



Génétique et asthma: Quoi de neuf ?

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INSERM U946

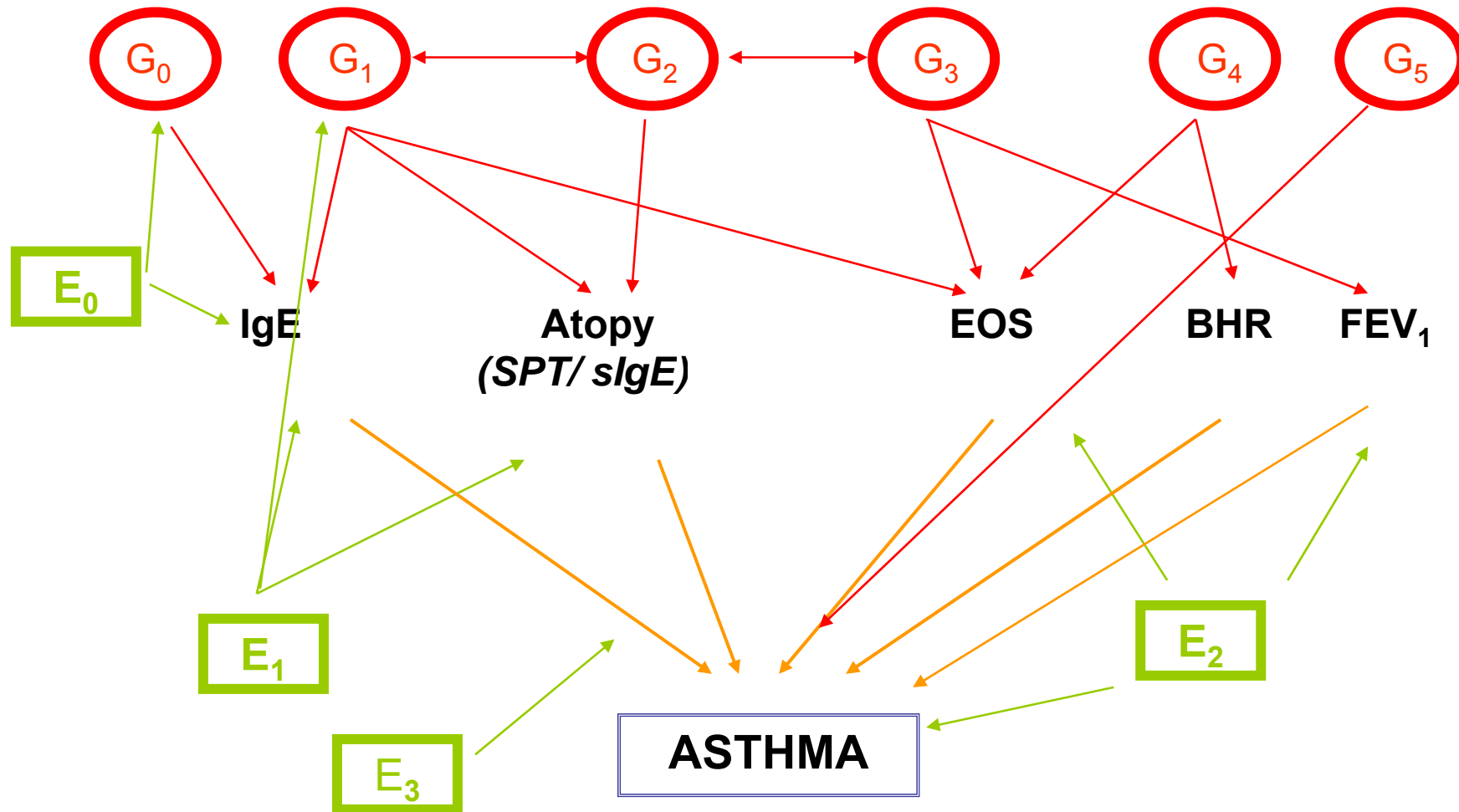
Fondation Jean Dausset-CEPH, Paris

A GABRIEL Consortium Large-Scale

Genome-Wide Association Study of Asthma

Moffatt M., Gut I., Demenais F. *et al.* N Eng J Med 2010

Biological & physiological « intermediate » phenotypes involved in the pathological process



GABRIEL Phase 2

Study type	Cases	Controls
19 studies contributing Childhood-onset asthma cases (including MRCA, MAGICs)	6,783	7,720
10 studies contributing Adult-onset asthma	1,947	3,669
3 studies with unknown age of onset or severe asthma	1,106	4,023
4 studies with Industrial asthma	529	698
TOTAL	10,365	16,110

Asthma: Doctor Diagnosed Asthma or self reported

Childhood onset / Adult Onset asthma using cutoff of 16 yrs

Controls: unaffecteds (not selected as « hypernormal »)



CNG, Paris:

Genotyping using Illumina
Human 610 Quad array
Data processing of
> 15 Billions genotypes

WTCHG, Oxford:

Centralised data analysis by
study and age of asthma onset
36 genome-wide analyses

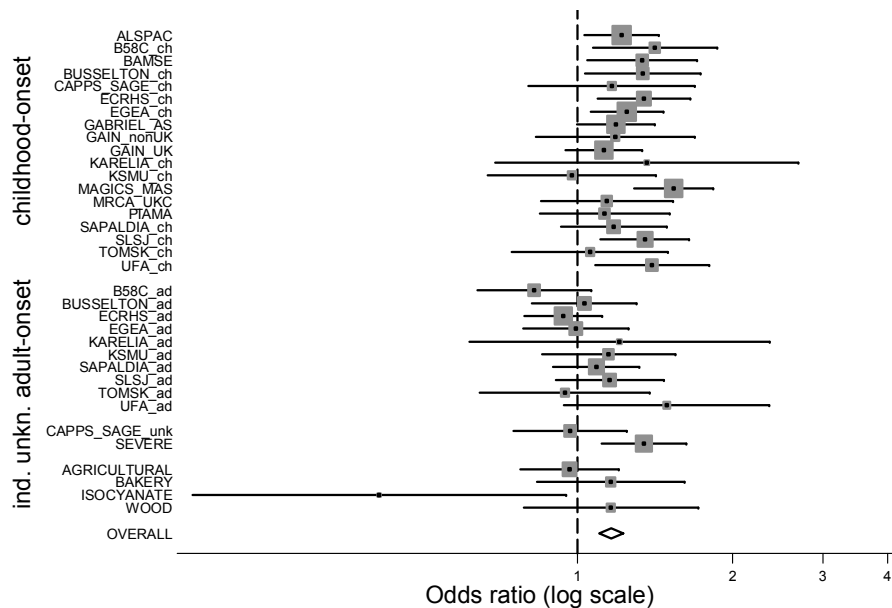
Imputation to 2.5M SNPs

INSERM, Paris:

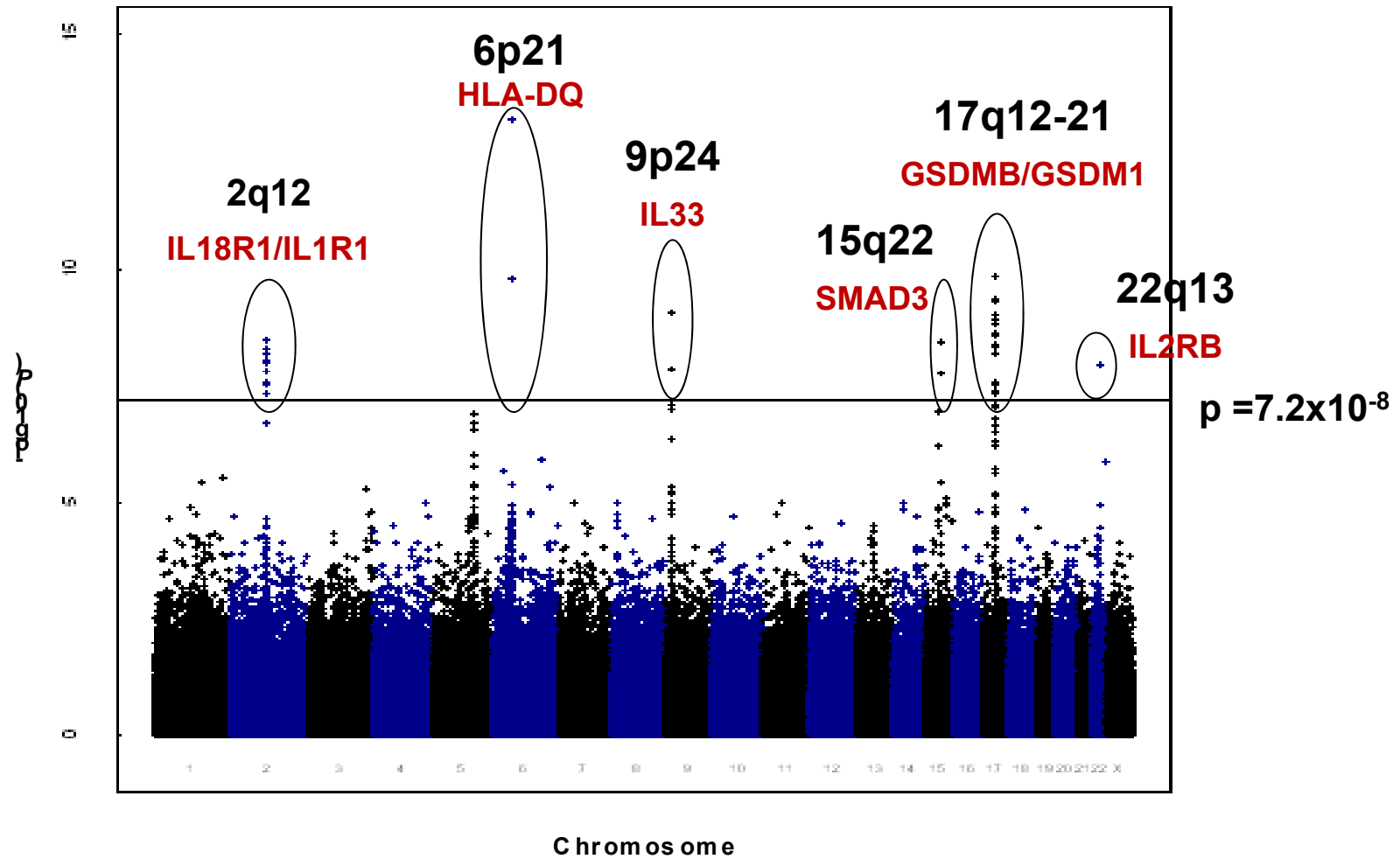
Meta-analysis of asthma

St George's, University of London

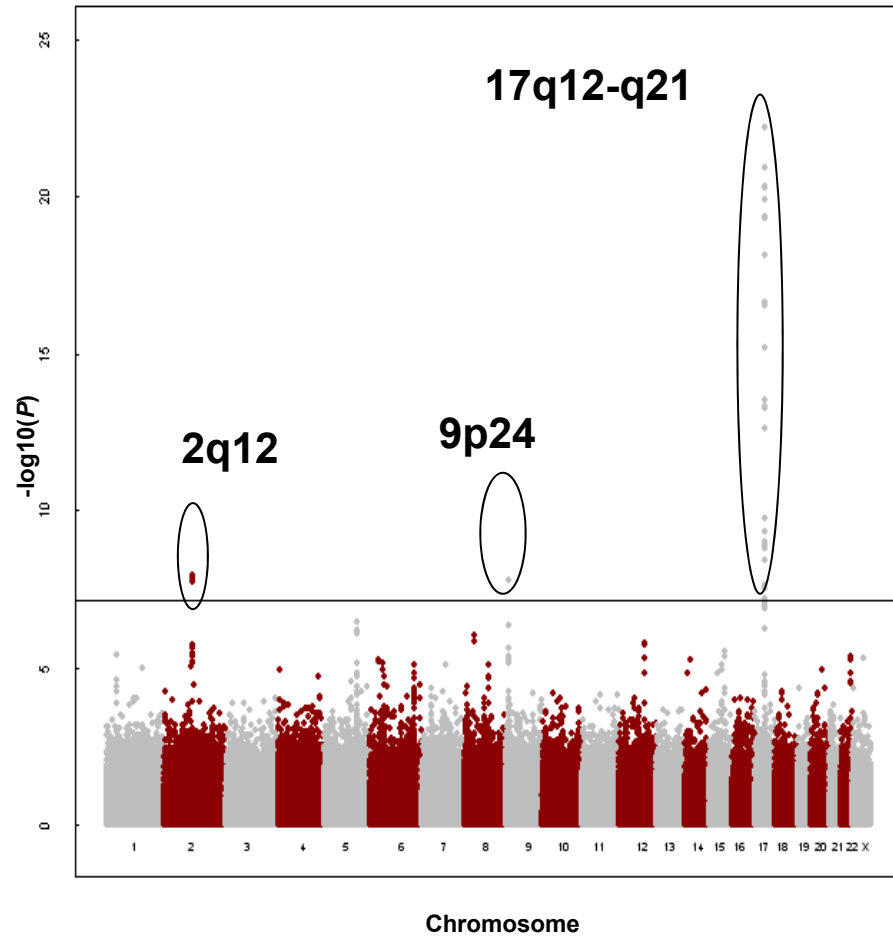
Meta-analysis of IgE



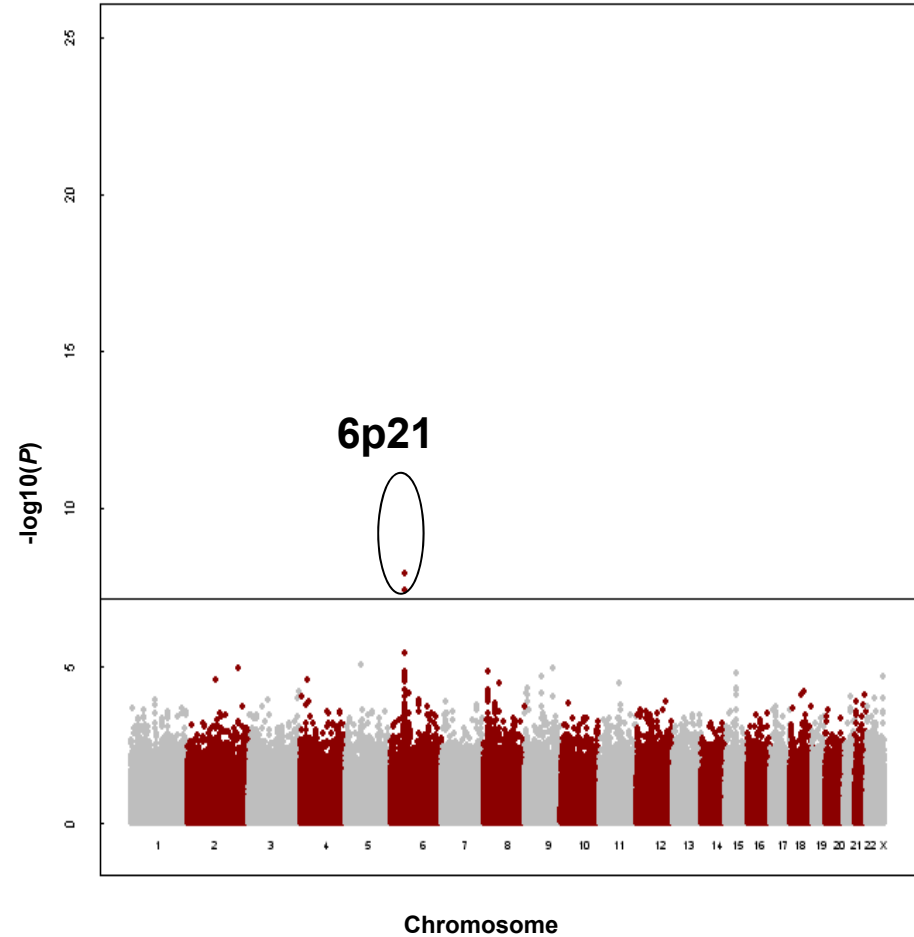
Manhattan Plots for meta-analysis of asthma GWAS (36 studies) using random effects model



Childhood onset asthma (19 studies) *random effects model*

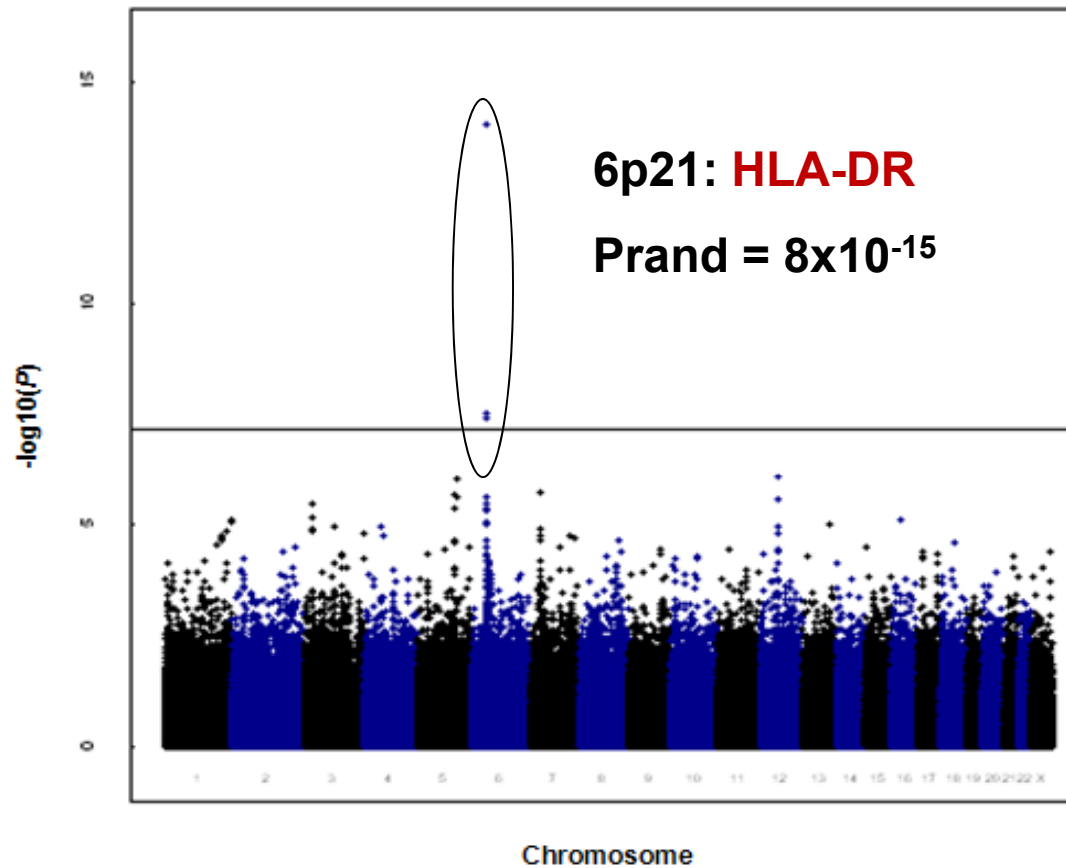


Adult onset asthma (10 studies) *random effects model*



Meta-analysis for IgE levels

7087 asthmatics / 7667 controls have IgE measurements
16 studies in each set of cases & controls



IgE Meta-analysis

HLA-DR & Other IgE Top Hits

Chrom	Gene	Marker	IgE <i>P</i> random	IgE <i>P</i> fixed	<i>P</i> Heterog
1	<i>FCER1A</i>	rs2252226	6.6×10^{-5}	1.9×10^{-7}	0.05
5	<i>IL13</i>	rs20541	1.0×10^{-6}	9.4×10^{-8}	0.29
6	<i>HLA-DR</i>	rs9271300	8.3×10^{-15}	8.3×10^{-15}	0.76
12	<i>STAT6</i>	rs167769	8.5×10^{-7}	2.6×10^{-10}	0.06
16	<i>IL4-R/IL21R</i>	rs1859308	8.2×10^{-6}	2.6×10^{-7}	0.20

**GW significant result in MHC region
& replication of published results**

IgE vs Asthma Results

Association of IgE Top Hits with Asthma

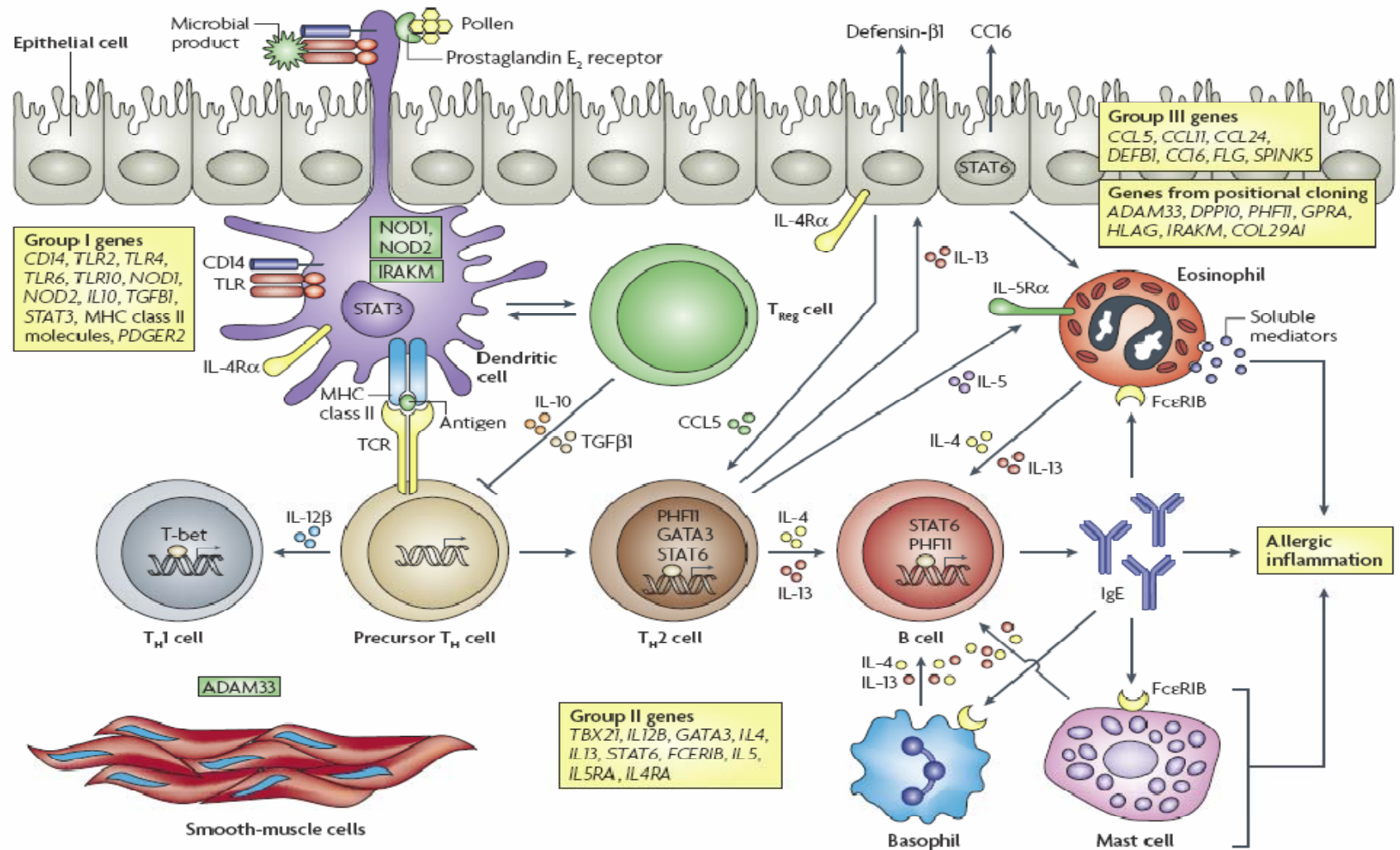
Chr	Gene	Marker	IgE <i>P</i> random	Asthma <i>P</i> random
1	<i>FCER1A</i>	rs2252226	6.6×10^{-5}	0.47
5	<i>IL13</i>	rs20541	1.0×10^{-6}	2.8×10^{-7}
6	<i>HLA-DR</i>	rs9271300	8.3×10^{-15}	0.32
12	<i>STAT6</i>	rs167769	8.5×10^{-7}	7.2×10^{-4}
16	<i>IL4-R/IL21R</i>	rs1859308	8.2×10^{-6}	0.35

Association of Asthma Top Hits with IgE

Chr	Gene	Marker	Asthma <i>P</i> random	IgE <i>P</i> random
2	<i>IL18R1</i>	<i>rs3771166</i>	3.4×10^{-9}	0.20
6	<i>HLA-DQA</i>	<i>rs9273349</i>	7.0×10^{-14}	5.4×10^{-5}
9	<i>IL33</i>	<i>rs1342326</i>	9.2×10^{-10}	0.60
15	<i>SMAD3</i>	<i>rs744910</i>	3.9×10^{-9}	0.15
17	<i>GSDMB</i>	<i>rs2305480</i>	9.6×10^{-8}	0.06
17	<i>GSDM1</i>	<i>rs3894194</i>	4.6×10^{-9}	0.30
22	<i>IL2RB</i>	<i>rs2284033</i>	1.2×10^{-8}	0.39
5	<i>SLC22A5</i>	<i>rs2073643</i>	2.2×10^{-7}	0.02
5	<i>IL13</i>	<i>rs1295686</i>	1.4×10^{-7}	2.4×10^{-6}
15	<i>RORA</i>	<i>rs11071559</i>	1.1×10^{-7}	0.03

ASTHMA SUSCEPTIBILITY GENES

PHYSIOLOGICAL PATHWAYS



SNPs & Risk of disease

Individual Risk of asthma predicted by the SNPs

→ SNPs were not effective in classifying individuals as asthmatics or non-asthmatics

Childhood onset asthma using GW sig SNPs:

Sensitivity = 35% Specificity = 75%, Area under the ROC curve = 0.58

Population Attributable Risk Fraction (PARF)

→ 38% of childhood onset asthma attributable to combination of GW SNPs

Conclusions

5 loci identified by the GABRIEL GWAS

Heterogeneity between childhood/adult onset asthma mainly for chr17 loci (lower power for adult-onset studies)

Some of the gene products expressed in bronchial epithelium & seem to communicate epithelial damage to adaptative immune system

But a lot of work still needed to better characterize these loci (→ causal SNPs) & understand their function

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.

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