severe asthma

Arguments for rare variants in severe asthma

1. Severe disease ≈ extreme phenotype ≈ variants of extreme (severe) effect
2. Monogenic disease often initially misdiagnosed as asthma
3. The filaggrin story
4. Severe asthma could be a rare disease

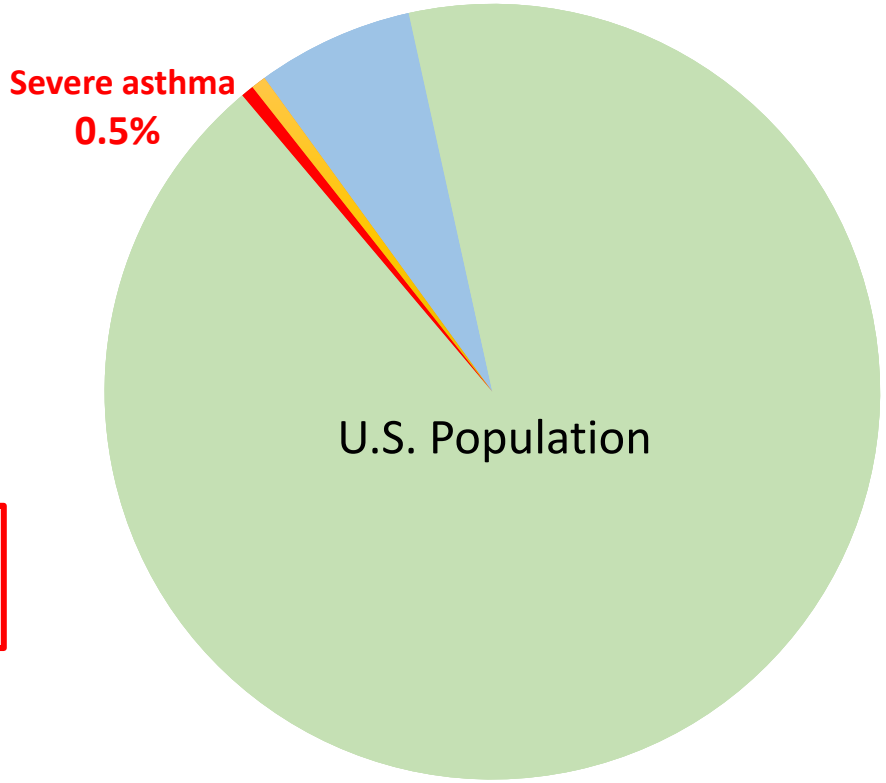
Asthma prevalence: 7.6% of U.S. pop.

"Severe asthma": 15% of asthma
1.1% of U.S. pop.

Compliance
"Non-genetic"

"Biologic severe asthma": 7% of asthma
0.5% of U.S. pop.

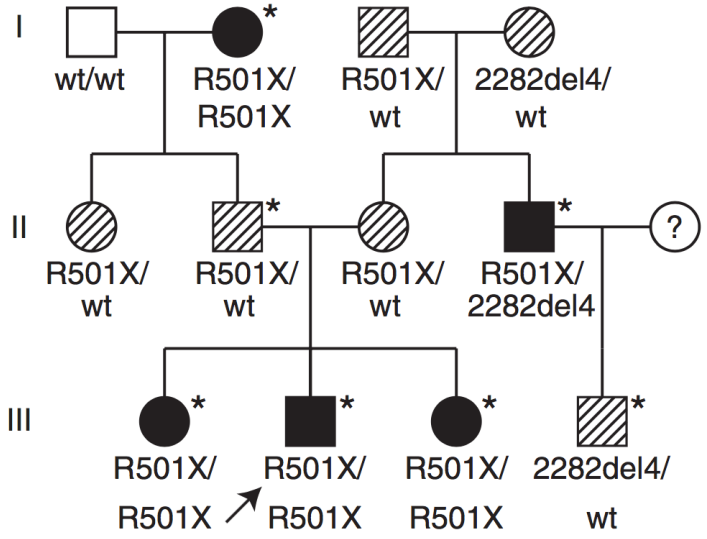
Prevalence of severe asthma in France:
0.21-0.49%



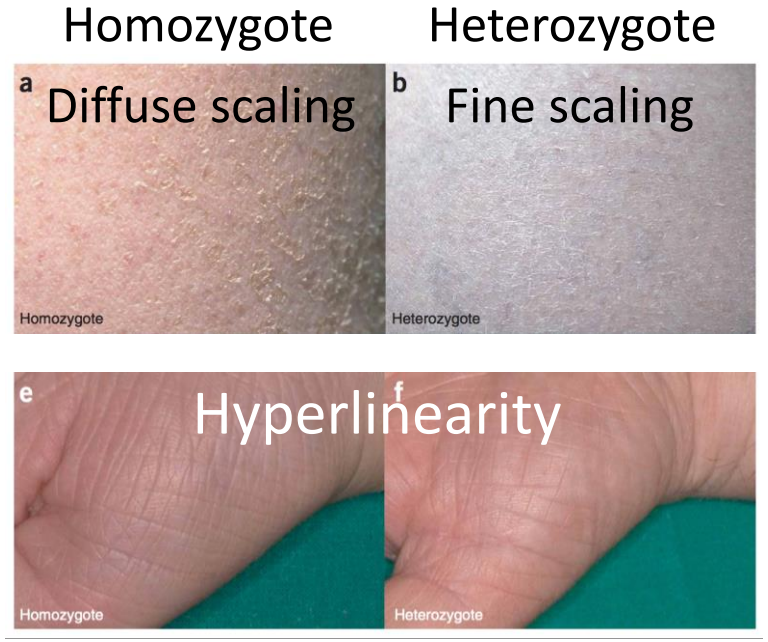
Prevalence of
Sickle Cell Disease:
1-6%

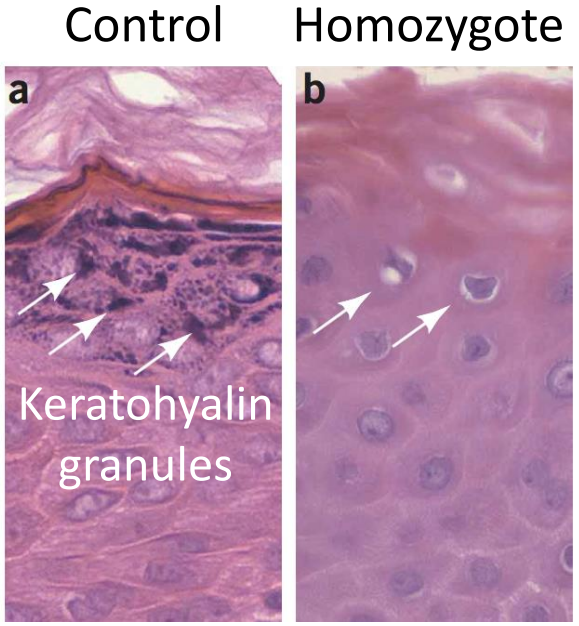
Prevalence of
hemachromatosis:
0.2-0.5%

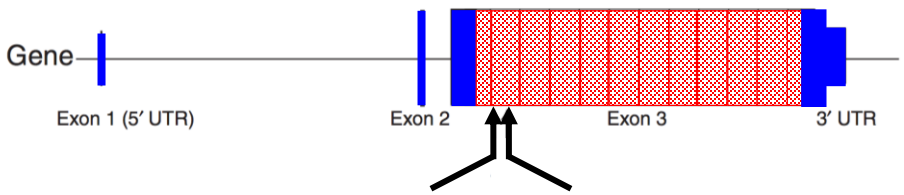
Filaggrin (FLG), ichthyosis vulgaris and atopic dermatitis



Smith FJD et al. Nat Genet (2006) 38: 337-42.





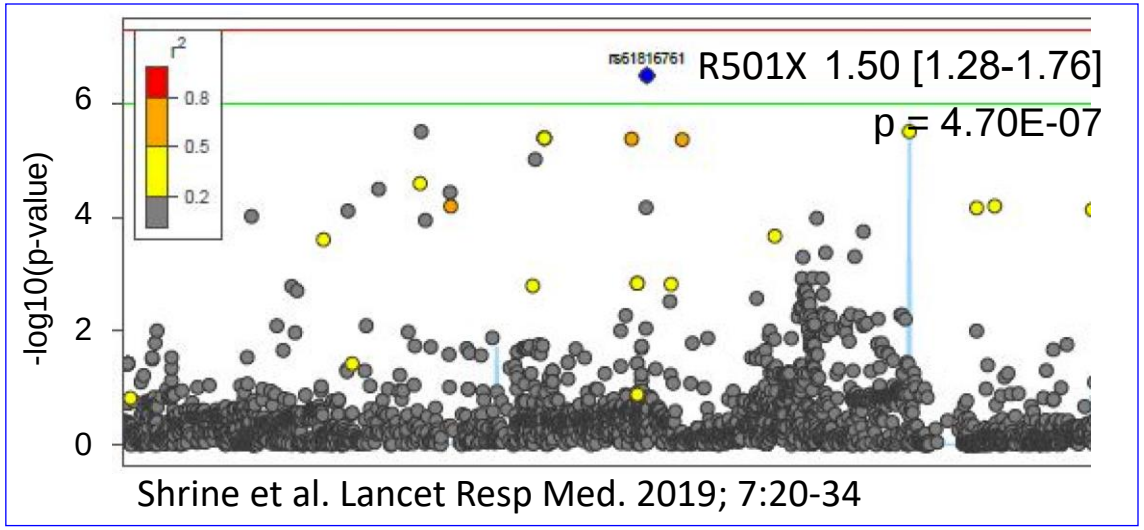


R501X 2282del4

2.1%-4.1% 0.5%-1.2%

Filaggrin (FLG) and severe asthma

Asthma Severity GWAS



Shrine et al. Lancet Resp Med. 2019; 7:20-34

Monogenic disorders misdiagnosed as severe asthma

Disorder	Genes	Genetic mechanism	Mode of inheritance	Major manifestations	Specific therapy
Cystic Fibrosis	CFTR	Aberrant chloride transport → impaired MCC	AR	**Bronchiectasis** Pancreatic insufficiency Infertility	Ivacaftor Lumacaftor Tezacaftor
Primary Ciliary Dyskinesia	37 genes	Impaired ciliary assembly → impaired MCC	AR, X-linked	**Bronchiectasis** Dextrocardia, situs inversus Infertility and ectopic pregnancy	Promote mucociliary clearance
Alpha-1-antitrypsin deficiency	SERPINA1	Neutrophil elastase deficiency → protease and pro-inflammatory activity	AR	**Bronchiectasis** and emphysema Accelerated lung function decline, abnormal liver function	Enzyme replacement therapy (ERT)
Hypereosinophilic syndrome	FIP1L1-PDGFRA fusion	Tyrosine kinase fusion protein → clonal eosinophil proliferation	Somatic mutation	Eosinophilic tissue infiltration, most commonly of the heart, skin, lungs, PNS and CNS	Imatinib Mepolizumab
Hyper-IgE (Job) Syndrome	STAT3 DOCK8 ZNF341 PGM3	Impaired Th17differentiation → dysregulated immune responses	AD AR AR AR	**Eczema**, retained primary teeth, **recurrent Staphylococcal abscesses, recurrent fungal and viral infections**, pneumatocoeles	Hematopoietic stem cell transplantation (HSCT)
Icthyosis Vulgaris	FLG	Impairment of epithelial barrier function	AD	Diffuse patches of dry, scaly skin, palmer hyperlinearity and keratosis pilaris, **eczema** and allergic rhinitis	Skin hydration
Comel-Netherton Syndrome	SPINK5	Loss of epithelial anti-protease activity → inflammation and desquamation	AR	Icthyosis, **eczema**, bamboo hair	None
Adenosine deaminase deficiency	ADA	impaired DNA synthesis and lymphocyte maturation	AR	Lymphopenia, **recurrent, opportunistic, and severe infections**; **rash**; growth delay	ERT HSCT Gene therapy

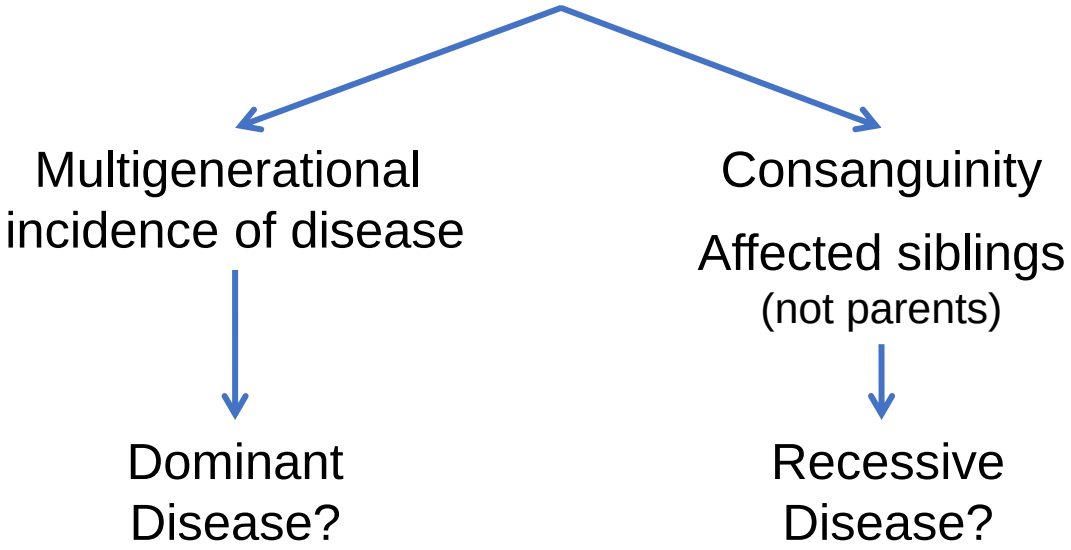
Clinical approach to identify genetic forms of severe asthma

Recognizing genetic disease

- Personal history:
  - Severe disease
  - ~~Early-onset of disease~~
  - Atypical / rare symptoms or physical findings (more to come)

- The family history is helpful:

Pattern of Inheritance



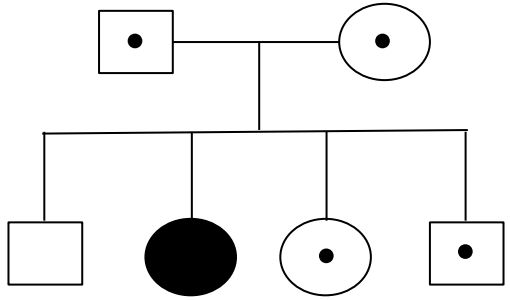
Familial manifestations of disease

Trait	Disorder
Situs Inversus	Primary Ciliary Dyskinesia
Retained teeth	Job Syndrome
Severe eczema	Ichthyosis

A negative family history: very common

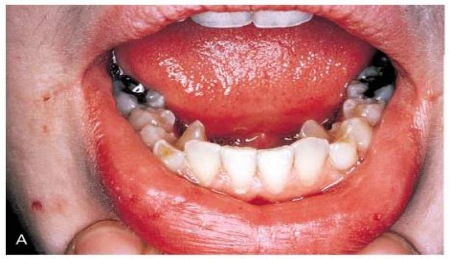
Autosomal recessive diseases

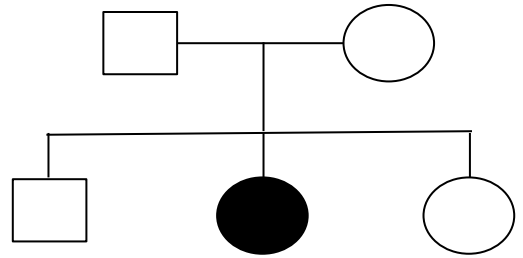
(Cystic Fibrosis, Alpha-1 antitrypsin deficiency, primary ciliary dyskinesia)



Incomplete penetrance or incomplete expressivity

(Hyper-IgE / Job's syndrome)

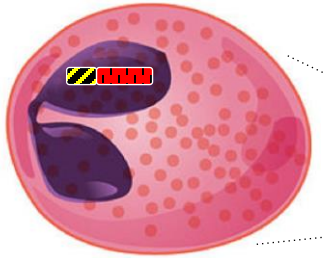


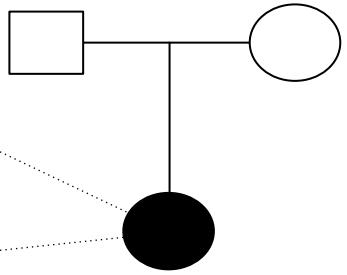


IgE = 13,000

Spontaneous mutation

(Hypereosinophilic syndrome)



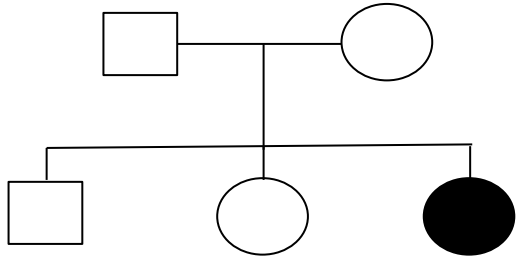


FIP1L1-PDGFA

Eosinophils: 7,400 cells/mm^3

Inaccurate or unavailable history

(in diagnosis, non-paternity, adoption)



Abnormal LFTs

Bronchiectasis

Gene-focused history, physical, and labs

	History		Physical Examination
HEENT:	Recurrent otitis	**CF**	Glue ear
	Chronic sinusitis	**PCD**	Reduced auditory acuity
	Chronic nasal congestion		
	Allergic rhinitis	**Ichthyosis**	
		Hyper-IgE	Retained teeth
CVS:	Heart failure	**HES**	
			Dextrocardia
		PCD	Pectus excavatum (10%)
Abdo:	Pancreatitis	**CF**	Heterotaxy
	Fat soluble vitamin def.	**HES**	
			Organomegally
Repro:	Infertility	**CF / PCD**	Bilateral absence of the vas deferens
	Ectopic pregnancy		
Neuro:	Neuritis	**HES**	Focal Neurologic Deficits
Skin:	Eczema	**Hyper-IgE, Ichthyosis**	Rash Ichthyosis / Hair
Infection:	Staphlococcal / fungal	**Hyper-IgE**	
	Opportunistic	**ADA deficiency**	

Labs

Blood work	Disorder
Lymphopenia	ADA deficiency
Eos	HES
LFTs	A1ATD HES
IgE	Hyper-IgE HES
Hypogamma	Hyper-IgE ADA deficiency
Vitamin Deficiency	CF

Radiology	Disorder
Bronchiectasis or Reduced PFTs	CF PCD A1ATD Immune deficiency
Infiltrates	HES
Pneumatocoele	Hyper-IgE
Heterotaxy	PCD

Corroborative tests

Disorder	Tests	Comments	Genetic testing
Cystic Fibrosis	Sweat chloride test	Diagnostic test	CFTR sequencing
Primary Ciliary Dyskinesia	Nasal Nitric Oxide Nasal EM	Levels < 77ng/dL with high sens / spec Not diagnostic, difficult to obtain Poor sensitivity and specificity	37 gene panel
Alpha-1-antitrypsin deficiency	A1AT levels and SPEP	Diagnostic test	Pi locus genotyping
Hypereosinophilic syndrome	FIP1L1-PDGFRA fusion	Diagnostic test	
Hyper-IgE (Job) Syndrome	None	Clinical Dx	STAT3, DOCK8, ZNF341, PGM3
Icthyosis Vulgaris	None	Dermatologic Dx	FLG
Comel-Netherton Syndrome	None	Dermatologic Dx	SPINK5
Adenosine deaminase deficiency	ADA enzyme levels	More detailed immunologic survey often needed	ADA

Recognizing genetic disease is challenging

- Family history often lacking
- Suspecting rare disease requires vigilance
- Lack of pathognomonic manifestations:
  - Forme Fruste disease - late onset, “mild” cystic fibrosis
  - Limited expressivity - lack of extra-pulmonary manifestations
- Available exposures for attribution
  - Smoking history
  - Occupational exposures

The importance of genetic counseling

- Pre-test:
  - Understanding role of testing in clinical evaluation
  - Preparation for VUS and “incidentalisms”
  - Determine the patient-specific appropriateness of test
  - Consenting process

- Post-test:
  - Result reporting and interpretation
  - Review of result implications
  - Role of genetic determinism
  - Family counseling
  - Reproductive counseling

BWH Pulmonary Genetics Center

- We are happy to provide you with genetic counseling and diagnostic testing services for your patients

- Email me with questions:
  - braby@bwh.harvard.edu
  - Benjamin.Raby@childrens.harvard.edu

Online resources

- GeneTests:
    - Clinical resource for genetic testing, including:
        - a laboratory directory of over 600 labs offering testing;
        - a Clinic Directory of over 1000 international genetics clinics
        - GeneReviews – summaries of diseases and genes
        - www.genetests.org

- OMIM: Online Mendelian Inheritance of Man
    - Annotated catalog of disease-associated genes and genetic traits
    - omim.org

- Disease Foundations:

Summary

- Recognizing genetic forms of severe asthma is very important
  - For the patient (treatment implications)
  - Potentially for their family
- Take a good family history
  - But family history is not the end all and be all!
- Look for unusual phenotype, early presentation
- Early referral to specialist, particularly with genetic counseling, is advised, often prior to sequencing.
- Most “severe asthma” susceptibility variants are “asthma” susceptibility variants. More work is needed to understand their potential clinical utility.