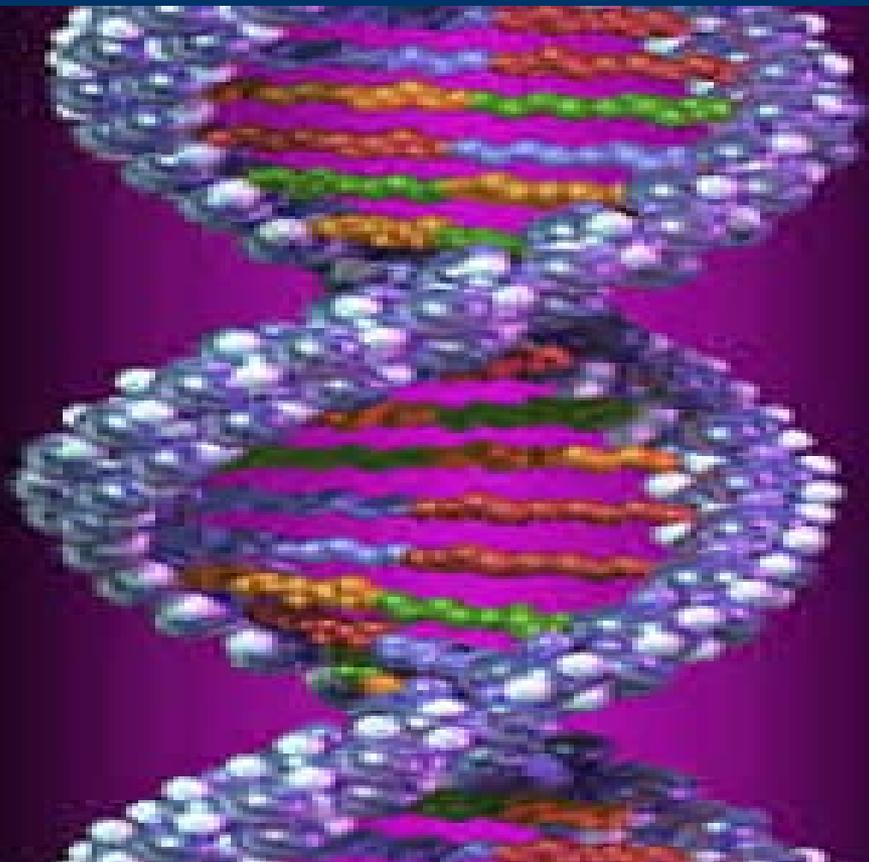


Genetics of asthma & allergy: from Gee-Whizz to GWAS to GWIS



David Strachan, St George's, University of London

The 1990s: waiting to exhale

- Epidemiology faces its limits (1995)
 - Bias, confounding and weak associations
 - False alarms, media scares, loss of credibility
- Asthma genetics “waiting to exhale” (1997)
 - Twin and family studies
 - Confidence about molecular mechanisms

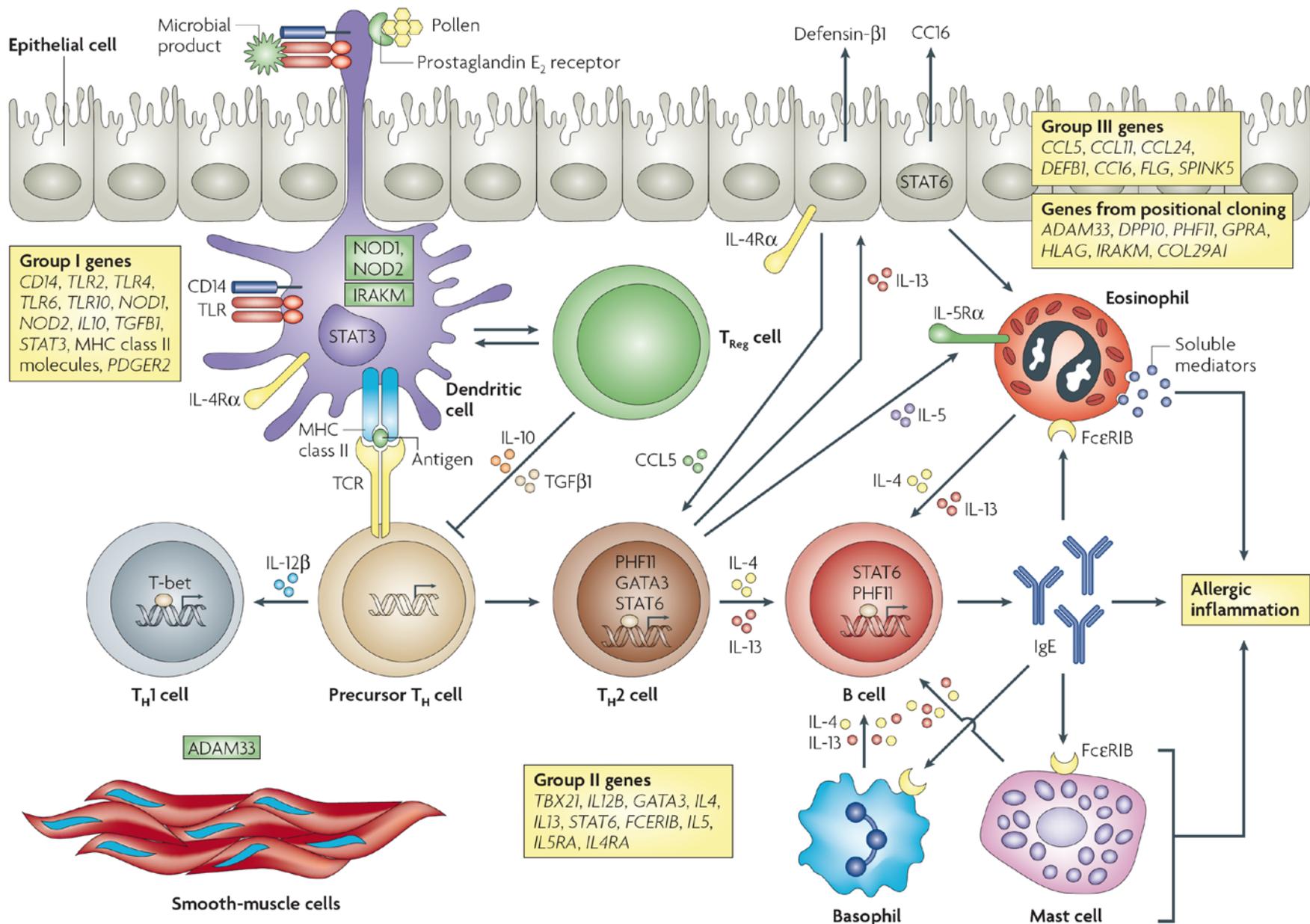


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- Asthma genetics “waiting to exhale” (1997)
 - Twin and family studies
 - Confidence about molecular mechanisms
- Sequencing of the human genome (c.2001)
 - Can genetics rescue epidemiology?



85 letters stretch 4.5 metres

3,000 million letters = 4 times around the world



*"The guardian angel
of asthma research"*

Participating studies

ALSPAC	UK
BAMSE	Sweden
B58 cohort	UK
BUSSELTON	Australia
CAPPS & SAGE	Canada
ECRHS	Europe
EGEA	France
FINRISK	Finland / Russia
GABRIELA	Alpine (AT/CH/D)
GAIN	Europe
Kursk	Russian Fed.
Industrial	Denmark / NL
ISAAC	Europe (plus)
MAGICS	Germany
MAS	Germany
MRC families	UK
PIAMA	Netherlands
SAPALDIA	Switzerland
Severe asthma	UK
SLSJ families	Canada
Tomsk	Russian Fed.
UFA	Russian Fed.



*"The guardian angel
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2001-6: from Gee-Whizz to GWAS

- Finding single nucleotide polymorphisms
 - 1.4 million SNPs (SNP consortium, 2001)
 - 2.5 million common SNPs (HapMap, 2005)
 - 15 million SNPs (1000 Genomes, Oct 2010)
- Defining haplotype structure
 - HapMap consortium (2005)
 - Common ancestry (“Out of Africa”)
 - Imputation from 300-500K “tagSNPs” to 2.5M
- High-throughput genotyping “chips” (2006)



The best laid schemes
o' Mice an' Men
gang aft agley,

An' leave us nought
but grief an' pain
for promis'd joy!

*From **To A Mouse** by
Robert Burns*

GABRIEL phase 1: GWAS for asthma (994 child asthmatics, 1243 controls)

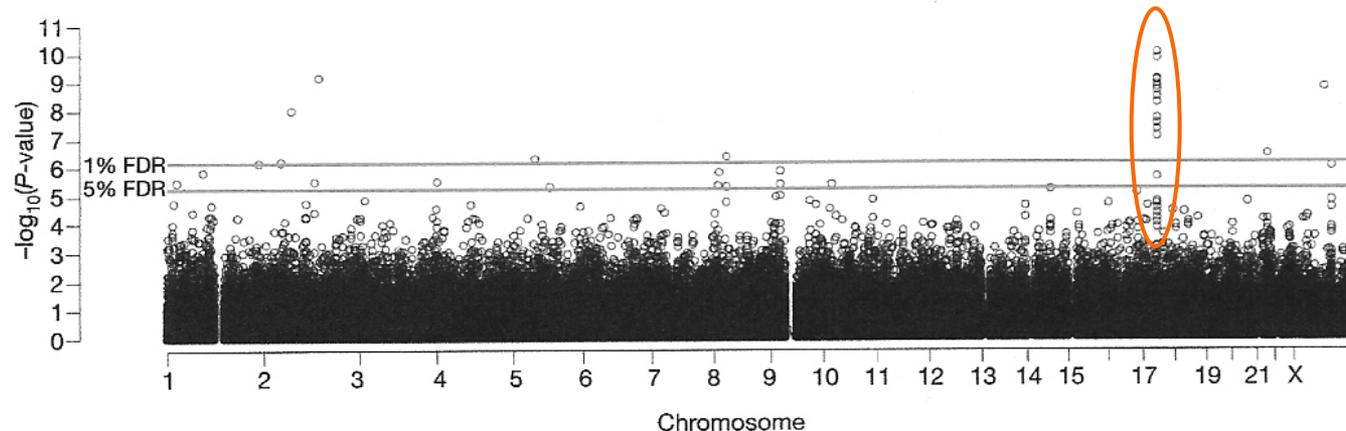


Figure 2 | Genome-wide association of 317,447 SNPs and asthma in 994 asthmatic children and 1,243 non-asthmatic children. Position in the genome, divided by chromosome, is depicted along the x axis. Strength of association is shown on the y axis. The result for each individual marker is

depicted as a black circle. The genome-wide thresholds for 1% and 5% false discovery rates (FDR) are shown as horizontal red lines. Numerous markers on chromosome 17q21 show association to asthma above the 1% FDR threshold in the region of maximum association.

GABRIEL phase 1: GWAS for asthma (994 child asthmatics, 1243 controls)

Candidate genes confirmed	0
Positionally cloned genes confirmed	0
New discoveries (with replication)	1

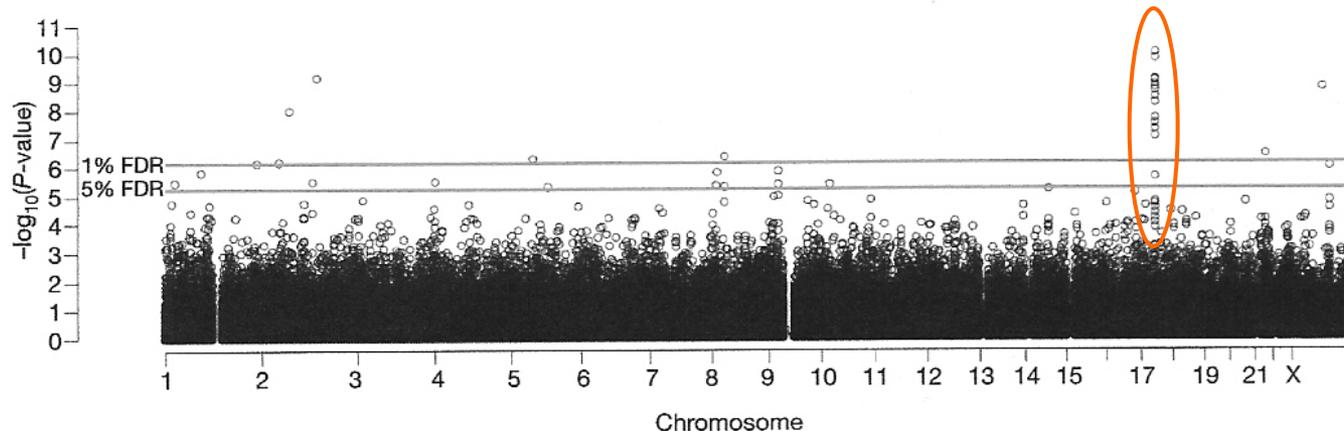
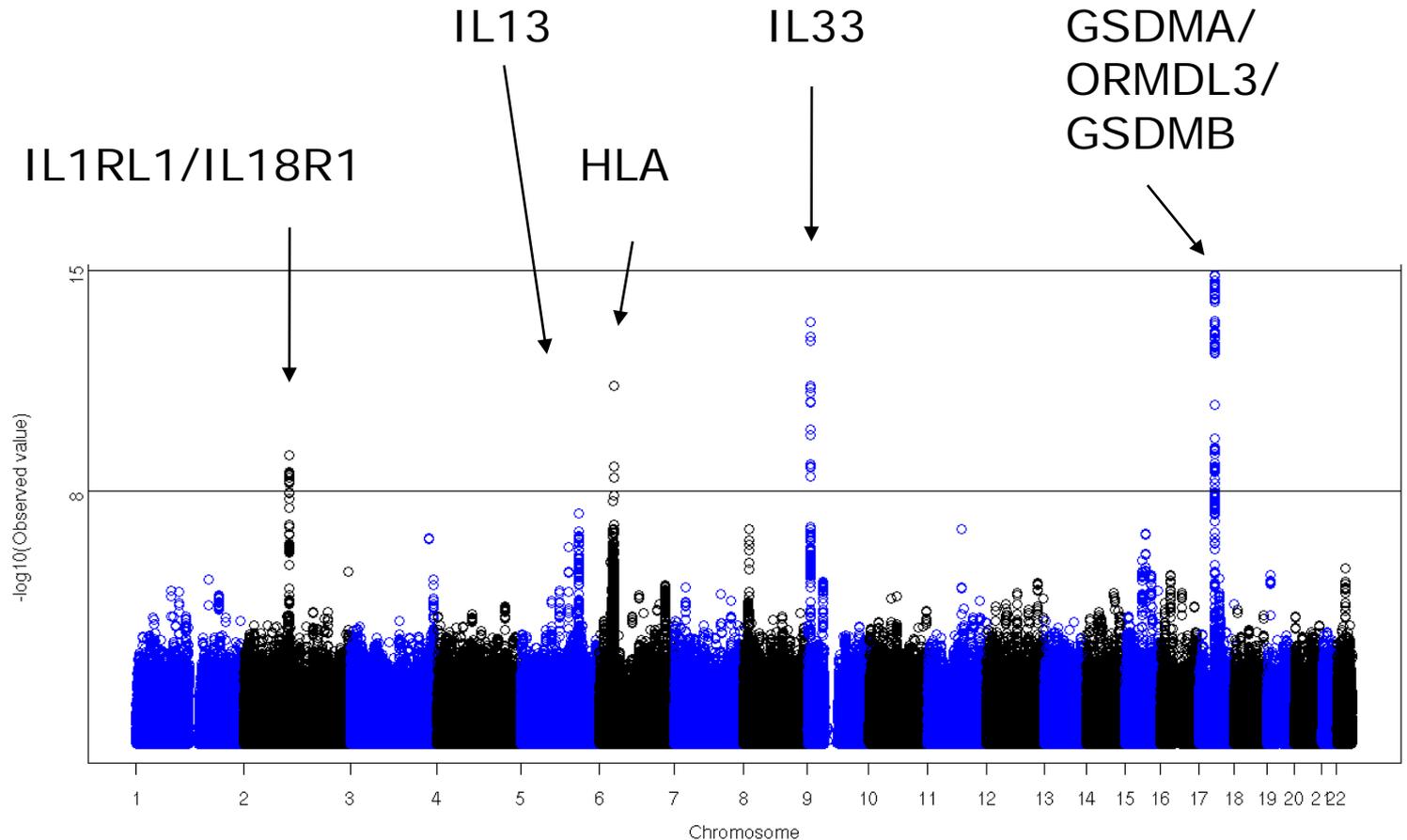


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GABRIEL phase 2: GWAS for asthma (10,365 asthmatics, 16,110 controls)

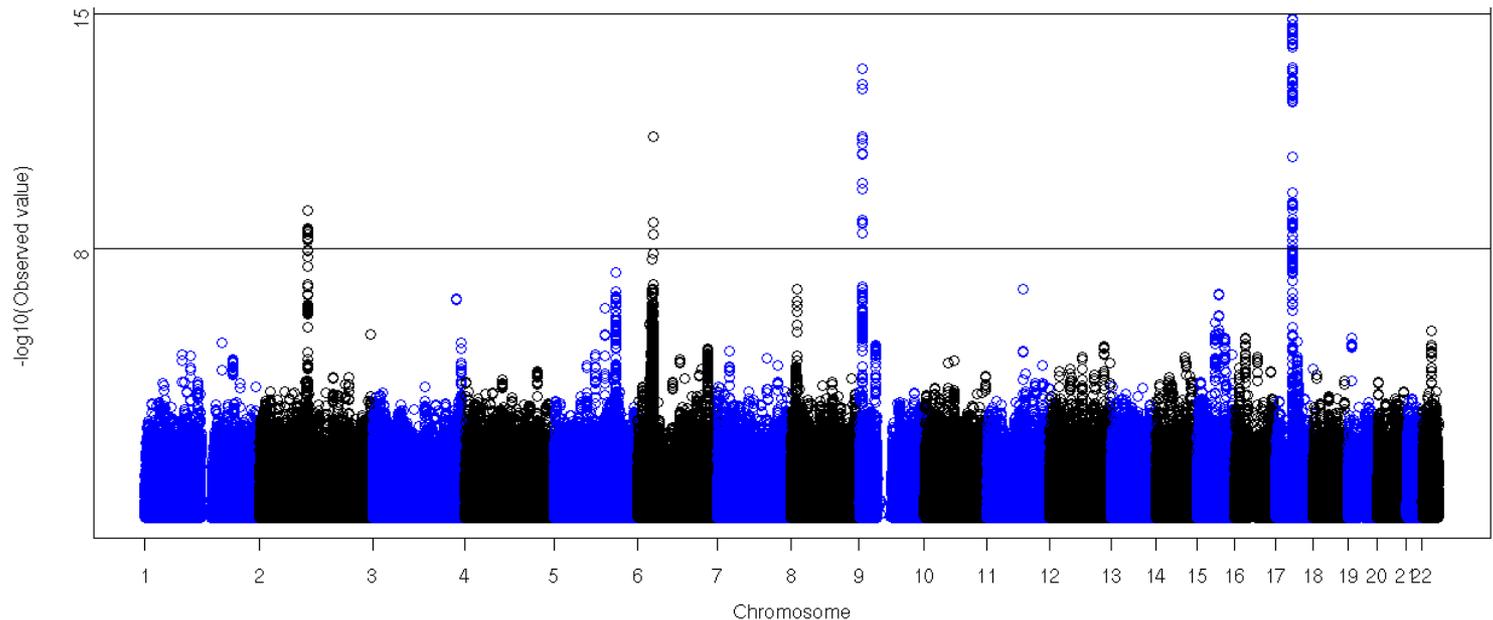
Asthma
All ages
of onset
combined



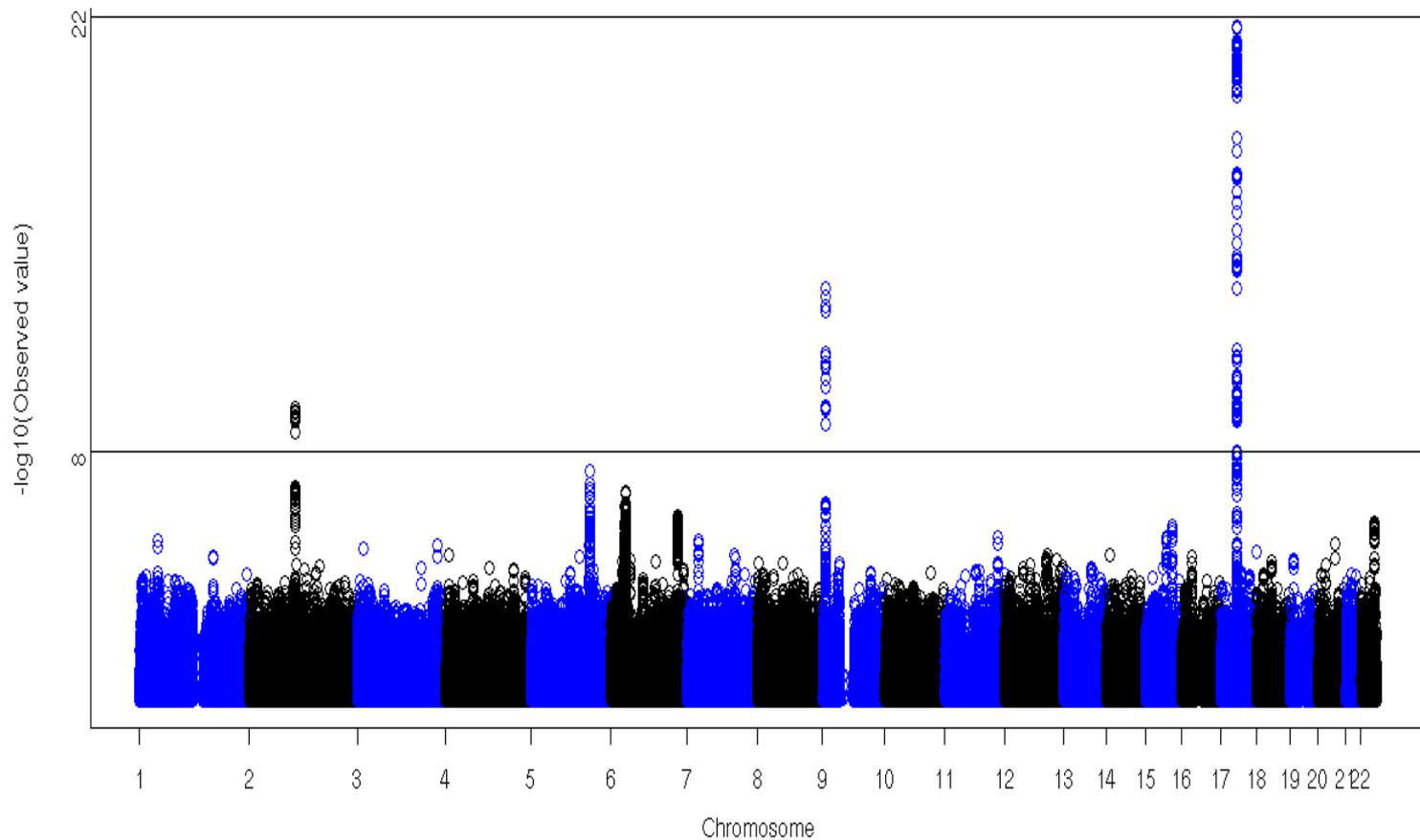
GABRIEL phase 2: GWAS for asthma (10,365 asthmatics, 16,110 controls)

Candidate genes confirmed	1-2
Positionally cloned genes confirmed	0
New discoveries (with replication)	3

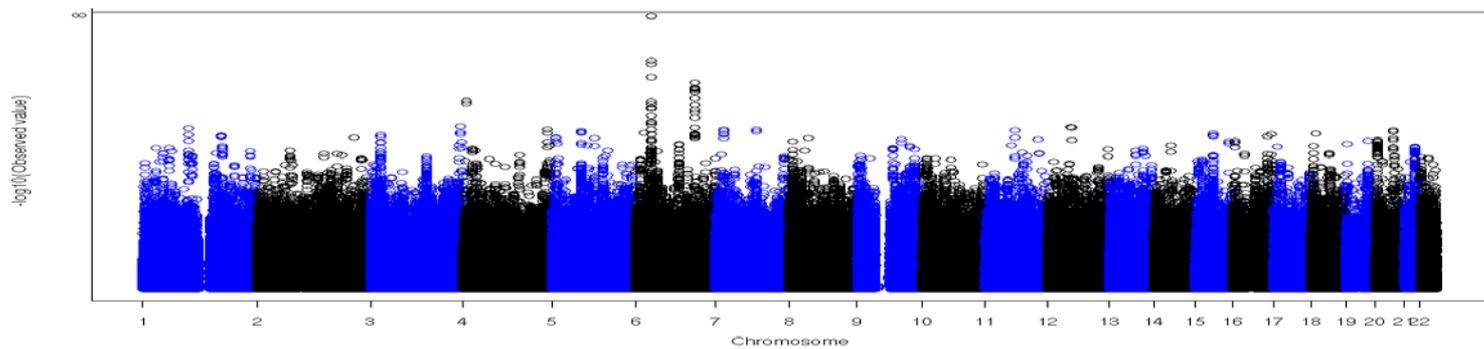
Asthma
All ages
of onset
combined



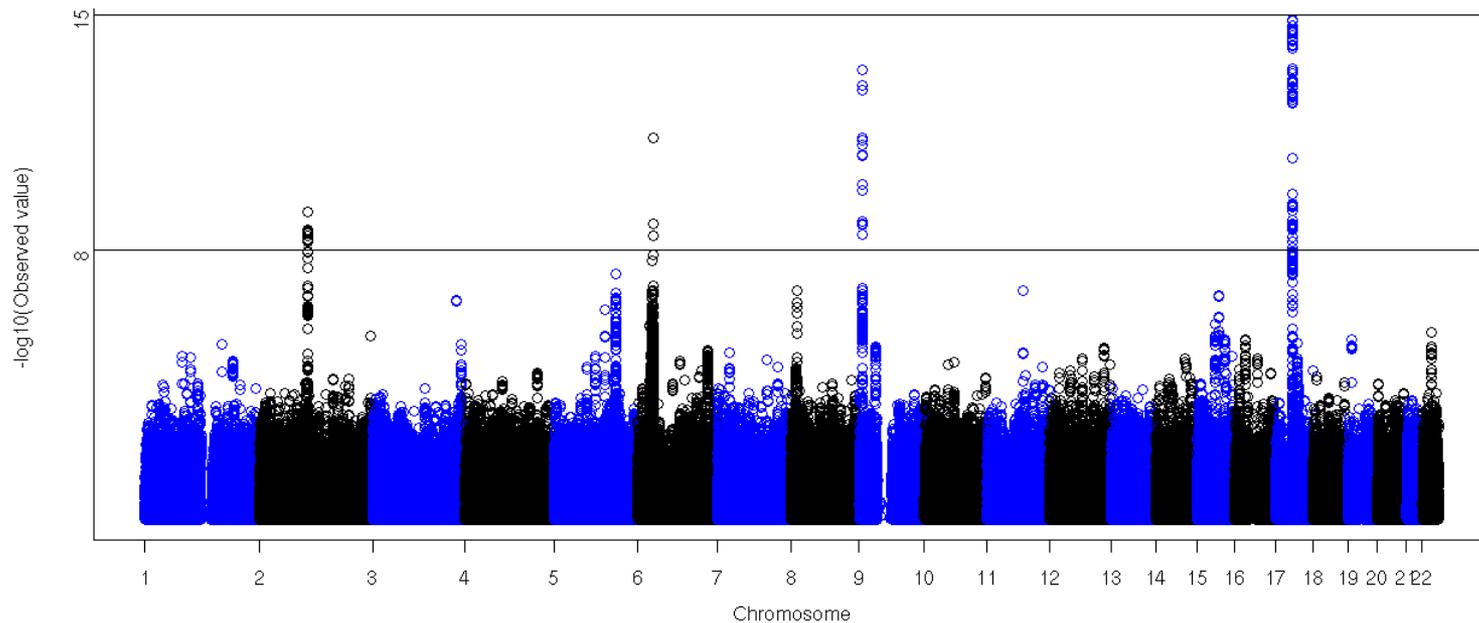
Asthma Childhood onset



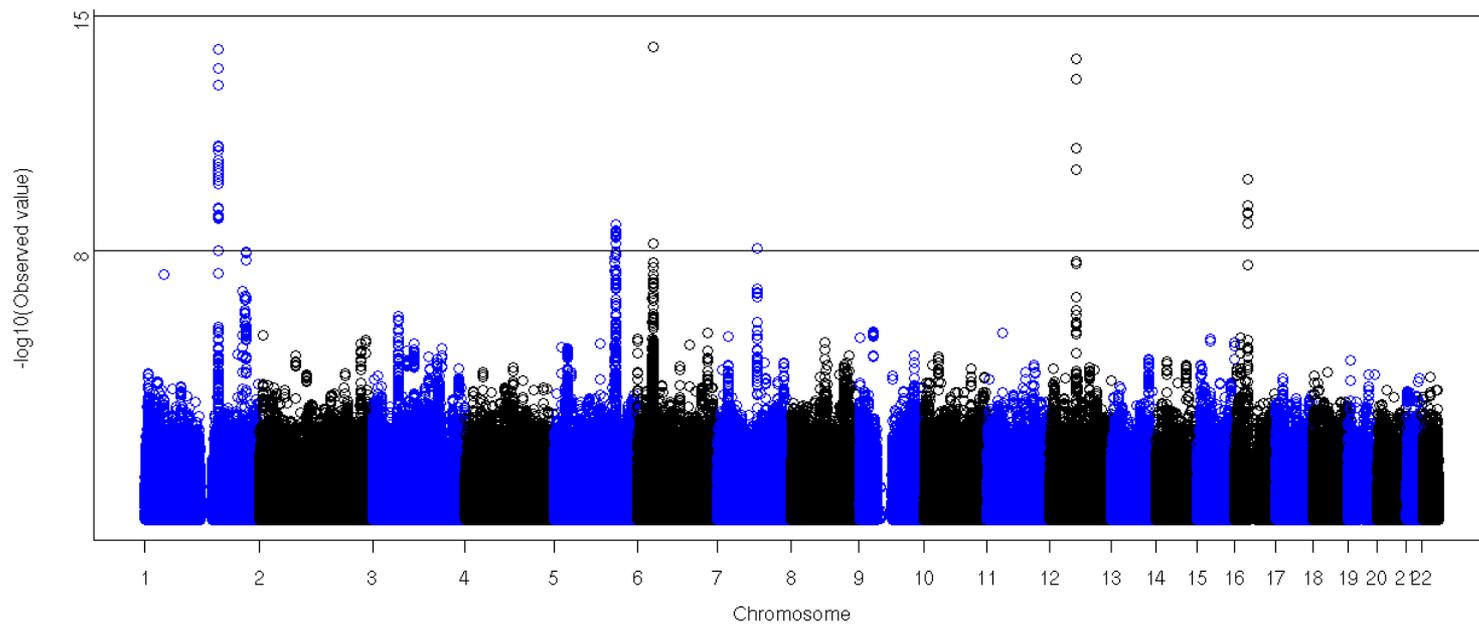
Asthma Adult onset



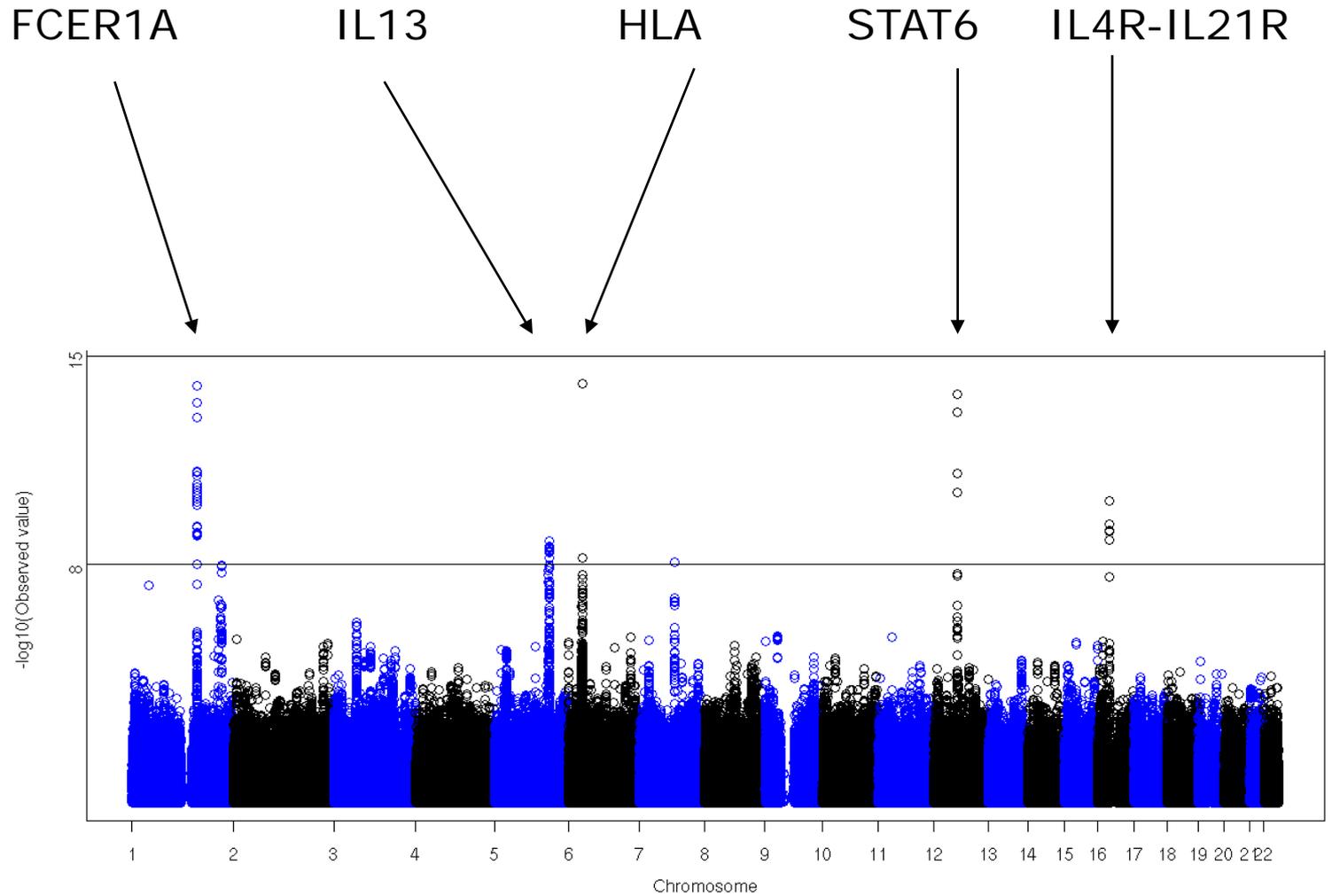
Asthma
All ages
of onset
combined



Total IgE
Cases and
controls
combined



Total IgE
Cases and
controls
combined



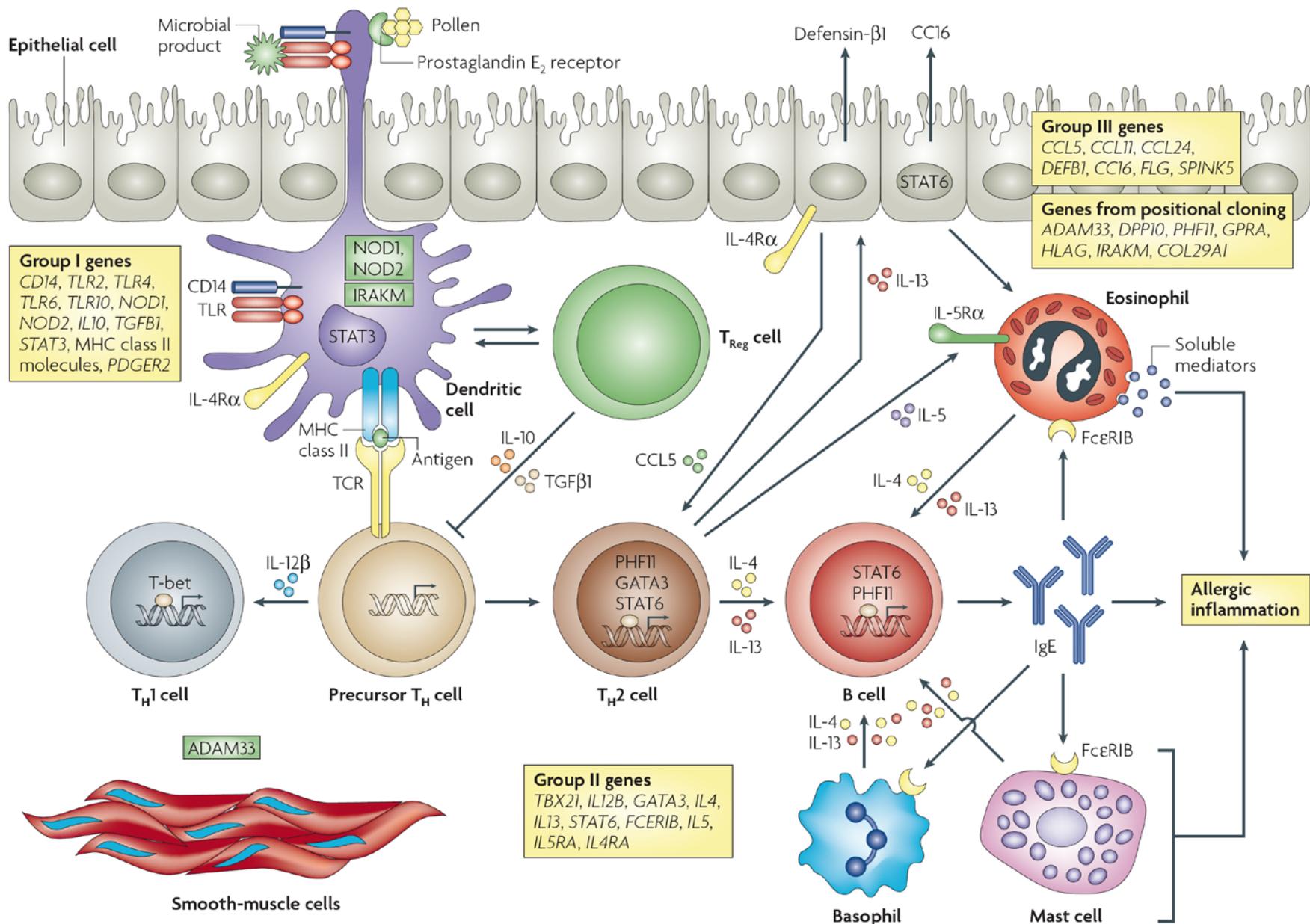


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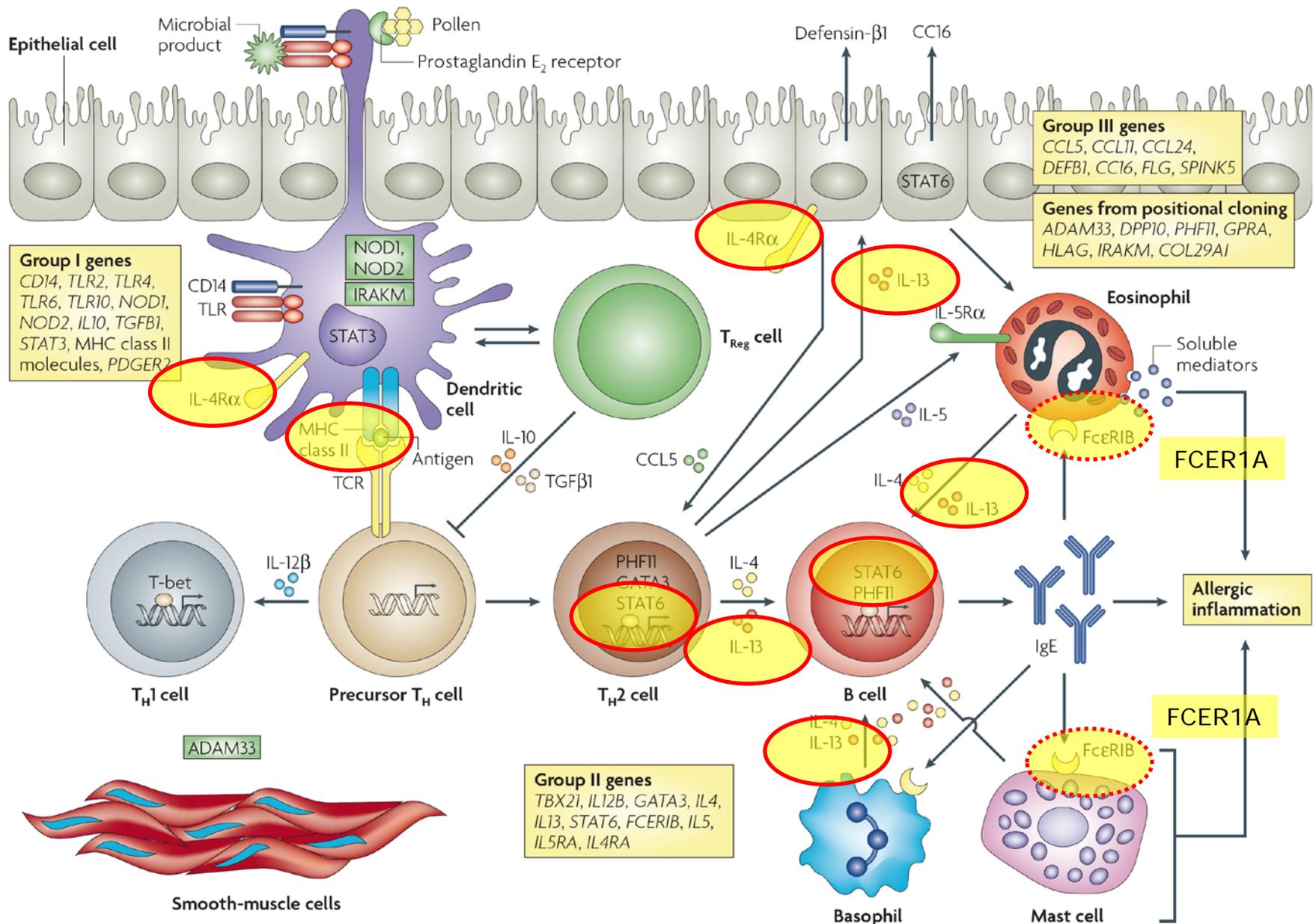
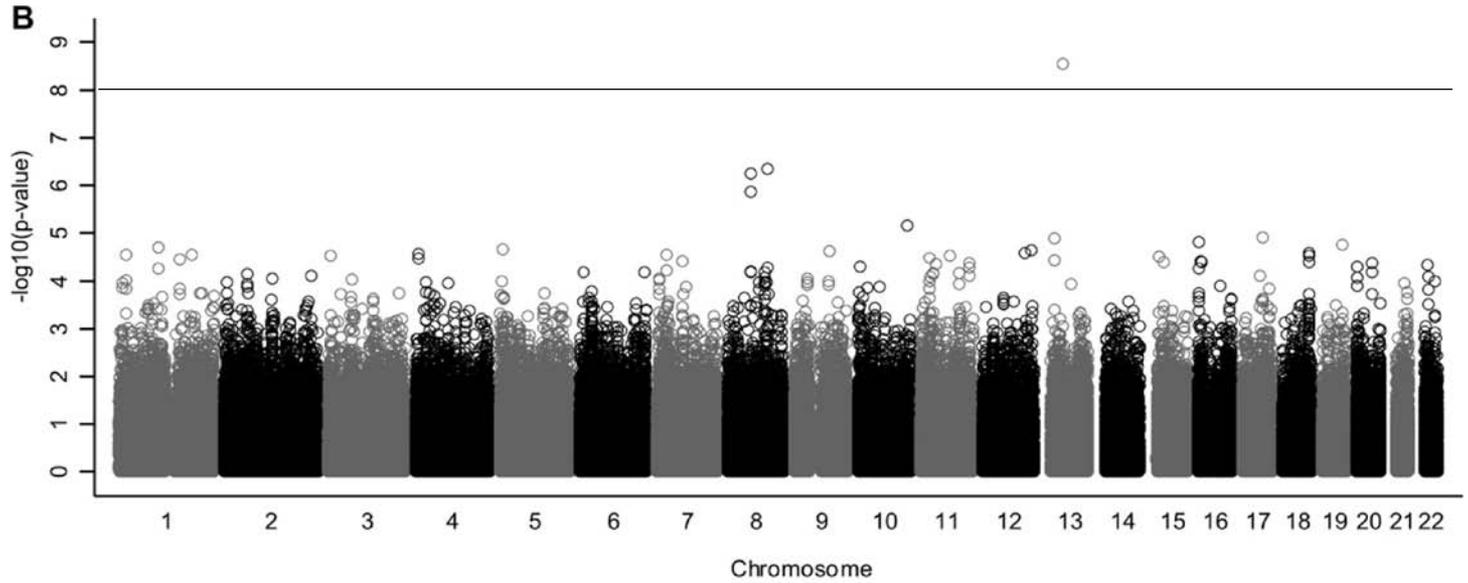


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**British
1958
cohort**

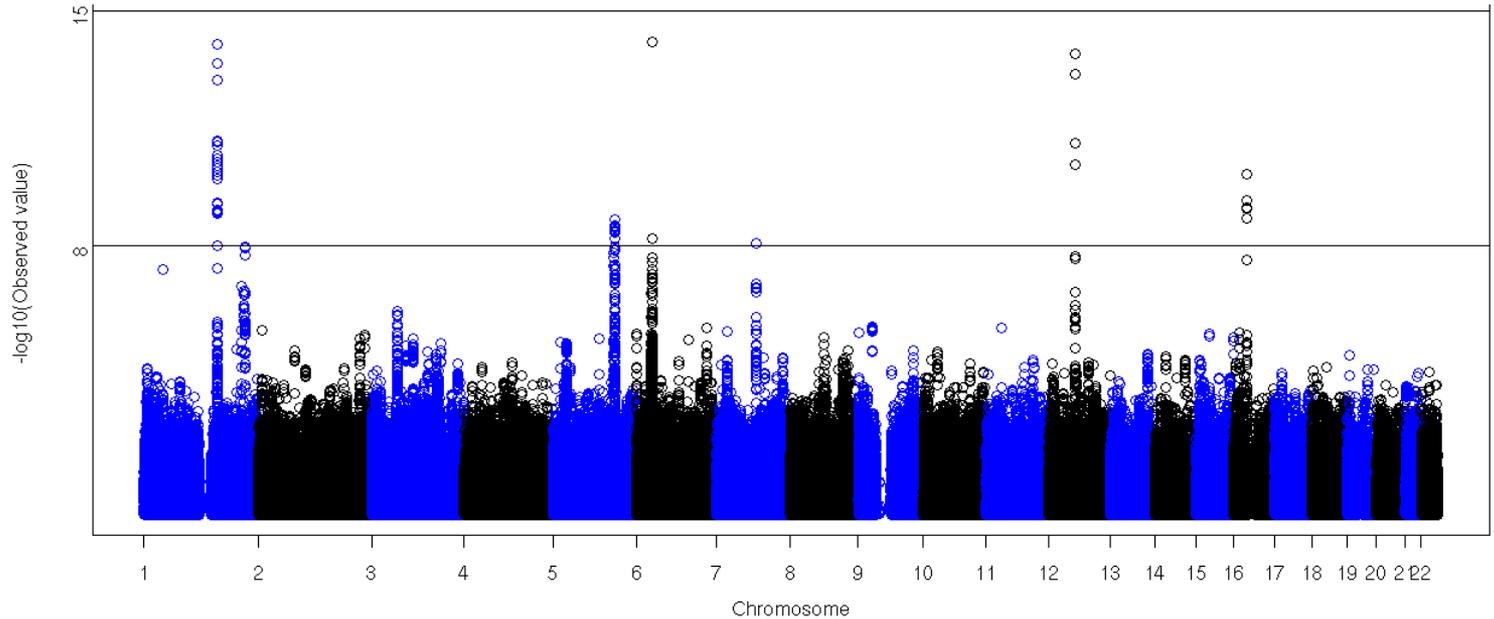
**Specific
IgE to
grass,
dust or
cat**



GABRIEL

Total IgE

**Cases and
controls
combined**



GWAS for grass-IgE and hay fever, 2010

Meta-analysis

Br 1958 cohort

NFBC 1966

ECRHS

SAPALDIA

Grass-sp-IgE

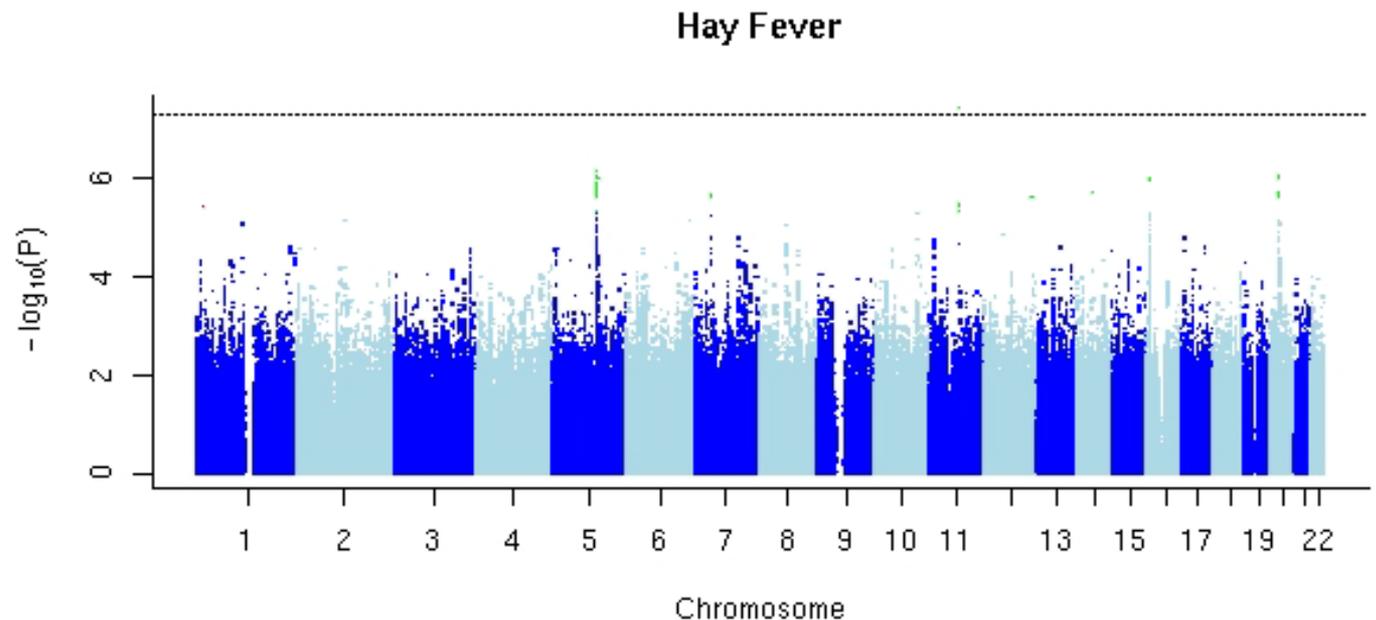
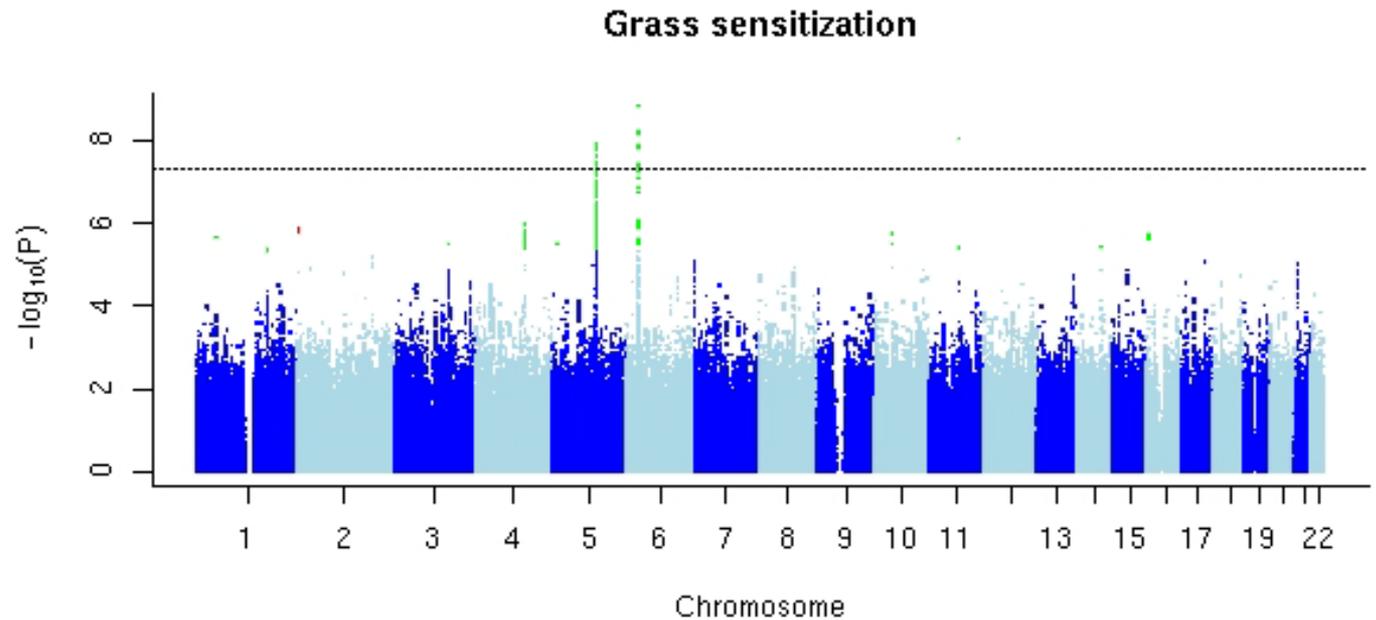
2568 cases

9779 controls

Hay fever

4106 cases

8732 controls



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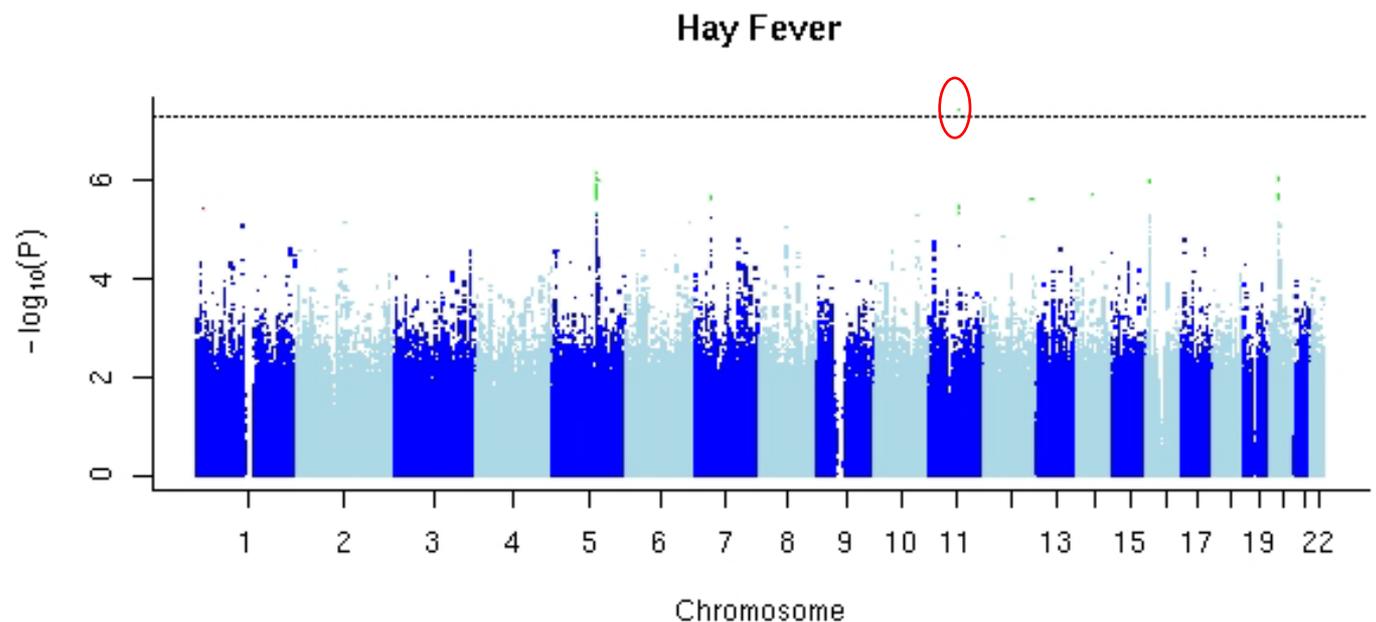
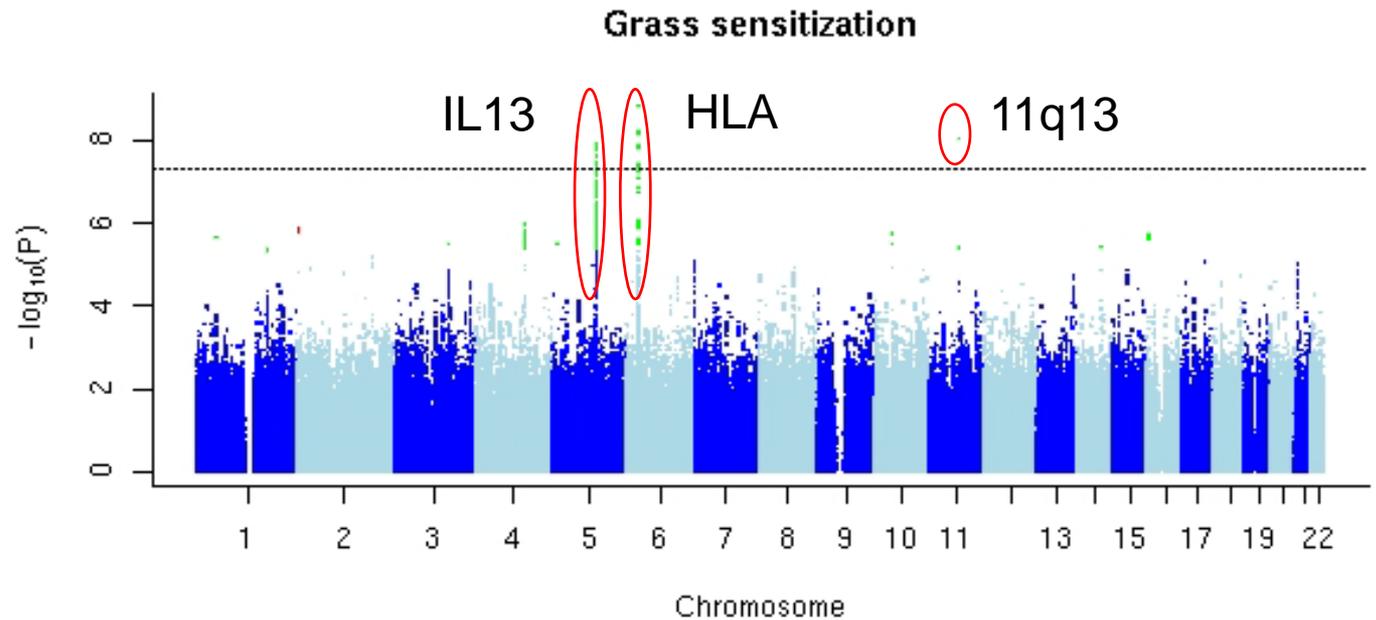
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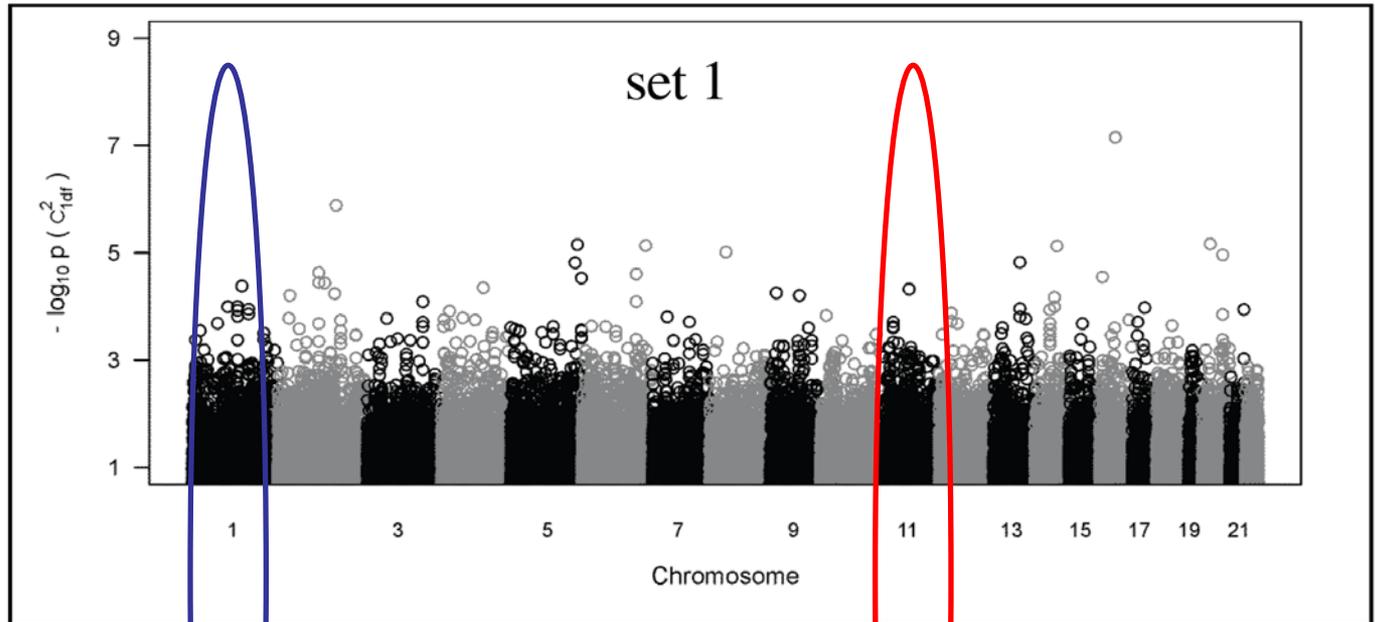
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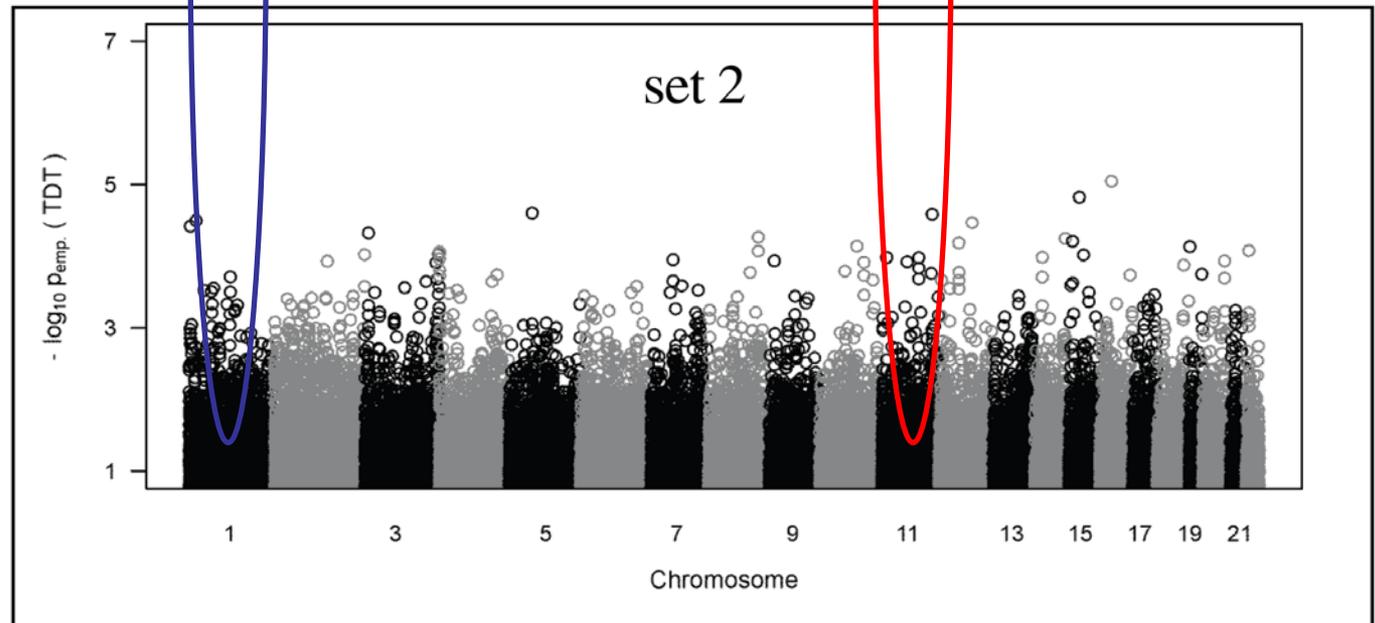


First GWAS for eczema

939 cases
975 controls
(set 1)



270 eczema families
(set 2)



Plus
independent
replication

GWAS: the end of the beginning

- If you don't measure it you won't find it
 - Total IgE and HLA-DR/DQ region
 - Eczema and filaggrin null mutations
- Imputation can help for common SNPs
 - 1000 Genomes template expected 2011
 - ... but of limited value for rare SNPs
 - ... and of no value for recent mutations
- Few biological candidate SNPs confirmed

GWAS: the beginning of the end

- GWAS to date identify **haplotypes** rather than **specific polymorphisms**
 - Significant SNPs may not be the true culprits
- Common SNPs explain only a fraction of familial aggregation (“missing heritability”)
 - G*G and G*E interactions?
 - Rare SNPs nested on common haplotypes?
- Relevant rare SNPs may not part of the “out of Africa” common ancestry

1990s

Epidemiology faces its limits

2000s

Can genetics rescue epidemiology?

2010s

Genetic epidemiology faces its limits

Can epidemiology rescue genetics?



Epidemiology rescues genetics?

- Genetic diversity
 - Replication studies in populations with African ancestry
- Phenotypic diversity
 - Which types of disease are associated with GWAS “hits”?
- Environmental diversity
 - Gene-environment interaction studies

Types of gene-environment interaction reported in studies of asthma and allergy

Effect concentration

Cross-over interaction

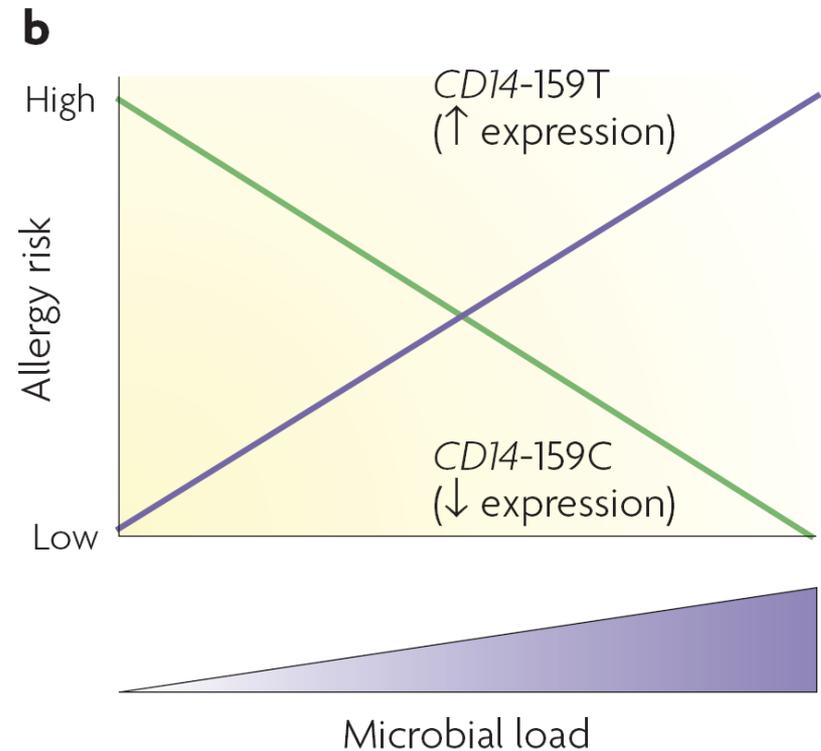
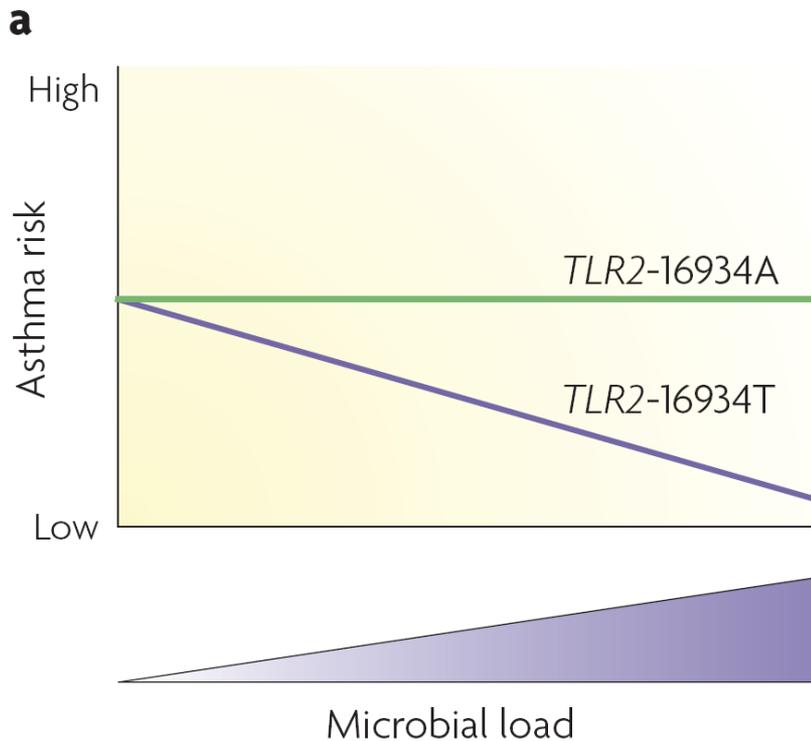


Figure from Vercelli D. *Nature Rev Immunol* 2008; **8**: 169-182

From GWAS to GWIS

- Biological candidate genes or SNPs
 - Known or suspected mechanisms
- GWAS “hot SNPs”
 - New mechanisms for known risk factors
- Genome-wide interaction studies (GWIS)
 - Data often exist once GWAS is completed
 - Multiple comparisons multiply..!!
 - Proceed with caution (as investigator or reviewer)



Some books are lies
frae end to end,

And some great lies
were never penn'd.