Genetic study in asthma

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호흡기내과 김우진

- Genetic study in general
- Genome-wide association studies in asthma

Genetic study

- Genetic vs. Genomic study
- Genetic epidemiology
  - Genetic association (genetic variation)
- Gene expression in various cells
  - Protein -> Metabolism

Genome

Epigenome

Transcriptome

Proteome

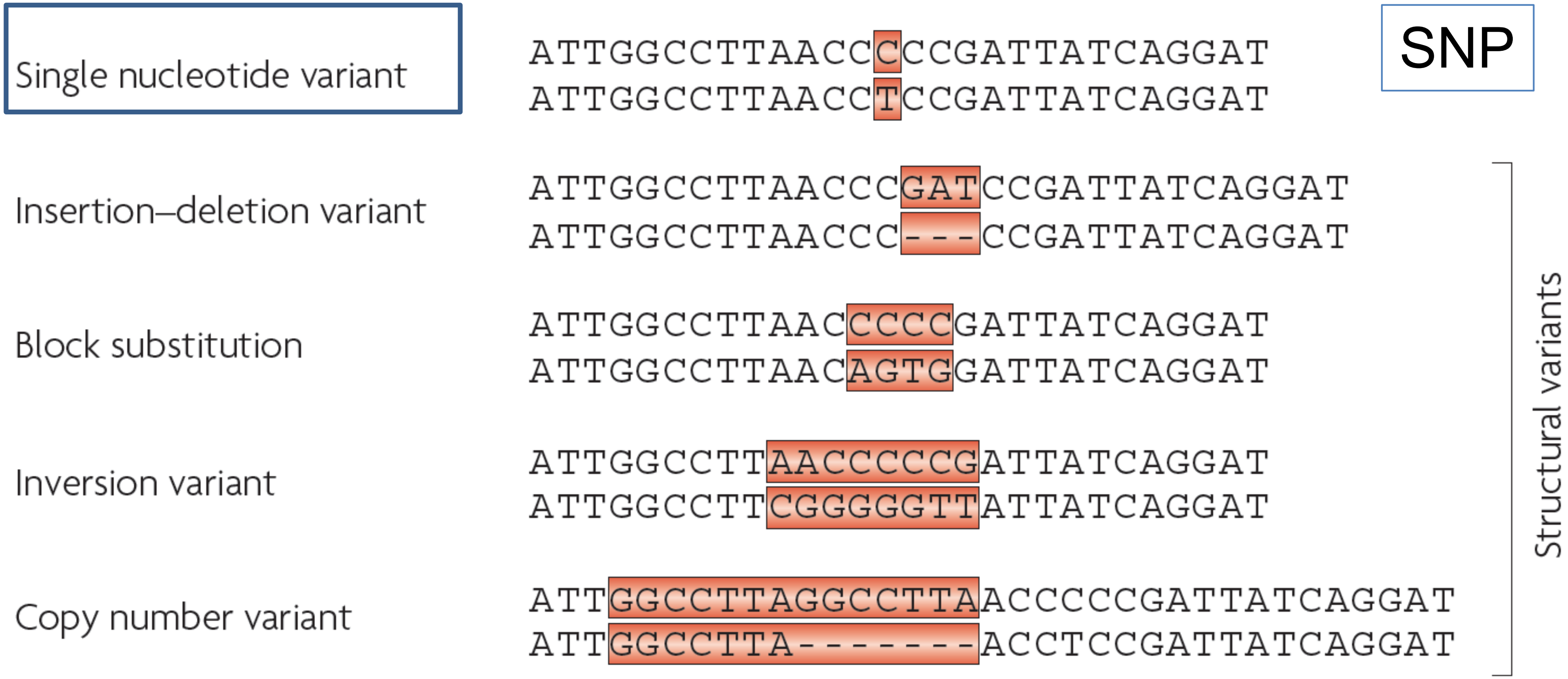
Metabolome

Systems biology

Genetic variation (DNA)

- Somatic mutation
  - Cancer tissue
- Germline mutation
  - Mendelian disorder
- Genetic variation
  - SNP, structural variation

Classes of human genetic variant



Single nucleotide variant

ATTGGCCTTAACCCCCGATTATCAGGAT
ATTGGCCTTAACCTCCGATTATCAGGAT

SNP

Insertion–deletion variant

ATTGGCCTTAACCCGATCCGATTATCAGGAT
ATTGGCCTTAACCC---CCGATTATCAGGAT

Block substitution

ATTGGCCTTAACCCCCGATTATCAGGAT
ATTGGCCTTAACAGTGGATTATCAGGAT

Inversion variant

ATTGGCCTTAACCCCCGATTATCAGGAT
ATTGGCCTTCGGGGTTATTATCAGGAT

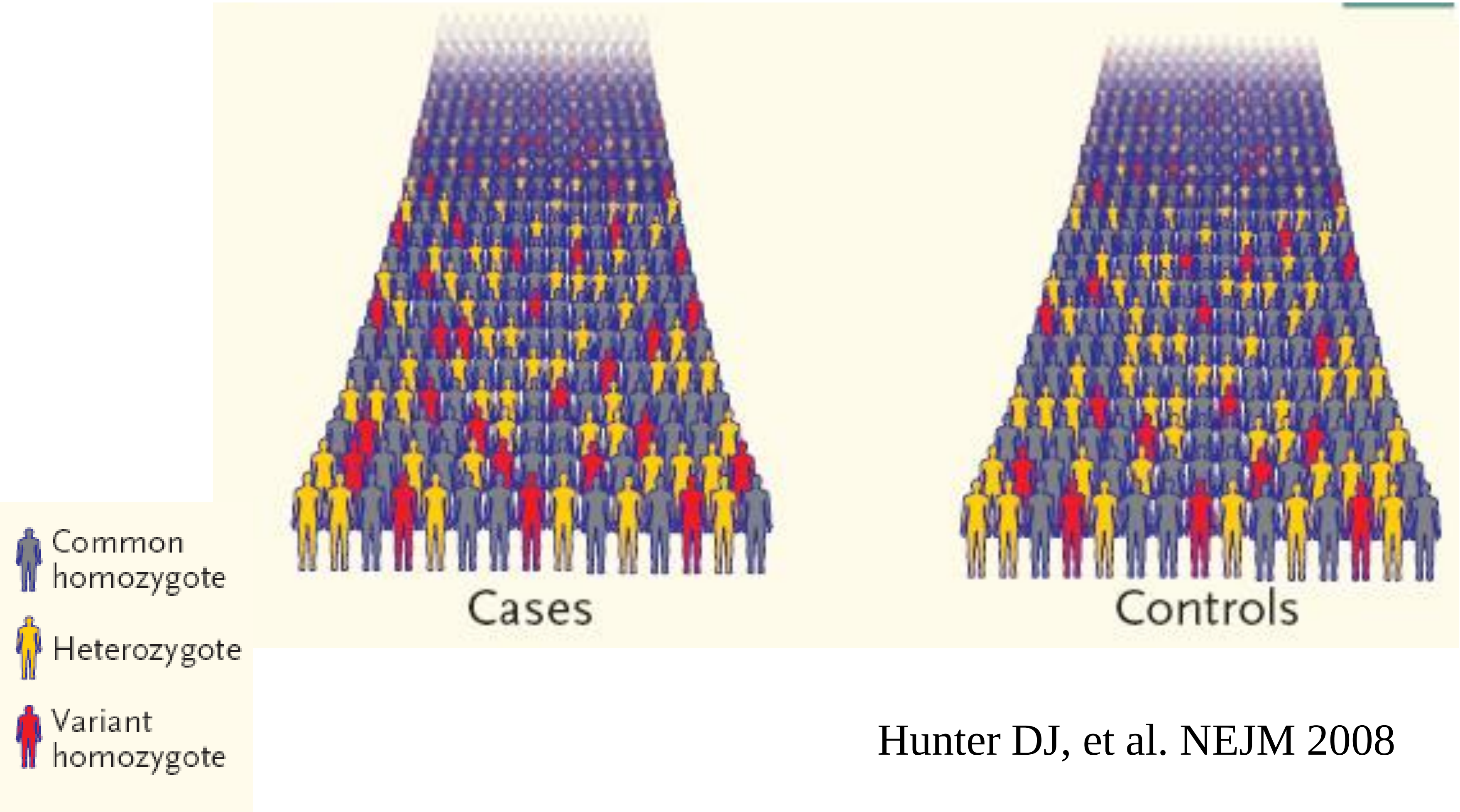
Copy number variant

ATTGGCCTTAGGCCTTAACCCCCGATTATCAGGAT
ATTGGCCTTA-------ACCTCCGATTATCAGGAT

Structural variants

Nature reviews genetics 2009;10

Genetic association study using SNP



Hunter DJ, et al. NEJM 2008

Genetic epidemiology

Flow of research

Disease characteristics: Descriptive epidemiology
Familial clustering: Family aggregation studies
Genetic or environmental: Twin/adoption/half-sibling/migrant studies
Mode of inheritance: Segregation analysis
Disease susceptibility loci: Linkage analysis
Disease susceptibility markers: Association studies

Genome-wide association study

Whole genome sequencing

Role of genomic studies

- Candidate gene discovery
  - Therapeutic target
  - Biomarker
  - Tailored therapy

Heritability

Any particular phenotype can be modelled as the sum of genetic and environmental effects:[4]

Phenotype (P) = Genotype (G) + Environment (E).

Likewise the variance in the trait – Var (P) – is the sum of genetic effects as follows:

$$\mathrm{Var}(P) = \mathrm{Var}(G) + \mathrm{Var}(E) + 2\,\mathrm{Cov}(G,E).$$

In a planned experiment Cov(G,E) can be controlled and held at 0. In this case, heritability is defined as:

$$H^2 = \frac{Var(G)}{Var(P)}$$

The proportion of the genetic variance to the total phenotypic variance in a defined population.

Hypothesis for association studies

- Genetic variation
  - Risk factor
- Disease susceptibility/phenotype
  - Outcome
- Known risk factors
  - Covariate

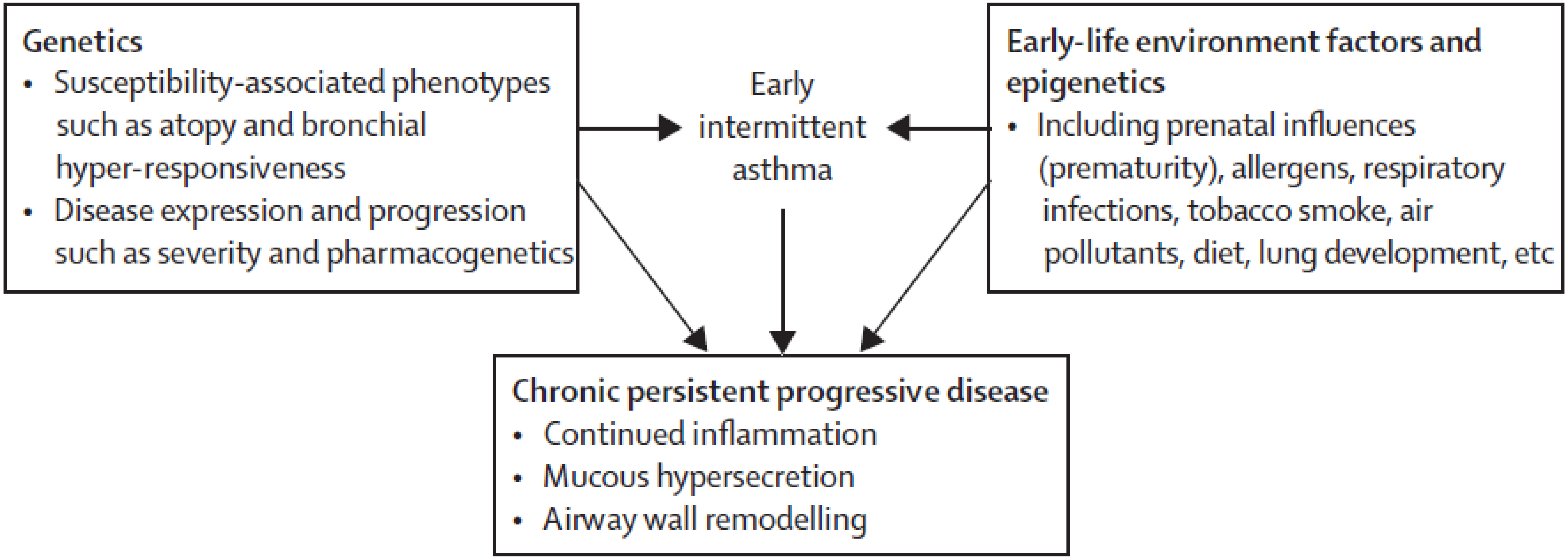
Genetic association study

- Statistically significant association
  - $P < 0.05$
  - Power?
    - MAF, OR, sample size
  - False positive (multiple test, stratification)
  - Bias

Genome-wide association study

- N more than thousands
- $P < 5 \times 10^{-8}$
- Population stratification adjustment
- Allele frequency more than 5%
    - Technical issues

Asthma pathogenesis and GWAS



Genetics

- Susceptibility-associated phenotypes such as atopy and bronchial hyper-responsiveness
- Disease expression and progression such as severity and pharmacogenetics

Early intermittent asthma

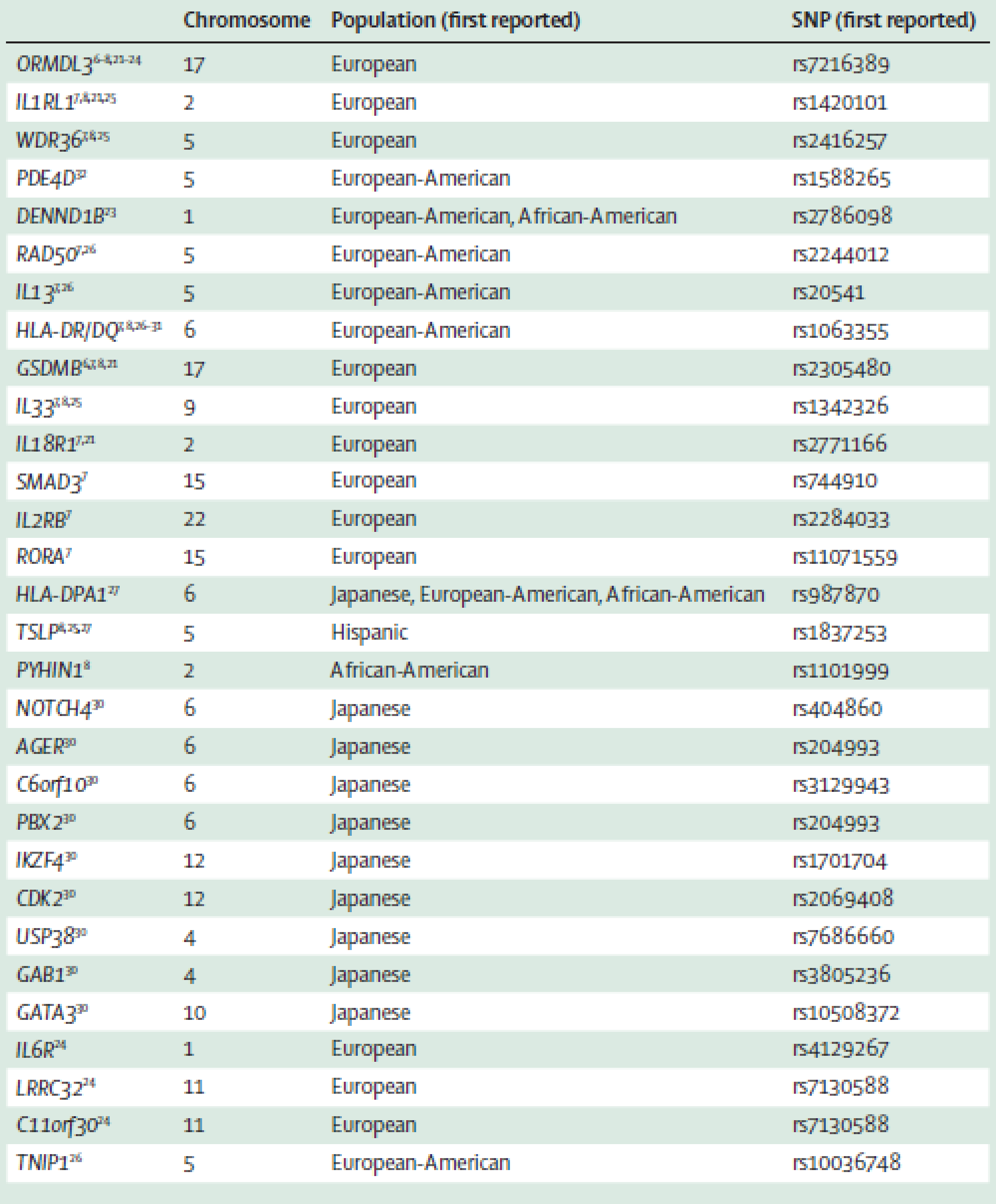
Early-life environment factors and epigenetics

- Including prenatal influences (prematurity), allergens, respiratory infections, tobacco smoke, air pollutants, diet, lung development, etc

Chronic persistent progressive disease

- Continued inflammation
- Mucous hypersecretion
- Airway wall remodelling

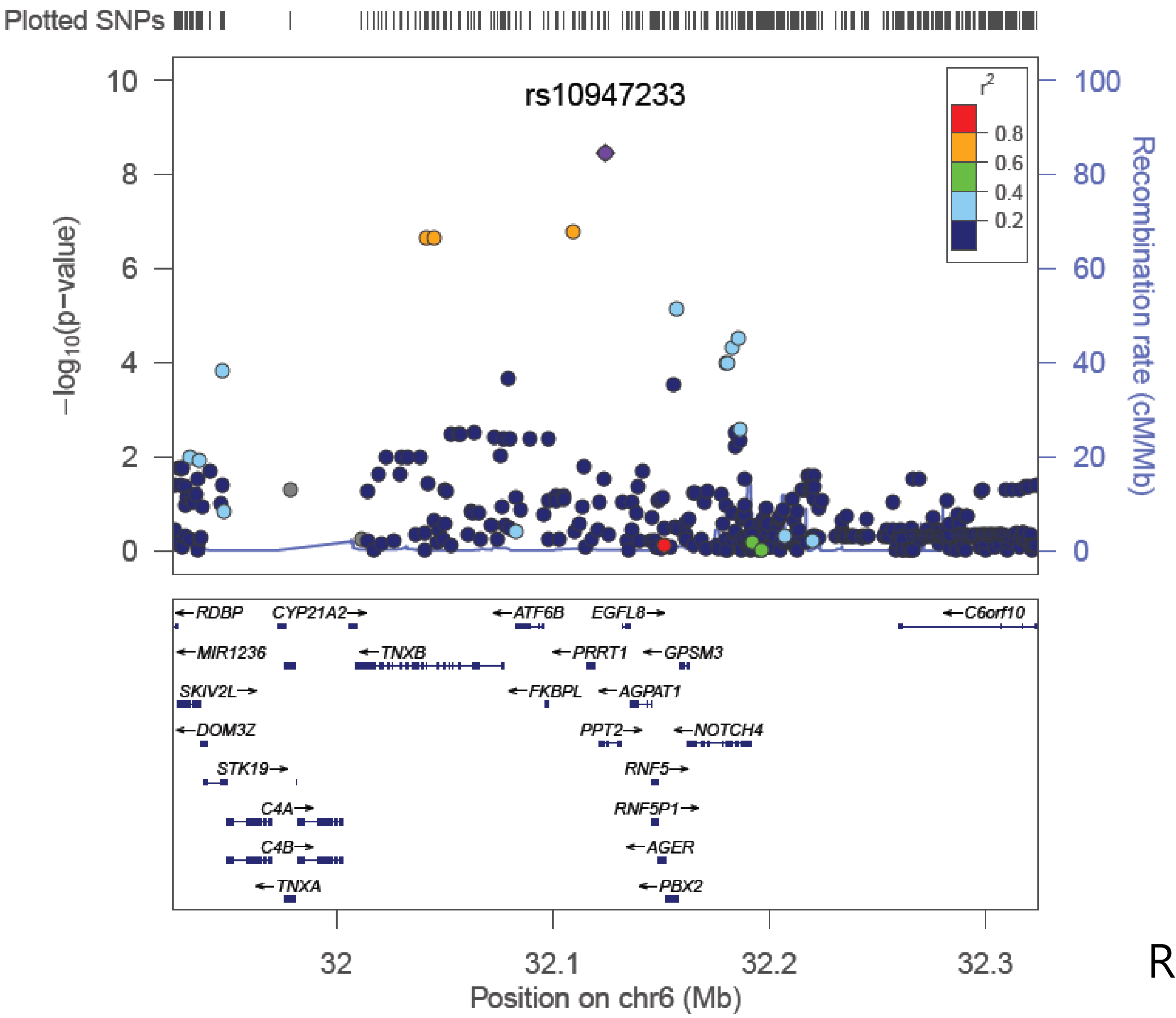
Genome-wide significant loci for asthma susceptibility



	Chromosome	Population (first reported)	SNP (first reported)
ORMDL3[6–8,21–24]	17	European	rs7216389
IL1RL1[7,8,21,25]	2	European	rs1420101
WDR36[7,8,25]	5	European	rs2416257
PDE4D[32]	5	European-American	rs1588265
DENND1B[23]	1	European-American, African-American	rs2786098
RAD50[7,26]	5	European-American	rs2244012
IL13[7,26]	5	European-American	rs20541
HLA-DR/DQ[7,8,26–31]	6	European-American	rs1063355
GSDMB[6,7,8,21]	17	European	rs2305480
IL33[7,8,25]	9	European	rs1342326
IL18R1[7,21]	2	European	rs2771166
SMAD3[7]	15	European	rs744910
IL2RB[7]	22	European	rs2284033
RORA[7]	15	European	rs11071559
HLA-DPA1[27]	6	Japanese, European-American, African-American	rs987870
TSLP[8,25,27]	5	Hispanic	rs1837253
PYHIN1[8]	2	African-American	rs1101999
NOTCH4[30]	6	Japanese	rs404860
AGER[30]	6	Japanese	rs204993
C6orf10[30]	6	Japanese	rs3129943
PBX2[30]	6	Japanese	rs204993
IKZF4[30]	12	Japanese	rs1701704
CDK2[30]	12	Japanese	rs2069408
USP38[30]	4	Japanese	rs7686660
GAB1[30]	4	Japanese	rs3805236
GATA3[30]	10	Japanese	rs10508372
IL6R[24]	1	European	rs4129267
LRRC32[24]	11	European	rs7130588
C11orf30[24]	11	European	rs7130588
TNIP1[26]	5	European-American	rs10036748

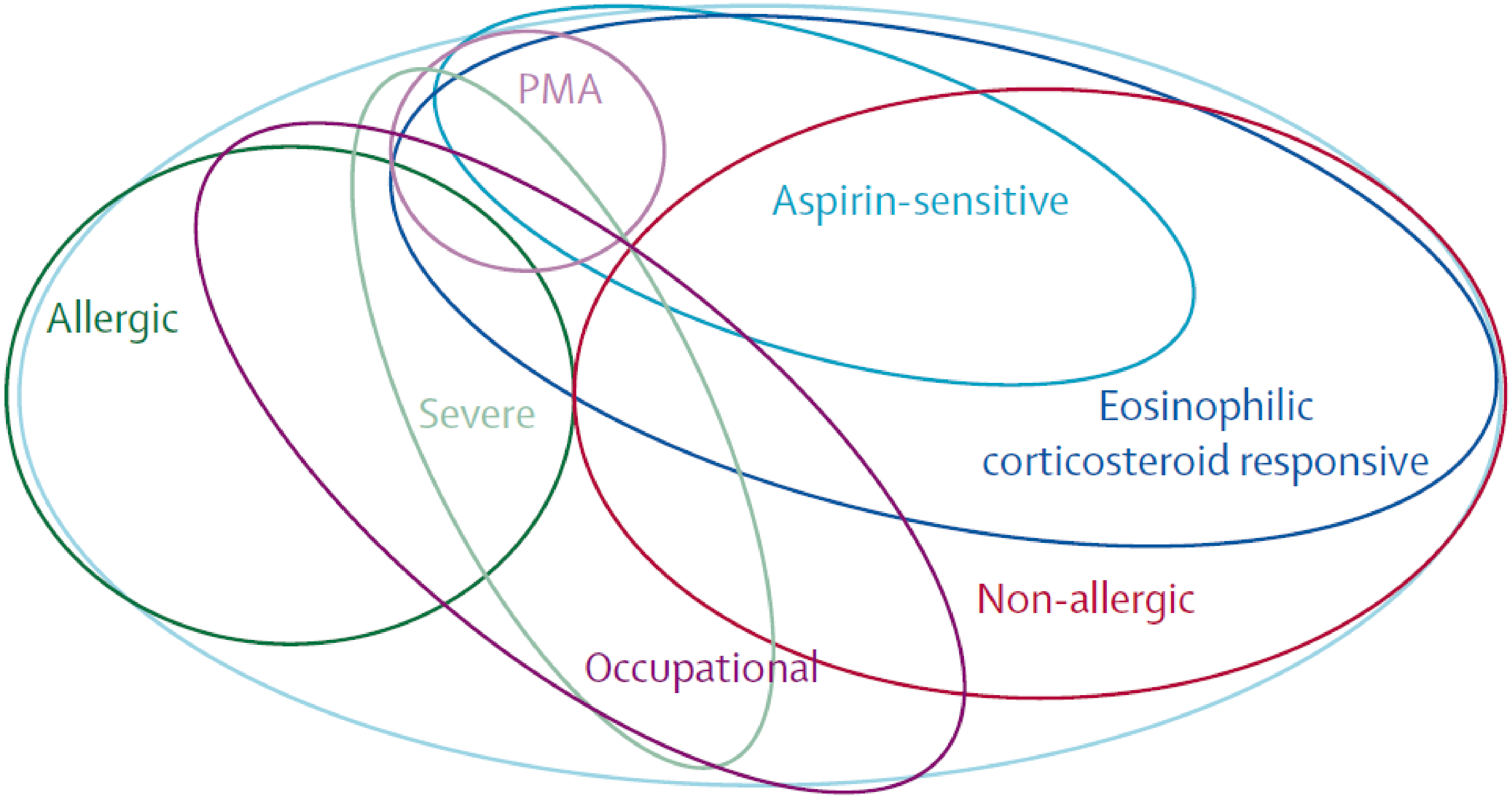
Lancet 2014

6p21 (*AGER*)



Respirology 2014

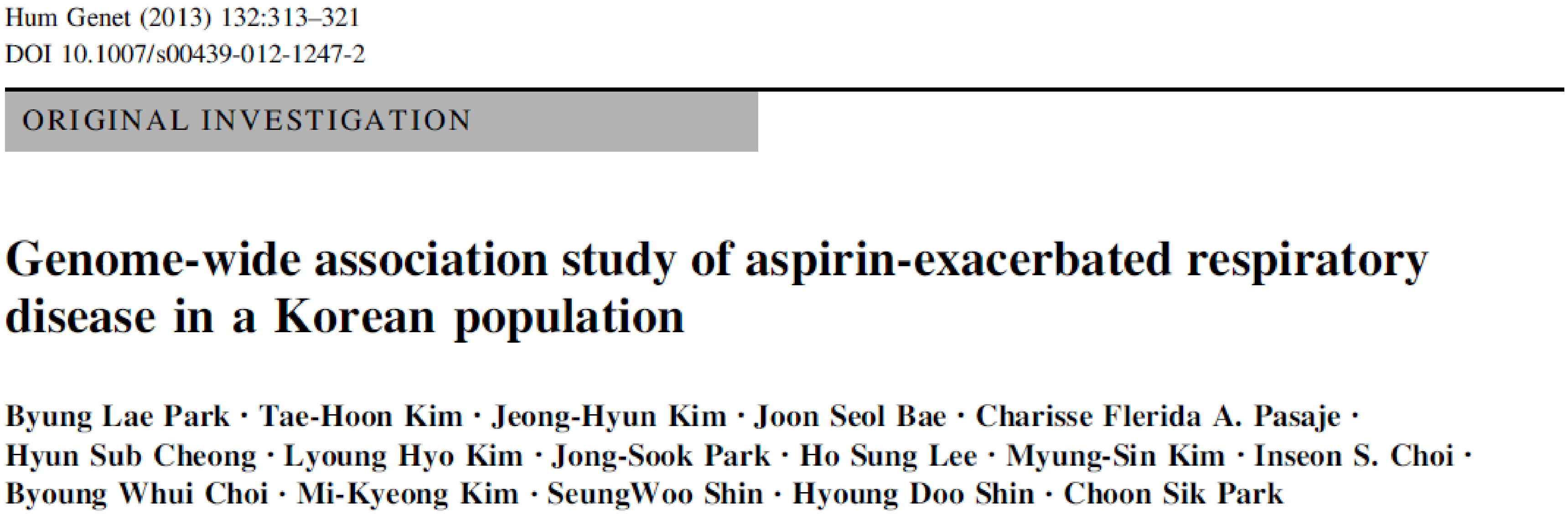
Asthma heterogeneity



Wenzel SE, et al. Lancet 2006

GWAS with subtype

- Aspirin-exacerbated



Hum Genet (2013) 132:313–321
DOI 10.1007/s00439-012-1247-2

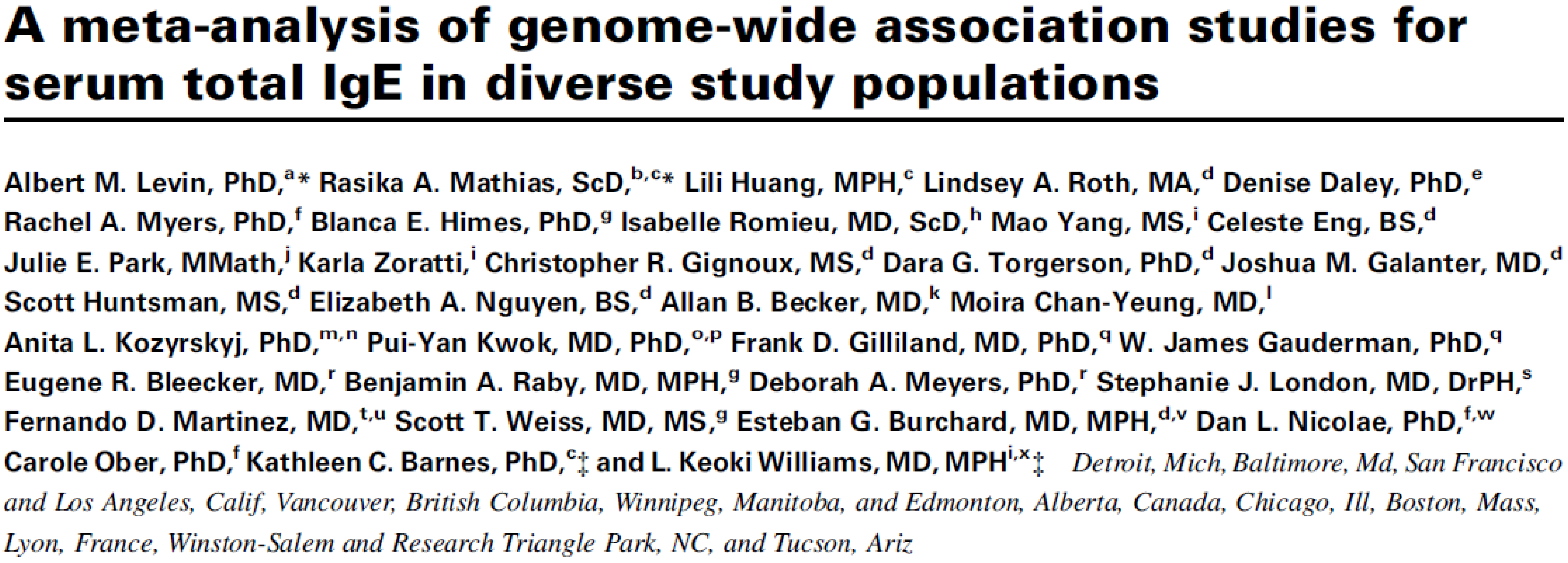
ORIGINAL INVESTIGATION

Genome-wide association study of aspirin-exacerbated respiratory disease in a Korean population

Byung Lae Park · Tae-Hoon Kim · Jeong-Hyun Kim · Joon Seol Bae · Charisse Flerida A. Pasaje · Hyun Sub Cheong · Lyoung Hyo Kim · Jong-Sook Park · Ho Sung Lee · Myung-Sin Kim · Inseon S. Choi · Byoung Whui Choi · Mi-Kyeong Kim · SeungWoo Shin · Hyoung Doo Shin · Choon Sik Park

GWAS with phenotype

- Eosinophil count, IgE



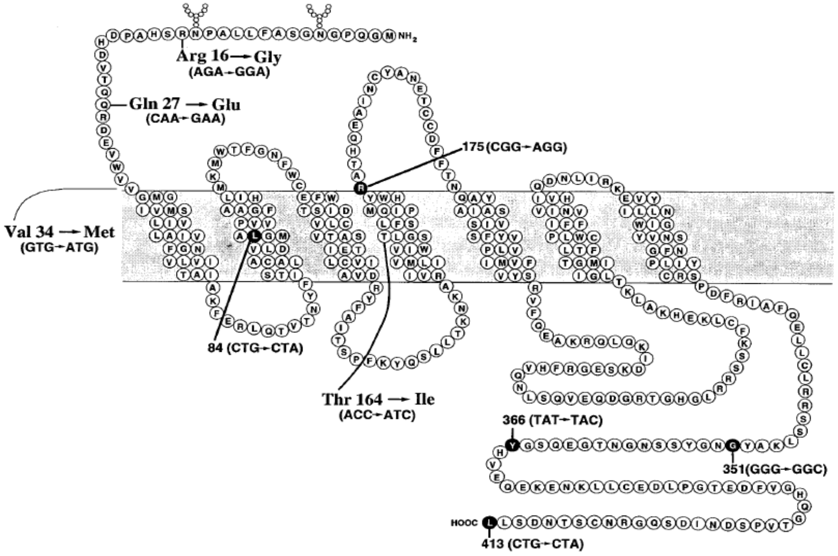
A meta-analysis of genome-wide association studies for serum total IgE in diverse study populations

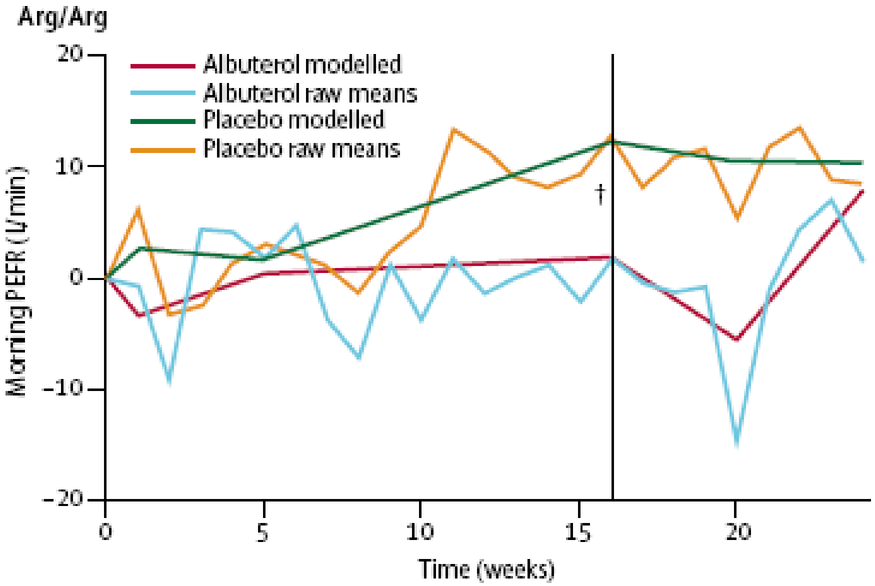
Albert M. Levin, PhD,[a]* Rasika A. Mathias, ScD,[b,c]* Lili Huang, MPH,[c] Lindsey A. Roth, MA,[d] Denise Daley, PhD,[e] Rachel A. Myers, PhD,[f] Blanca E. Himes, PhD,[g] Isabelle Romieu, MD, ScD,[h] Mao Yang, MS,[i] Celeste Eng, BS,[d] Julie E. Park, MMath,[j] Karla Zoratti,[i] Christopher R. Gignoux, MS,[d] Dara G. Torgerson, PhD,[d] Joshua M. Galanter, MD,[d] Scott Huntsman, MS,[d] Elizabeth A. Nguyen, BS,[d] Allan B. Becker, MD,[k] Moira Chan-Yeung, MD,[l] Anita L. Kozyrskyj, PhD,[m,n] Pui-Yan Kwok, MD, PhD,[o,p] Frank D. Gilliland, MD, PhD,[q] W. James Gauderman, PhD,[q] Eugene R. Bleecker, MD,[r] Benjamin A. Raby, MD, MPH,[g] Deborah A. Meyers, PhD,[r] Stephanie J. London, MD, DrPH,[s] Fernando D. Martinez, MD,[t,u] Scott T. Weiss, MD, MS,[g] Esteban G. Burchard, MD, MPH,[d,v] Dan L. Nicolae, PhD,[f,w] Carole Ober, PhD,[f] Kathleen C. Barnes, PhD,[c]‡ and L. Keoki Williams, MD, MPH[i,x]‡ *Detroit, Mich, Baltimore, Md, San Francisco and Los Angeles, Calif, Vancouver, British Columbia, Winnipeg, Manitoba, and Edmonton, Alberta, Canada, Chicago, Ill, Boston, Mass, Lyon, France, Winston-Salem and Research Triangle Park, NC, and Tucson, Ariz*

JACI 2013

Beta agonist treatment and *ADRB2*

- Beta$_2$-adrenergic receptor

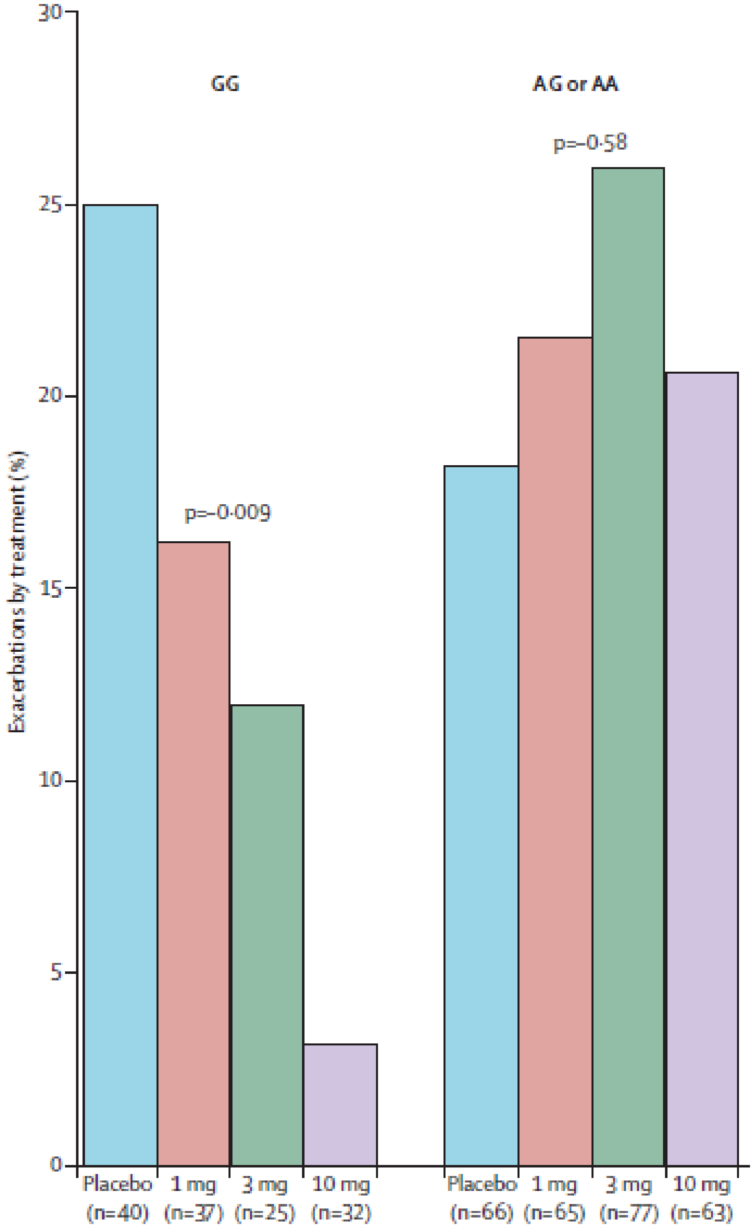




Am J Crit Care Med 1997;156:S156-62

Lancet 2004;364:1055-12

IL4R polymorphism



Anti-IL4 antagonist

Lancet 2014

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Genome-Wide Association Analysis in Asthma Subjects Identifies *SPATS2L* as a Novel Bronchodilator Response Gene

Blanca E. Himes[1,2,3]*, Xiaofeng Jiang[4], Ruoxi Hu[4], Ann C. Wu[5], Jessica A. Lasky-Su[1], Barbara J. Klanderman[3], John Ziniti[1], Jody Senter-Sylvia[1], John J. Lima[6], Charles G. Irvin[7], Stephen P. Peters[8], Deborah A. Meyers[8], Eugene R. Bleecker[8], Michiaki Kubo[9], Mayumi Tamari[9], Yusuke Nakamura[10], Stanley J. Szefler[11], Robert F. Lemanske Jr.[12], Robert S. Zeiger[13], Robert C. Strunk[14], Fernando D. Martinez[15], John P. Hanrahan[16], Gerard H. Koppelman[17], Dirkje S. Postma[18], Maartje A. E. Nieuwenhuis[18], Judith M. Vonk[19], Reynold A. Panettieri Jr.[20], Amy Markezich[21], Elliot Israel[22], Vincent J. Carey[1], Kelan G. Tantisira[1], Augusto A. Litonjua[1], Quan Lu[4], Scott T. Weiss[1,3]

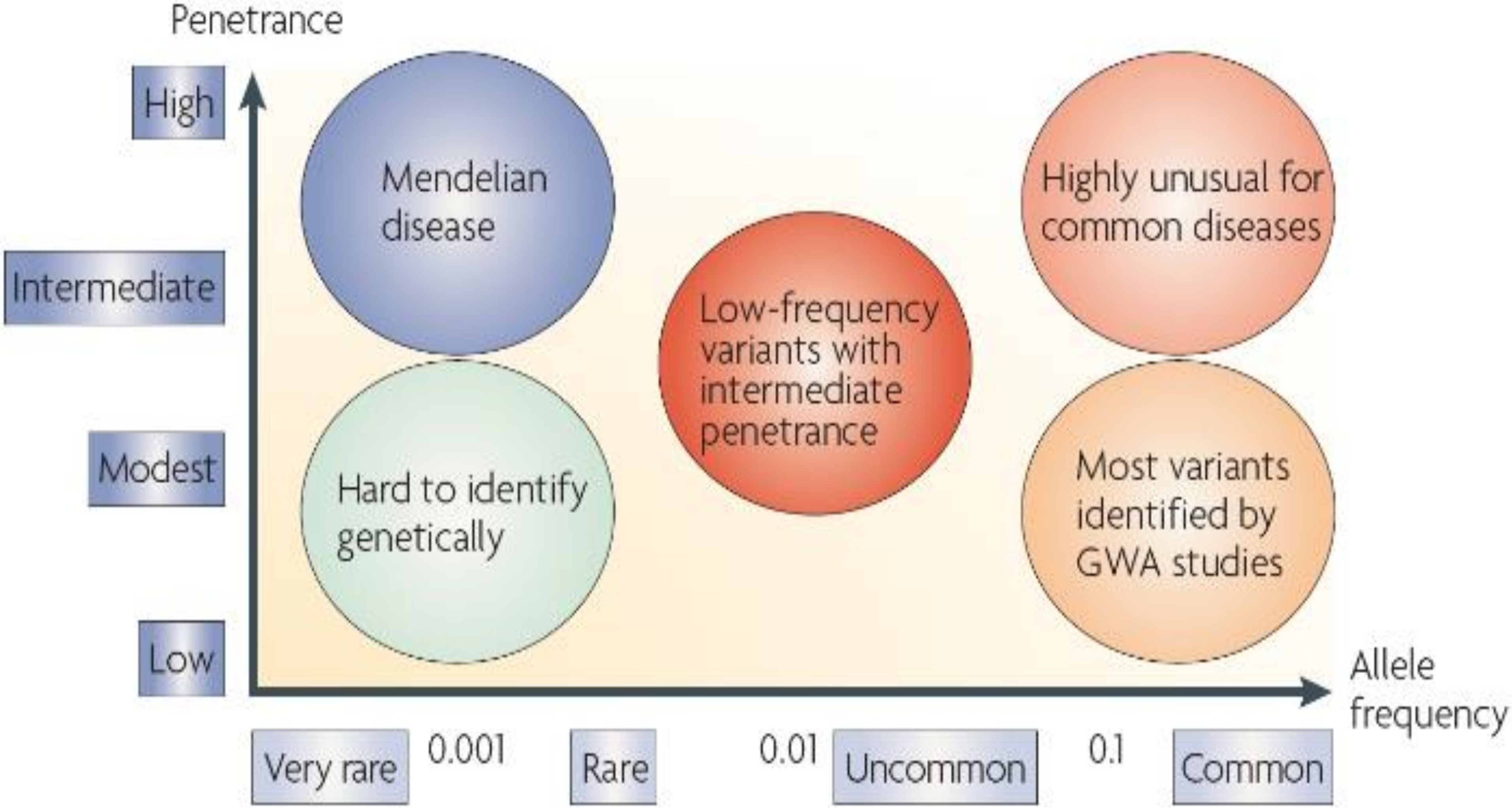
Functional Consequeces of SNPs

- SNPs in promoter/regulatory regions
  - Do not affect a.a. sequence
  - Can affect the level, location, or timing of gene expression
- SNPs in non-coding regions (most of SNPs)
  - No direct known impact on the phenotype
  - Useful as markers in population genetics and evolutionary studies

Role of genomic studies

- Candidate gene discovery
  - Therapeutic target
  - Biomarker
  - Tailored therapy

Common variant vs. Rare variant



Summary

- Genetics study in respiratory diseases
  - Genome-wide association study
  - Novel candidate genes
  - Replication studies and functional studies are on-going
  - GWAS with various phenotypes
    - Drug response associated genetic variants