

Genetics of Blood Pressure and Hypertension

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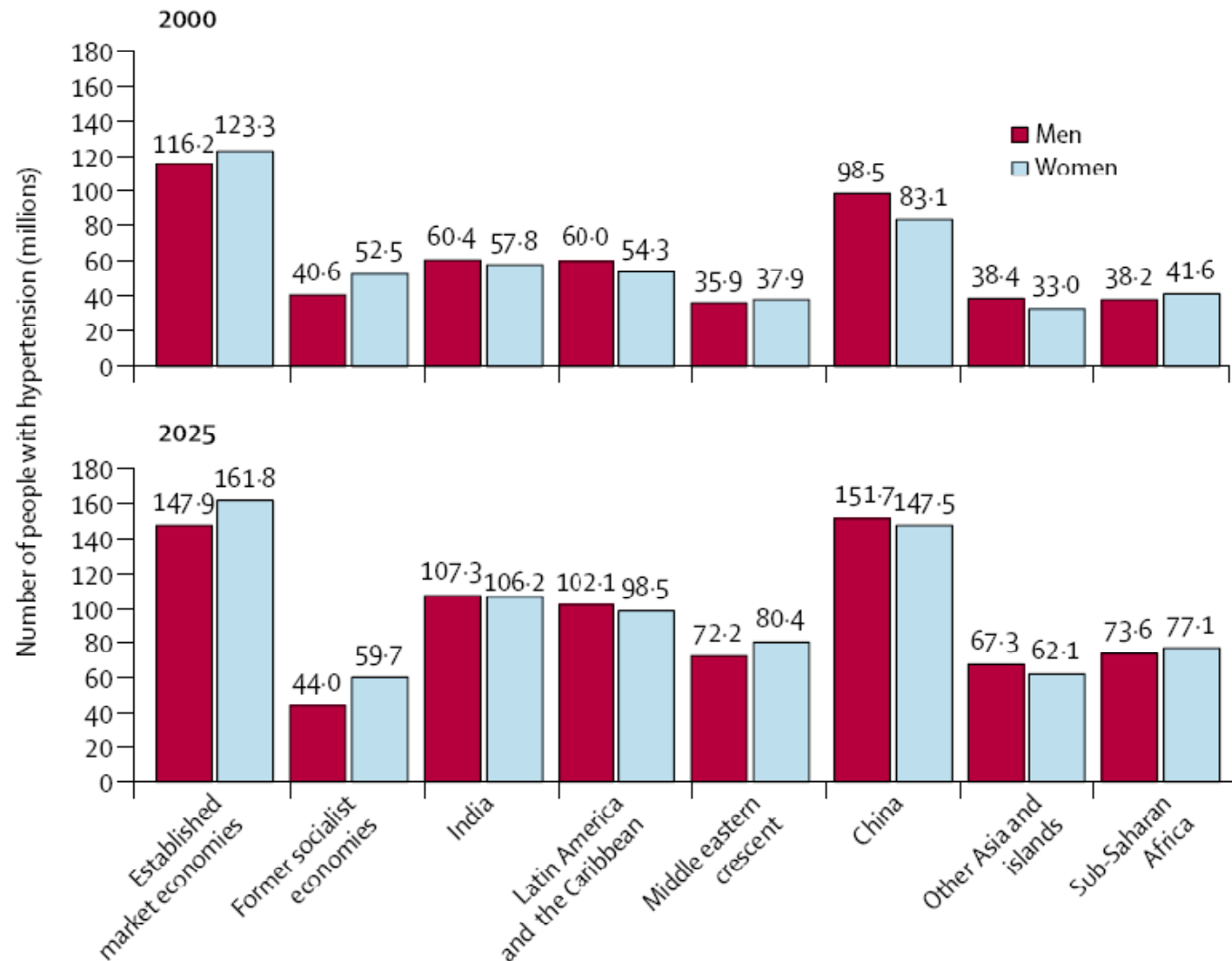
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Overview

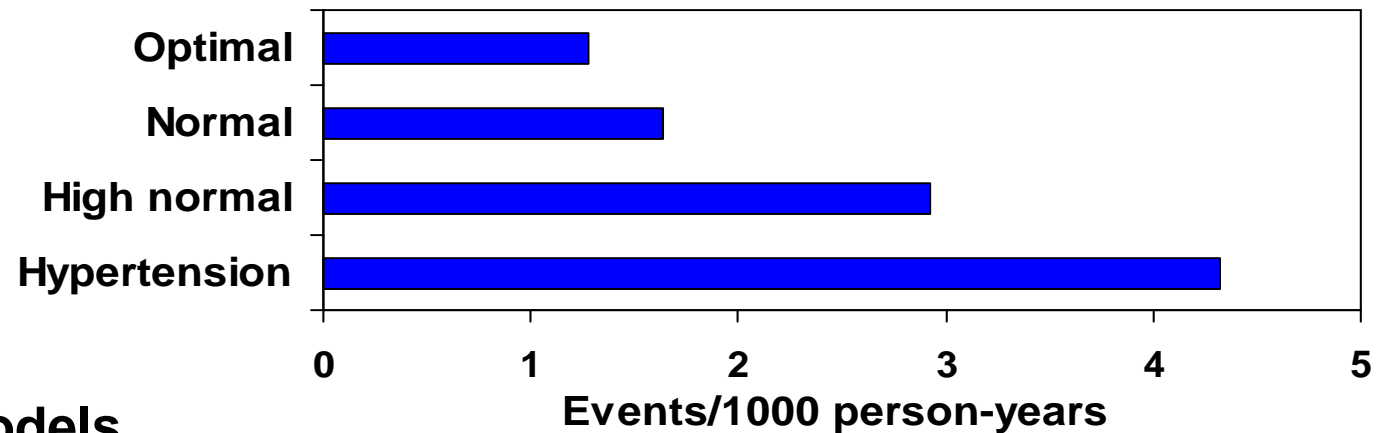
- Significance of elevated blood pressure
- Heritability of elevated blood pressure
- Genetic variation
- Candidate gene studies
- Genome-wide association studies
- Potential for improvement
- Future perspectives

Prevalence of Hypertension



BP & Cardiovascular Disease

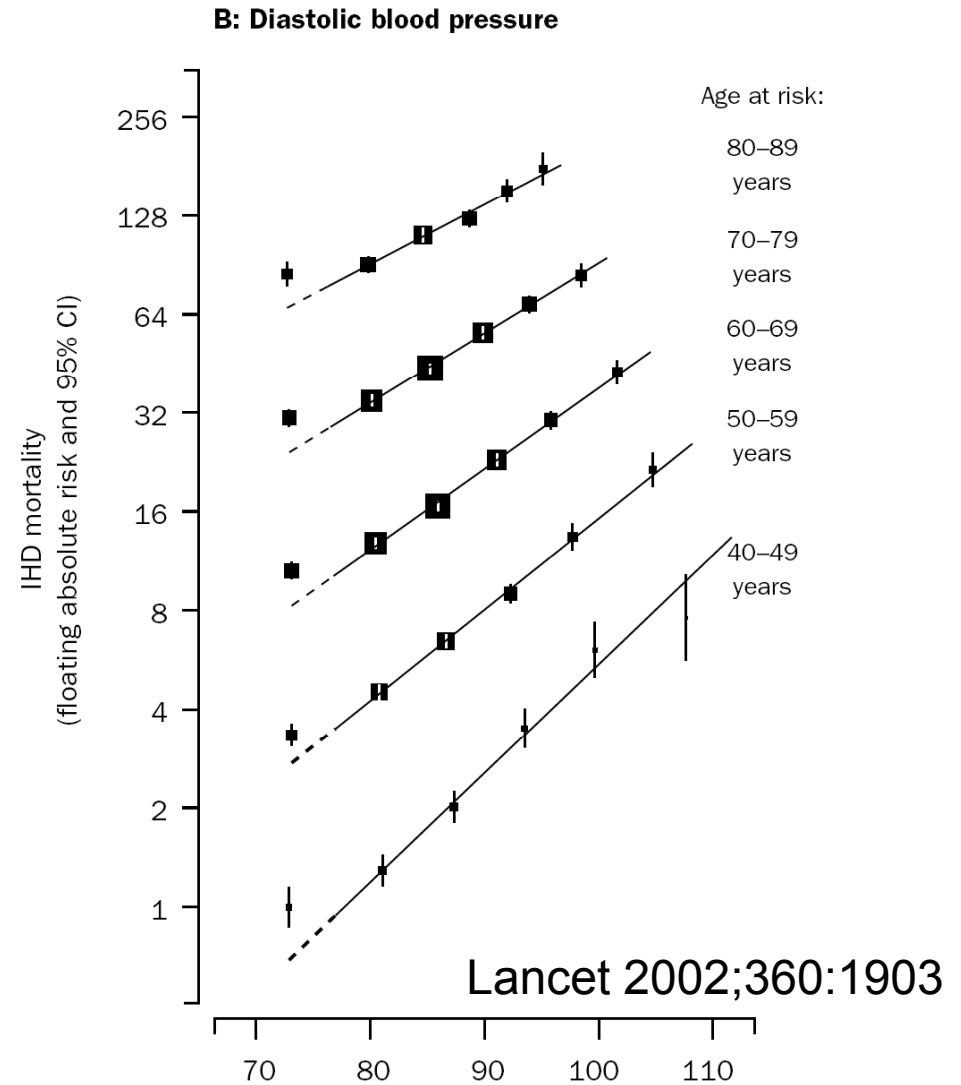
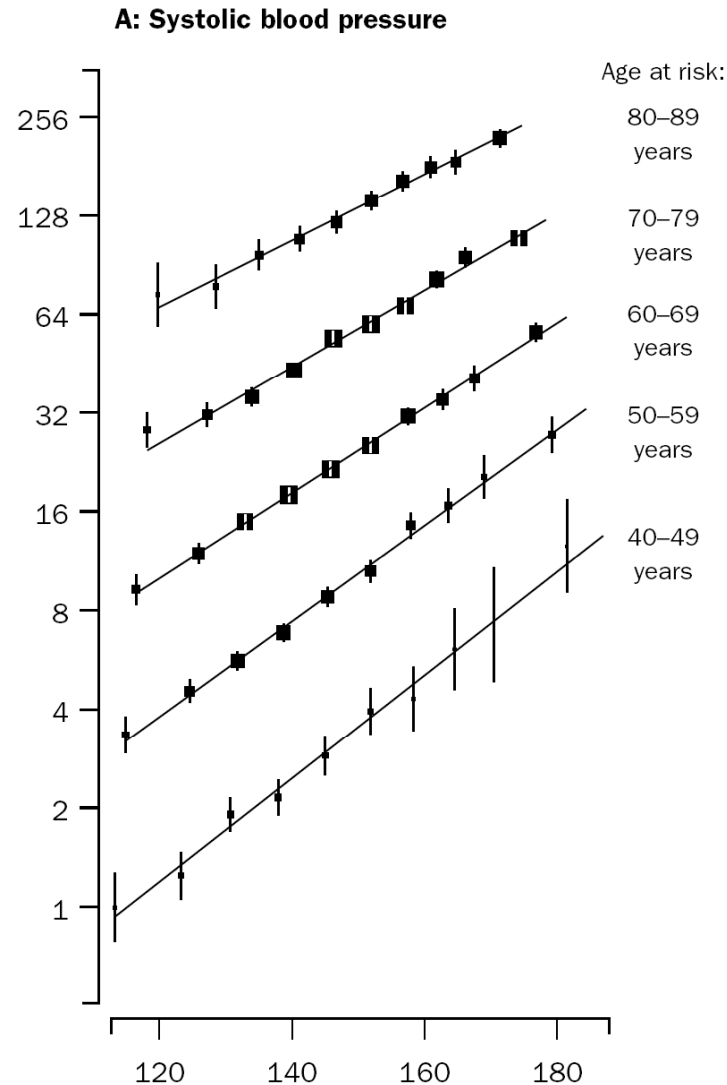
Age adjusted incidences



Cox regression models

| | Optimal N=12549 | Normal N=11326 | High normal N=4988 | Hypertension N=10459 |
|------------------|--------------------|-------------------|-----------------------|-------------------------|
| CV events | 134 | 176 | 159 | 513 |
| Age-adjusted | 0.44 (0.4-0.6) | 0.56 (0.5-0.7) | 1.0 | 1.41 (1.2-1.7) |
| Multivariable | 0.51 (0.4-0.6) | 0.61 (0.5-0.8) | 1.0 | 1.30 (1.1-1.6) |

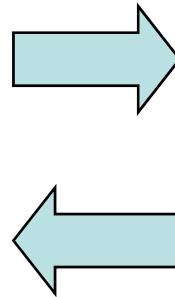
BP & Cardiovascular Disease



Pathogenesis of Hypertension

Lifestyle/environment

- Obesity
- Insulin resistance
- Dyslipidemia
- Inflammation



Genetics

- 30-60% of BP variability
- Many studies, but few consistent findings
- Where are all the genes?

Blood Pressure Heritability

Blood pressure heritability estimates from two large family studies:

| | Systolic BP | Diastolic BP |
|-------------------------|--------------------|---------------------|
| Framingham Study | | |
| Single examination | 0.42 | 0.39 |
| Long-term phenotype | 0.57 | 0.56 |
| GRAPHIC Study | | |
| Mean 24-hour BP | 0.63 | 0.68 |

- High heritability estimates for blood pressure, similar to other cardiovascular risk factors
- Multiple blood pressure measurements provide higher heritability estimates than single blood pressure measurements

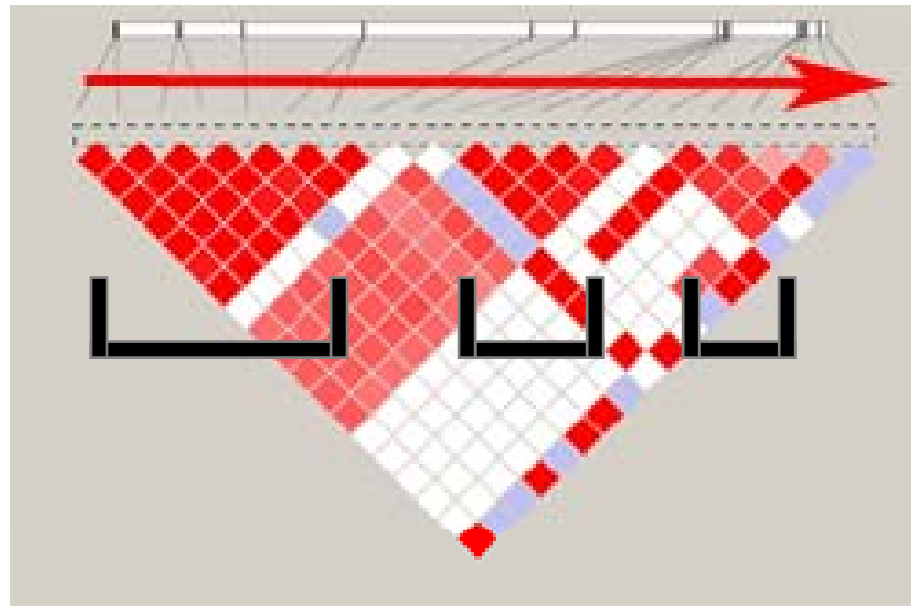
Levy et al. Hypertension 2000;36:477
Tobin et al. Circulation 2005;112:3423

Genetic Variation

- SNP = Single Nucleotide Polymorphism
 - Person 1: ACTGTCTGACTG
 - Person 2: ACTGTCTGACTT
- Alleles: G versus T
- Genotypes: GG versus GT versus TT
- Association: Differences in trait by genotype
- Other forms of genetic variation

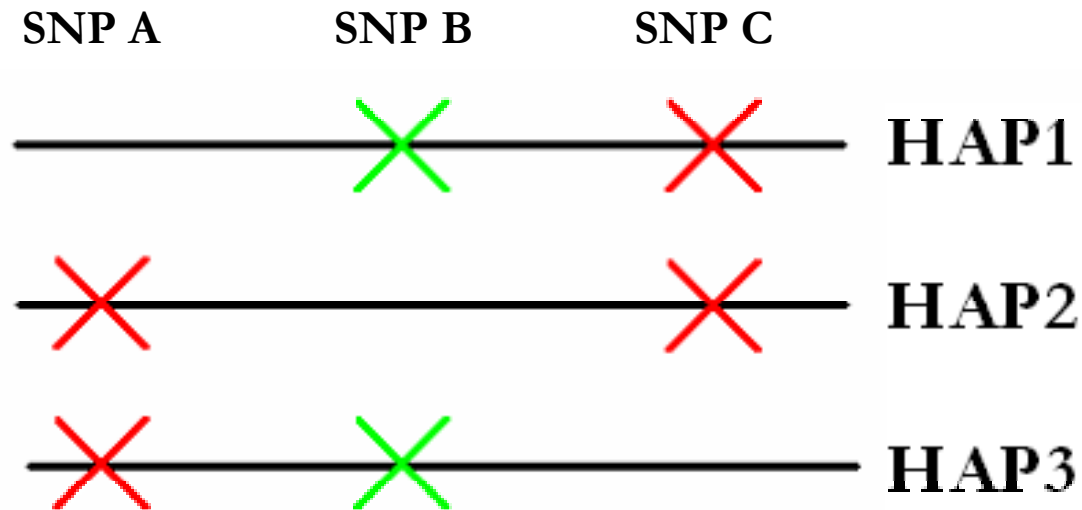
Genetic Variation

- Linkage disequilibrium:
“The tendency of alleles located close to each other on the same chromosome to be inherited together more frequently than expected.”

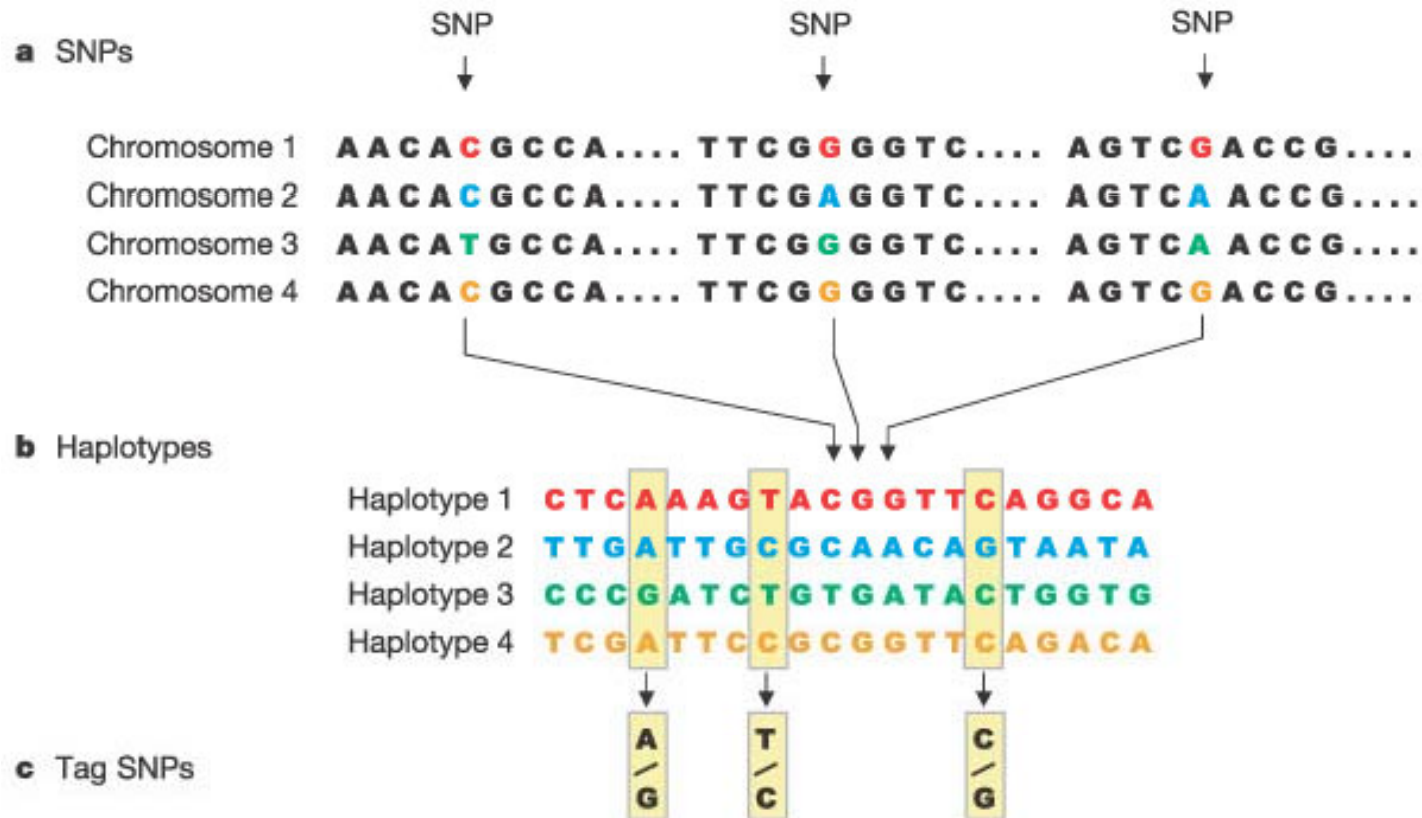


Genetic Variation

- Haplotypes:
 - “A way of denoting the collective genotype of a number of closely linked loci on a chromosome”



Genetic Variation



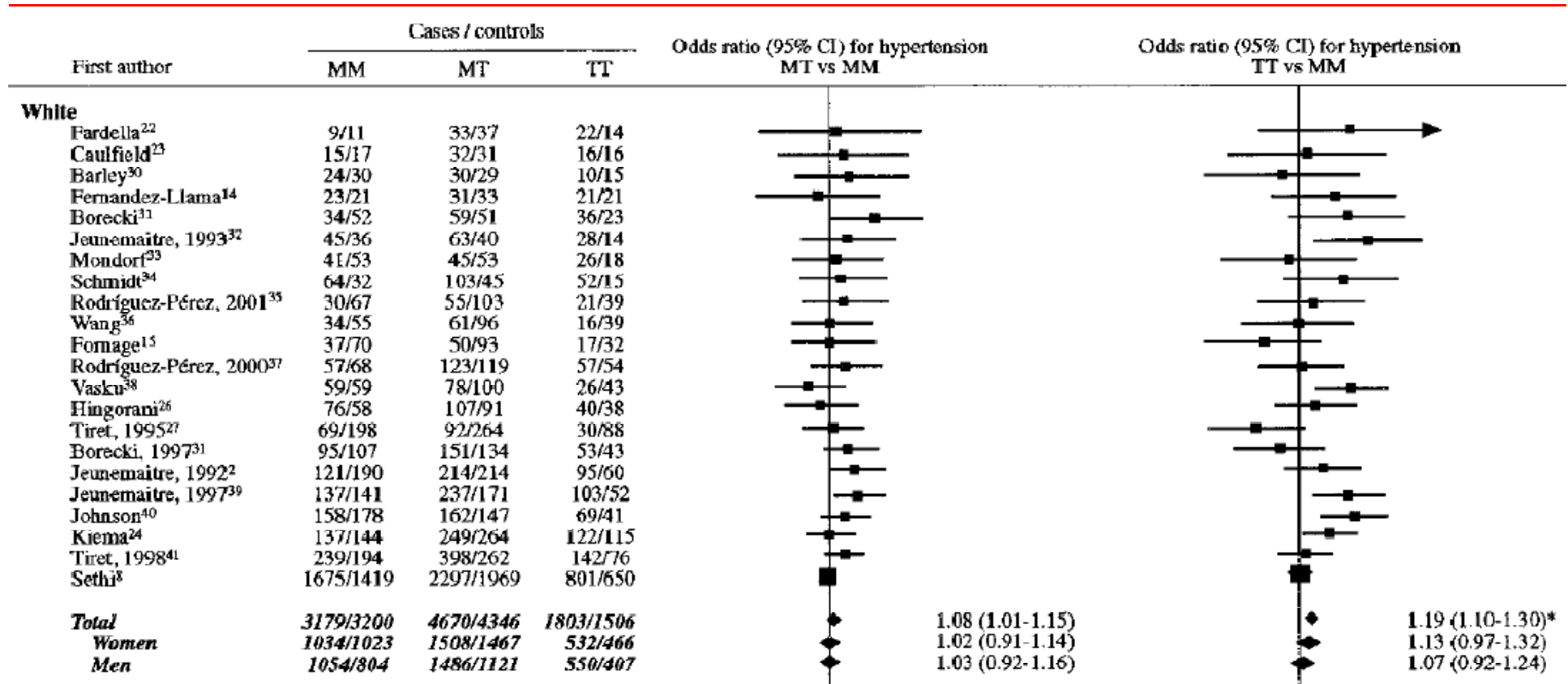
“A **tag SNP** is a representative SNP in a region of the genome with high linkage disequilibrium”

WNK1 Polymorphisms

- Mutations in WNK1 and WNK4 cause pseudohypoaldosteronism type II
- Polymorphisms within these genes may therefore be involved in BP regulation
- GRAPHIC Study assessed this hypothesis among 1005 white Europeans using 24-hour BP monitoring
- 9 tag SNPs in WNK1 and 1 SNP in WNK4

| Haplotype | Mean 24-h systolic BP | Mean 24-h diastolic BP |
|-----------|-----------------------|------------------------|
| h2 | Z=-0.512, P=0.61 | Z=2.291, P=0.021 |
| h4 | Z=-2.264, P=0.025 | Z=-2.159, P=0.032 |
| h7 | Z=2.248, P=0.022 | Z=2.707, P=0.0053 |
| h9 | Z=-1.749, P=0.083 | Z=-2.117, P=0.032 |

RAAS Polymorphisms



„Angiotensinogen M235T genotype was associated with a stepwise increase in angiotensinogen levels in white subjects and a corresponding increase in risk of hypertension in both white and Asian subjects“

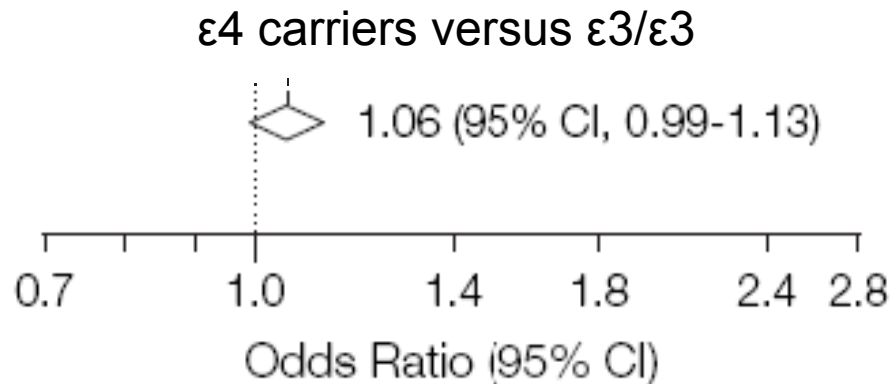
But...

- Bias
- Chance
- Confounding

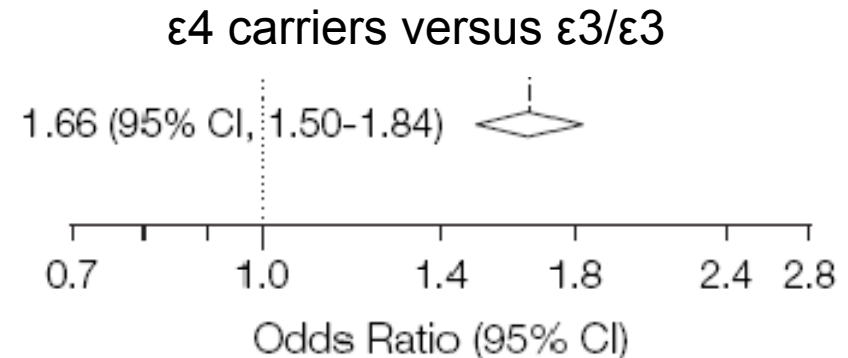
Publication Bias

Association of ApoE genotypes with coronary heart disease risk:

Studies with >500 CHD cases



Studies with < 500 CHD cases



„We noted strong evidence of selective publication in previous estimates based on smaller studies. This is a serious concern given that apoE genotypes and coronary risk had hitherto been considered among the few quantitatively secure associations in cardiovascular disease genetics“

RAAS Polymorphisms

Risk of blood pressure progression or incident hypertension according to 3 Renin-angiotensin system SNP's (N=18436):

| Outcomes | ACE rs1799752 | AGT rs699 | AGTR1 rs5186 |
|------------------------------|------------------|------------------|------------------|
| BP Progression | | | |
| Age-adjusted | 0.97 (0.93–1.01) | 1.03 (0.98–1.08) | 1.03 (0.98–1.08) |
| Fully adjusted | 0.96 (0.92–1.01) | 1.04 (0.99–1.08) | 1.03 (0.98–1.08) |
| Incident Hypertension | | | |
| Age-adjusted | 0.99 (0.96–1.03) | 1.02 (0.98–1.06) | 0.99 (0.95–1.03) |
| Fully adjusted | 0.99 (0.95–1.02) | 1.01 (0.97–1.05) | 0.99 (0.95–1.04) |

„Blood pressure progression and incident hypertension are not consistently associated with three well characterized genetic polymorphisms of the renin–angiotensin system in a large cohort of Caucasian women“

NPPA Polymorphisms

Risk of blood pressure progression or incident hypertension according to 2 SNP's in the NPPA gene (N=18437):

| Outcomes | NPPA rs5063 | NPPA rs5065 |
|------------------------------|---------------------|----------------------|
| BP Progression | | |
| Age-adjusted | 0.85 (0.77 to 0.94) | 0.94 (0.88 to 0.995) |
| Multivariable adjusted | 0.85 (0.76 to 0.94) | 0.94 (0.88 to 1.00) |
| Incident Hypertension | | |
| Age-adjusted | 0.90 (0.82 to 0.99) | 0.95 (0.90 to 1.01) |
| Multivariable adjusted | 0.88 (0.80 to 0.96) | 0.95 (0.90 to 1.00) |

“Natriuretic peptides may be involved in the pathogenesis of hypertension, but no replication available yet”

NPPA Polymorphisms

Three genetic polymorphisms at the NPPA-NPPB locus were found to be associated with circulating levels of natriuretic peptides (rs5068, rs198358 and rs632793)

Association of NPPA and NPPB gene polymorphisms with blood pressure:

| N=29717 | NPPA rs5068 | NPPA rs198358 |
|----------------|-----------------------------|-----------------------------|
| Systolic BP | -0.08, $p=2 \times 10^{-6}$ | -0.05, $p=6 \times 10^{-5}$ |
| Diastolic BP | -0.08, $p=1 \times 10^{-6}$ | -0.05, $p=5 \times 10^{-5}$ |

Association of NPPA and NPPB gene polymorphisms with hypertension:

| N=29717 | NPPA rs5068 | NPPA rs198358 |
|----------------|---------------------|----------------------|
| OR (95% CI) | 0.85 (0.79 to 0.92) | 0.90 (0.85 to 0.95) |

„Common genetic variants at the NPPA-NPPB locus found to be associated with circulating natriuretic peptide concentrations contribute to interindividual variation in blood pressure and hypertension.“

Common Variants in Monogenic Hypertension Genes

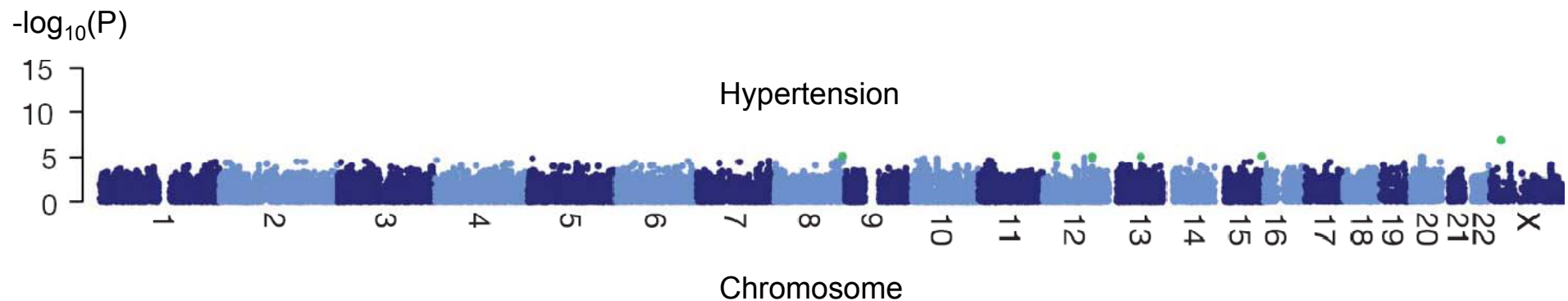
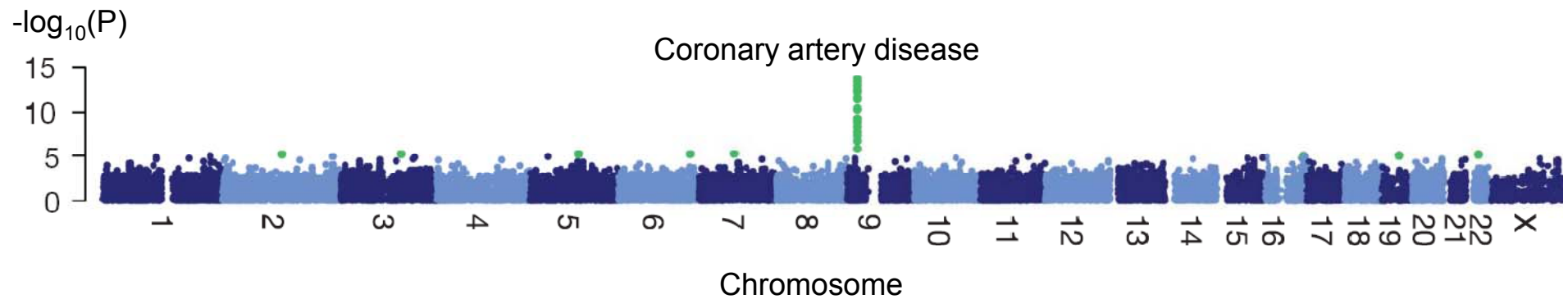
- Common variants in genes underlying monogenic forms of hypertension are obvious candidates as potential contributors to BP variation in the general population
- GRAPHIC Study (2037 white Europeans)
- 298 tag SNPs within 11 genes were genotyped

| Gene | SNP | Mean 24-h systolic BP | Mean 24-h diastolic BP |
|-------|-----------|-----------------------|------------------------|
| KCNJ1 | rs675759 | -1.44 mmHg, FPRP=0.15 | -0.99 mmHg, FPRP=0.13 |
| KCNJ1 | rs675388 | -1.41 mmHg, FPRP=0.19 | - 0.99 mmHg, FPRP=0.14 |
| KCNJ1 | rs2846679 | -1.58 mmHg, FPRP=0.05 | - 1.00 mmHg, FPRP=0.13 |
| KCNJ1 | rs2855800 | -1.21 mmHg, FPRP=0.08 | - 0.57 mmHg, FPRP=0.68 |
| KCNJ1 | rs2186832 | -1.42 mmHg, FPRP=0.07 | - 0.95 mmHg, FPRP=0.09 |

„Variants in KCNJ1, which causes Bartter syndrome type 2, were strongly associated with blood pressure in the general population“

Genome-Wide Association Studies

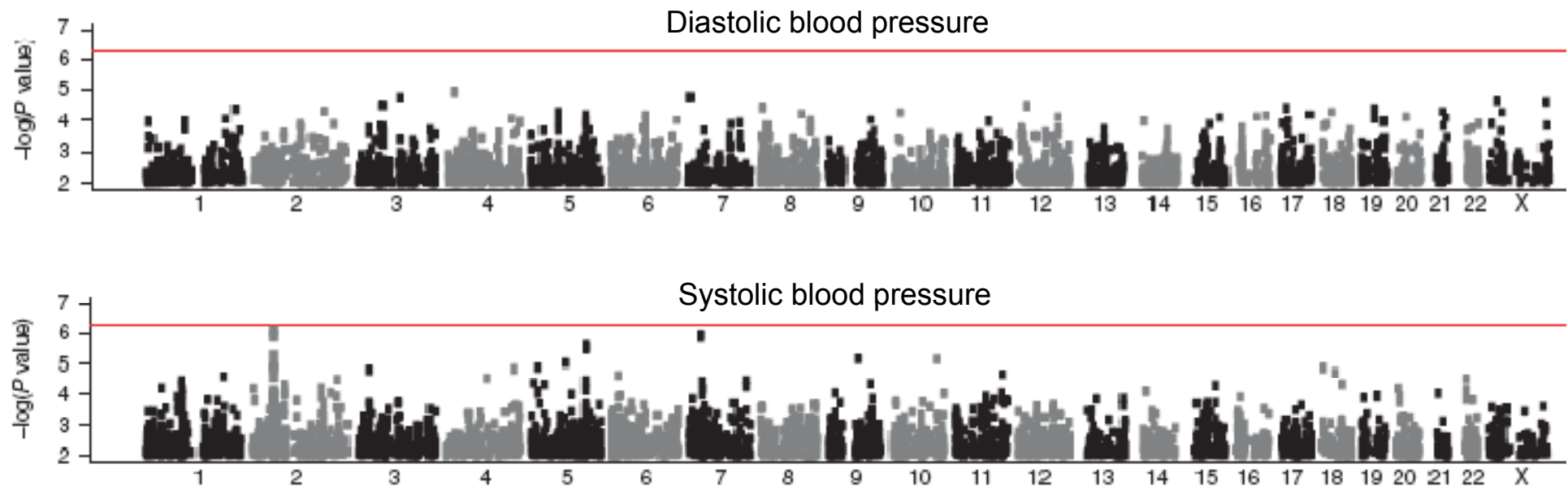
2000 cases for each of 7 common diseases and 3000 shared controls



$p < 5 \times 10^{-7}$ was considered to indicate statistical significance

Genome-Wide Association Studies

9 quantitative metabolic traits from a birth cohort in Finland (329'091 SNPs among 4763 participants)



„No individual locus achieved genome-wide significance for systolic or diastolic blood pressure in this cohort.”

Rare Mutations & BP Variation

Assessment of genetic variants in SLC12A1, KCNJ1 and SLC12A3 among 3125 participants of the Framingham Offspring Study:

| Outcomes | All mutation carriers (n=49) | Carriers with proven mutations (n=23) |
|---------------------------------------------------------|-----------------------------------------|--------------------------------------------------|
| % below mean SBP | 80 | 78 |
| Effect on long-term SBP | -6.3 mmHg, p=0.0009 | -6.8 mmHg, p=0.03 |
| Effect on SBP at age 60 | -9.0 mmHg, p=0.0002 | -9.8 mmHg, p=0.02 |
| Δ SBP between carrier and noncarrier siblings | -6.6 mmHg, p=0.009 | -9.2 mmHg, p=0.002 |
| Incident Hypertension | 0.41, p=0.003 | 0.55, p=0.13 |

„Because these 3 genes comprise only a small fraction of those in which mutations are known to alter BP, ..., it seems probable that the combined effects of rare independent mutations will account for a substantial fraction of BP variation in the population.“

Summary

- Interpretation of prior genetic association studies was often limited by (publication) bias, chance and confounding
- Few common genetic variants have been reproducibly associated with blood pressure or hypertension (e.g. NPPA)
- Most of the estimated genetic variation of blood pressure and hypertension remains unexplained

Potential for Improvement

- Dichotomous hypertension versus continuous blood pressure
- Misclassification bias (no assessment among control subjects)
- “Conventional” blood pressure measurement
- Focus on middle-aged to elderly participants
 - Subclinical cardiovascular disease
 - Cumulative exposure to environmental factors

Age of Study Participants

Studies suggest that genetic susceptibility becomes less pronounced in older age groups

Parental hypertension and risk of hypertension stratified by age:

| Age at risk, years | Late (>55 years) | Both early |
|---------------------------|----------------------------|-------------------|
| 35 | 1.9 (1.1 - 3.3) | 20.0 (8.4 - 47.9) |
| 45 | 1.7 (1.2 - 2.5) | 10.3 (5.6 - 18.9) |
| 55 | 1.6 (1.2 - 2.1) | 5.3 (2.6 - 10.6) |
| 65 | 1.5 (1.1 - 2.0) | 2.7 (0.9 - 7.8) |
| 75 | 1.4 (0.9 - 2.2) | 1.4 (0.3 - 6.3) |

Data are hazard ratio (95% confidence interval)

Future Perspectives

- Large and comprehensive genome-wide association studies using state-of-the art genotyping and phenotyping
- Well-selected candidate-gene studies, with replication of promising findings
- Detection of rare mutations with possible large effects
- Gene-gene interactions
- Gene-environment interactions