Genetics of Cardiovascular Diseases

From Single Mutations to the Whole Genome

Laurence Tiret
INSERM U525

Inserm

UNIVERSITE PIERRE & MARIE CURIE
LA SCIENCE A PARIS

The Future of Personal Genomics

Amy L. McGuire,[1] Mildred K. Cho,[2] Sean E. McGuire,[3] Timothy Caulfield[4]

SCIENCE VOL 317 21 SEPTEMBER 2007

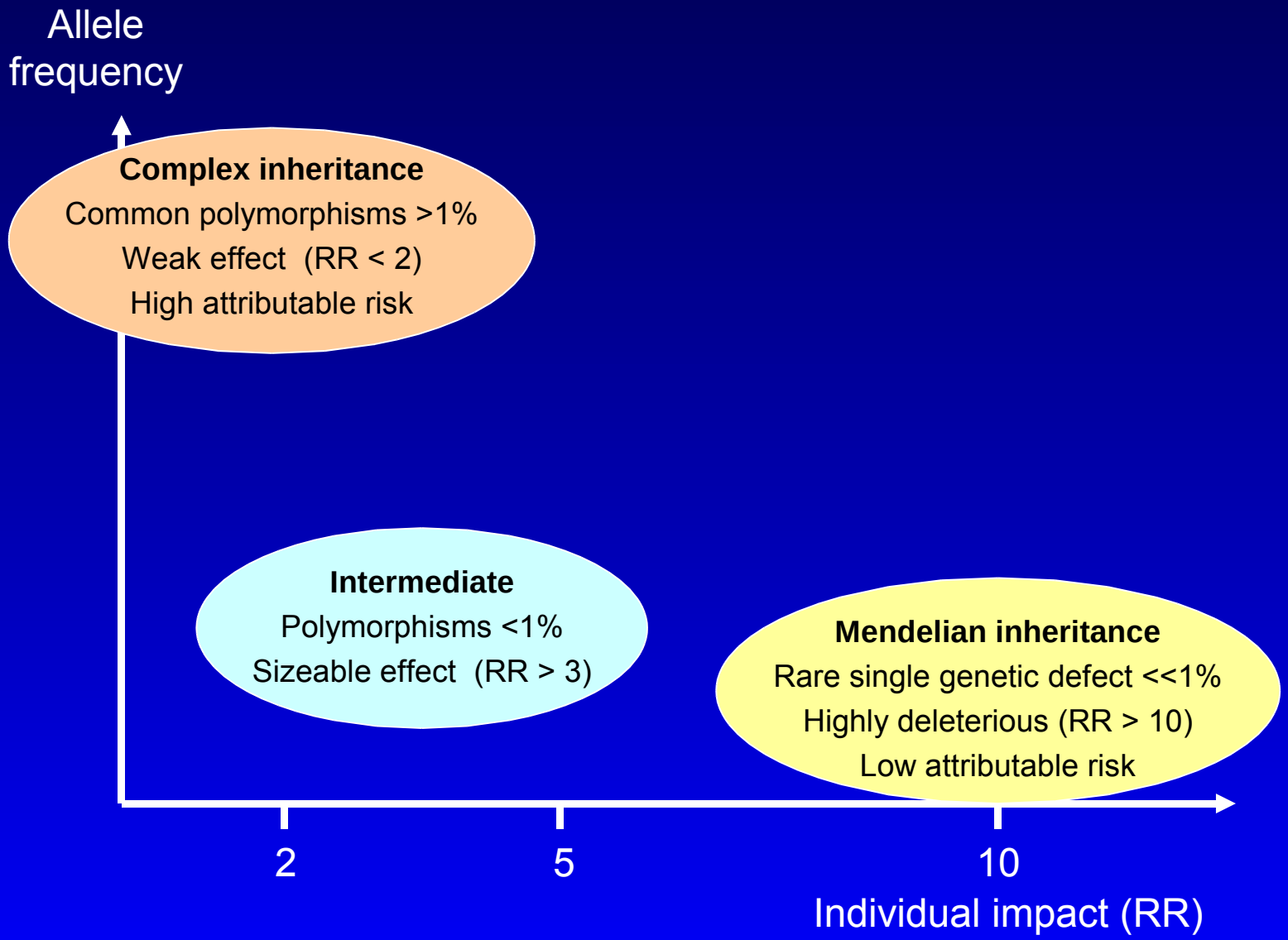
" …*Scientists predict that within 5 years DNA sequencing technologies will be affordable enough that personal genomics will be integrated into routine clinical care…* "

When the search for genes that predispose to cardiovascular diseases started > 20 years ago, it was anticipated that genetic polymorphisms might be analogous to the already known risk factors and could be incorporated in a risk model such as the Framingham score for prediction and prevention

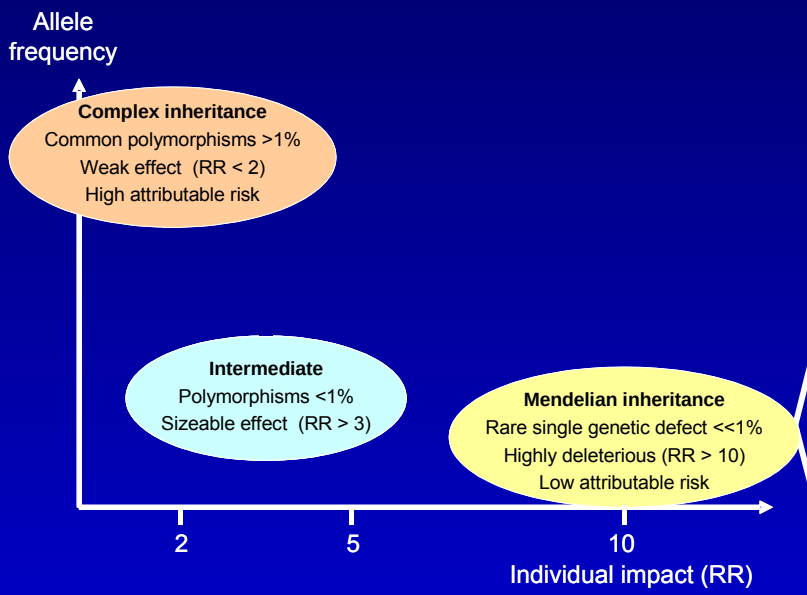
However, despite years of intensive research, not a single genetic risk factor is used for risk assessment (except for Mendelian disorders)

As time passes, the interest of for genetic research on common cardiovascular diseases moves progressively from the direct expectation of risk stratification to the more fundamental understanding of disease pathogenesis and its indirect diagnostic and therapeutic implications

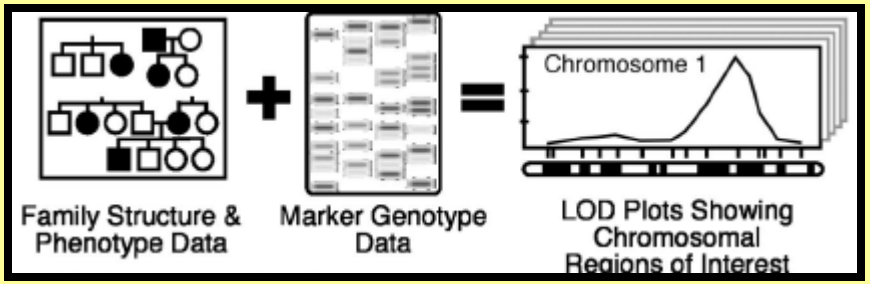
Genetic variants that predispose to human diseases



Mendelian diseases



Linkage analysis



FH → LDLR gene (700 mutations)

FDB → apoB (R3500Q)

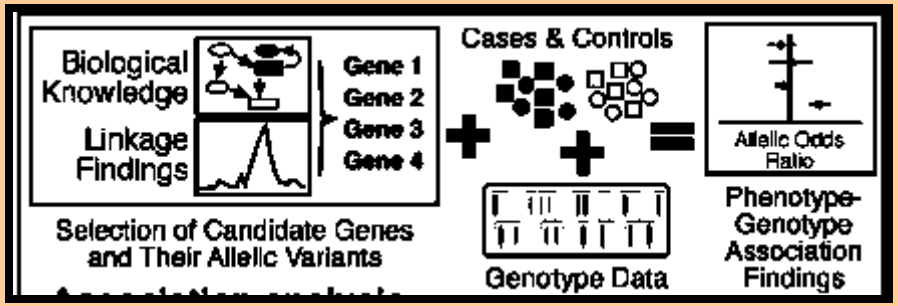
Tangier disease → ABCA1 (> 70 mut.)

...

Critical in advancing our understanding of cholesterol metabolism and developing effective pharmacological therapies

Complex cardiovascular diseases

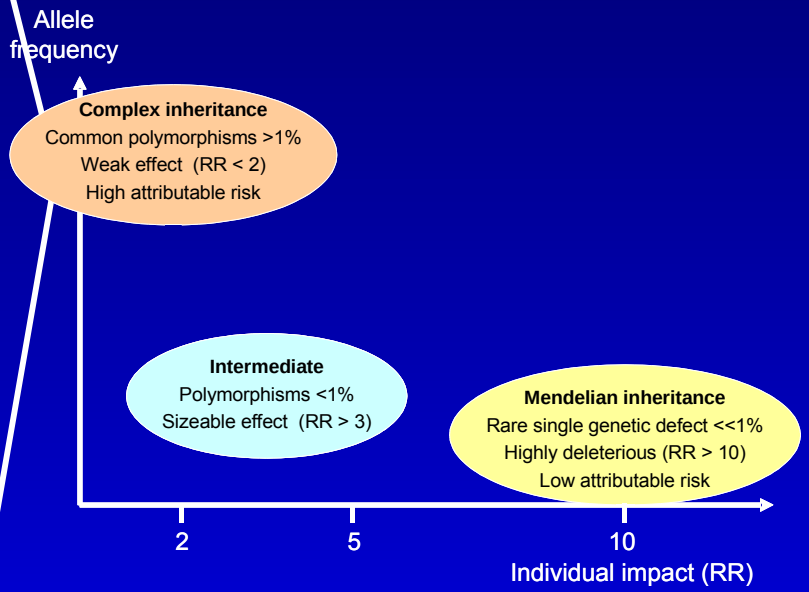
Association analysis



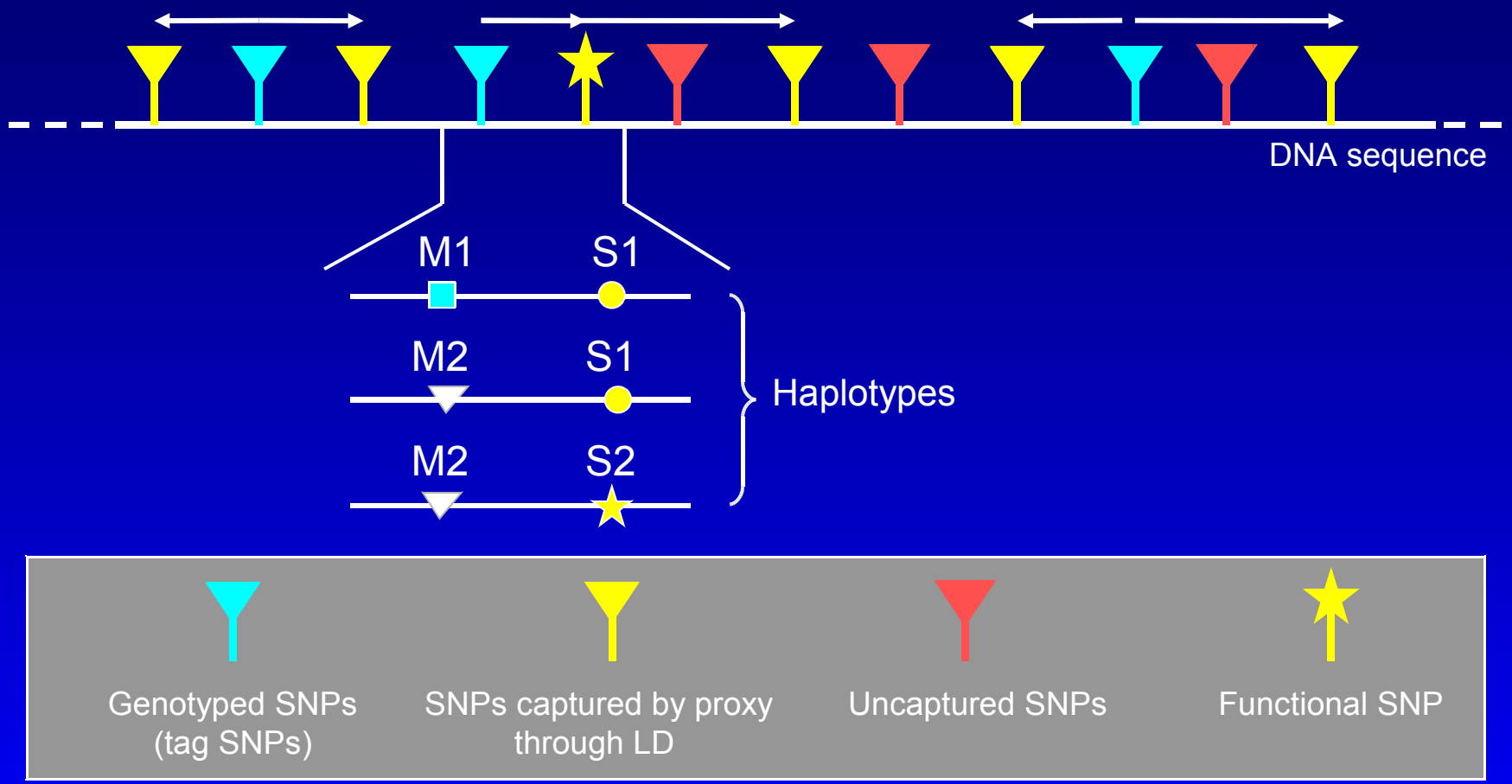
Hundreds of genes investigated
Relatively few robust associations
Weak effect (RR < 1.3)

apoE ε2/ε3/ε4
MTHFR C677T
PON1 Q192R
…

Problems of complex diseases
- Gene-gene and gene-environment interactions
- Heterogeneity across populations
- Small sample size in most studies

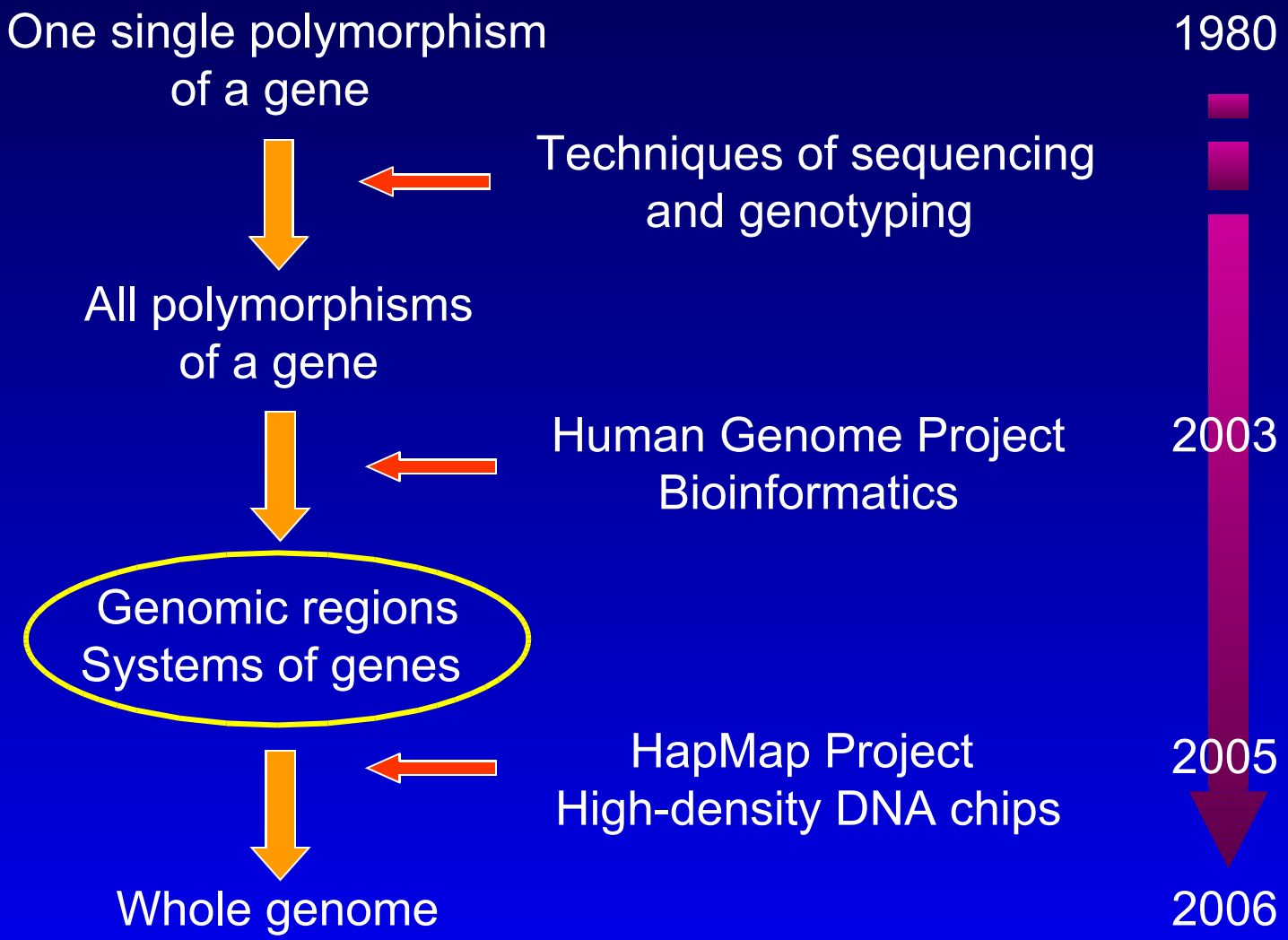


Principle of genetic association studies

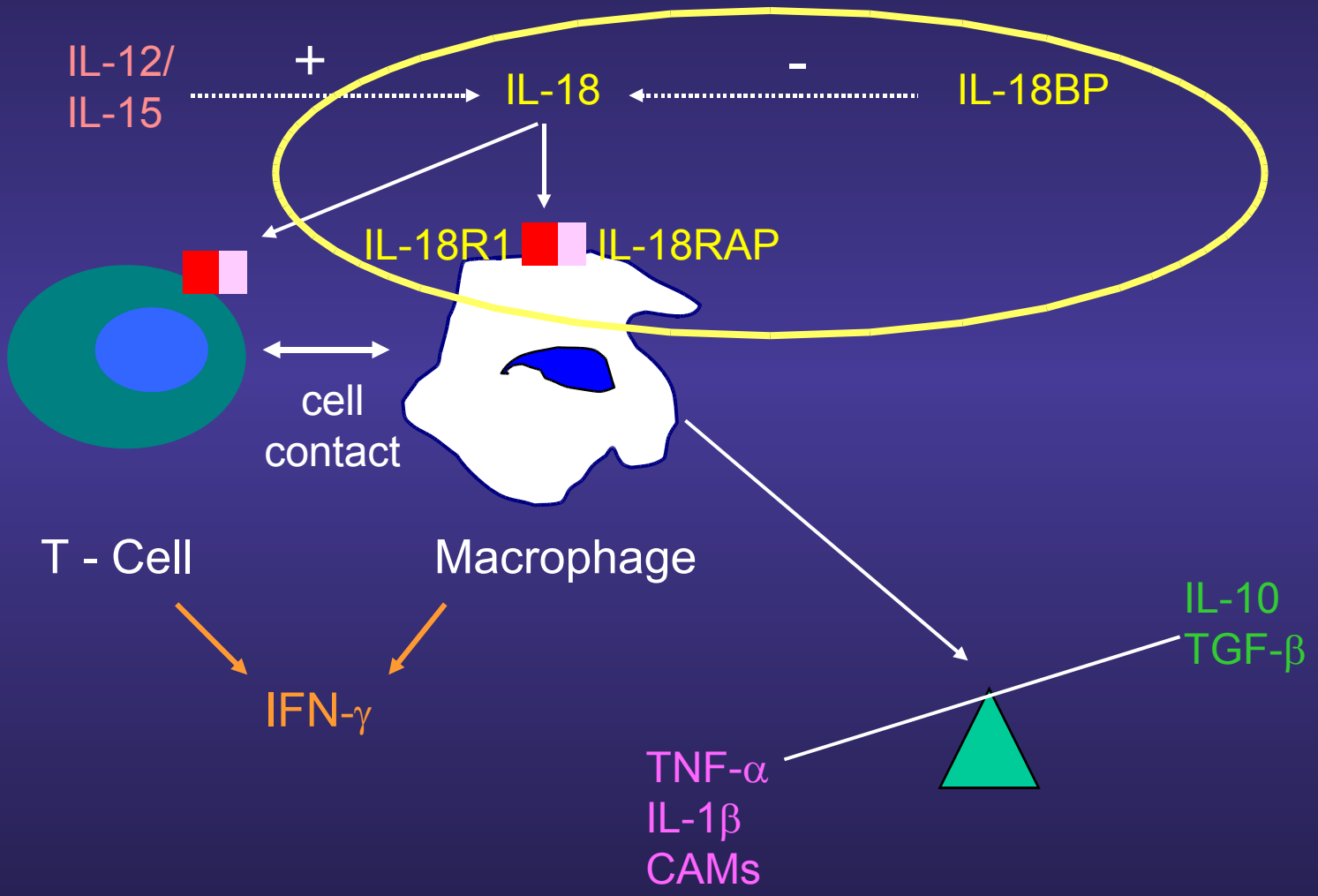


adapted from Kruglyak 2005

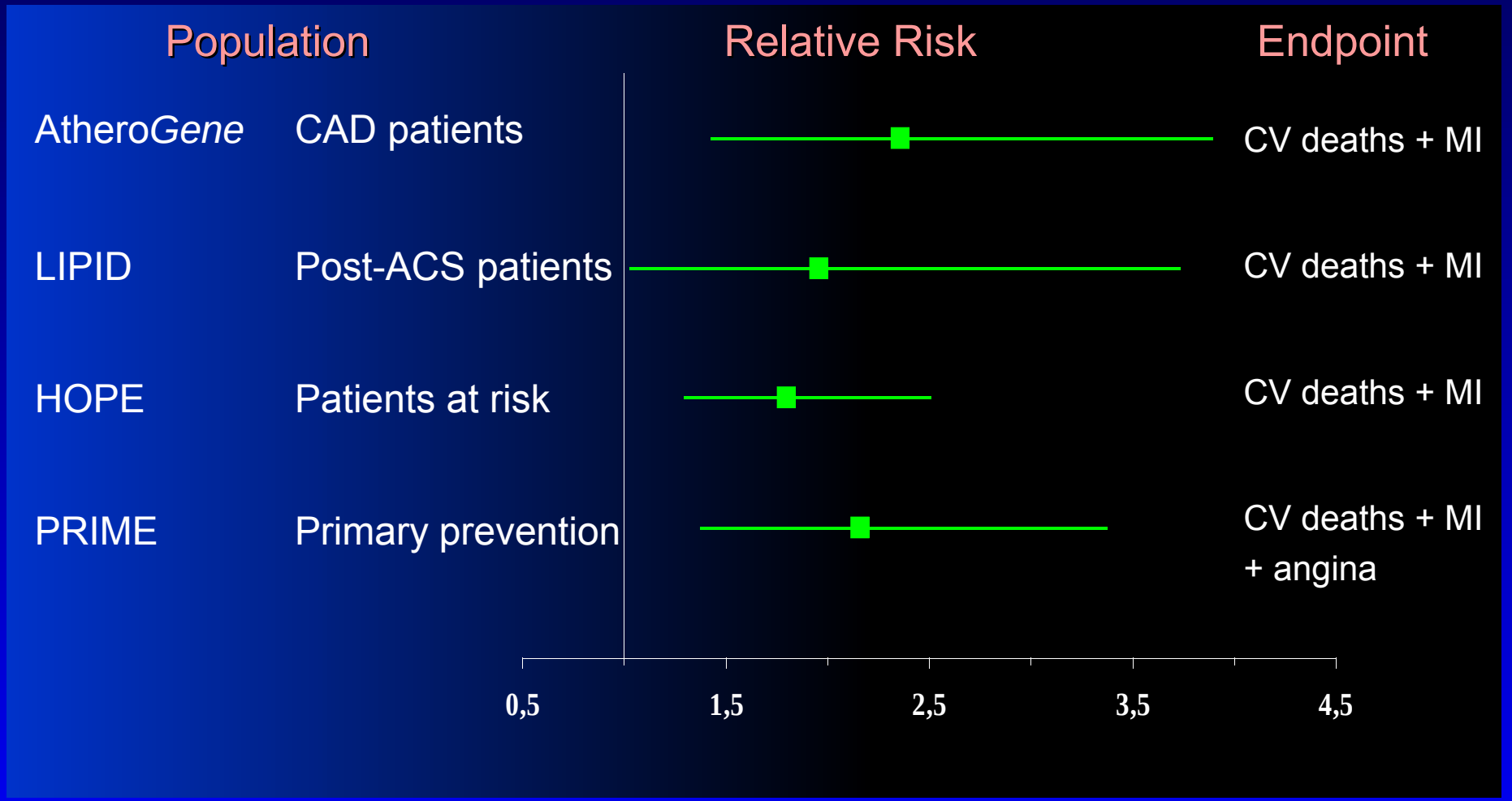
Genetic association studies



Interleukin –18



Interleukin-18 and cardiovascular risk in different prospective studies



4th vs 1st quartile of baseline IL-18

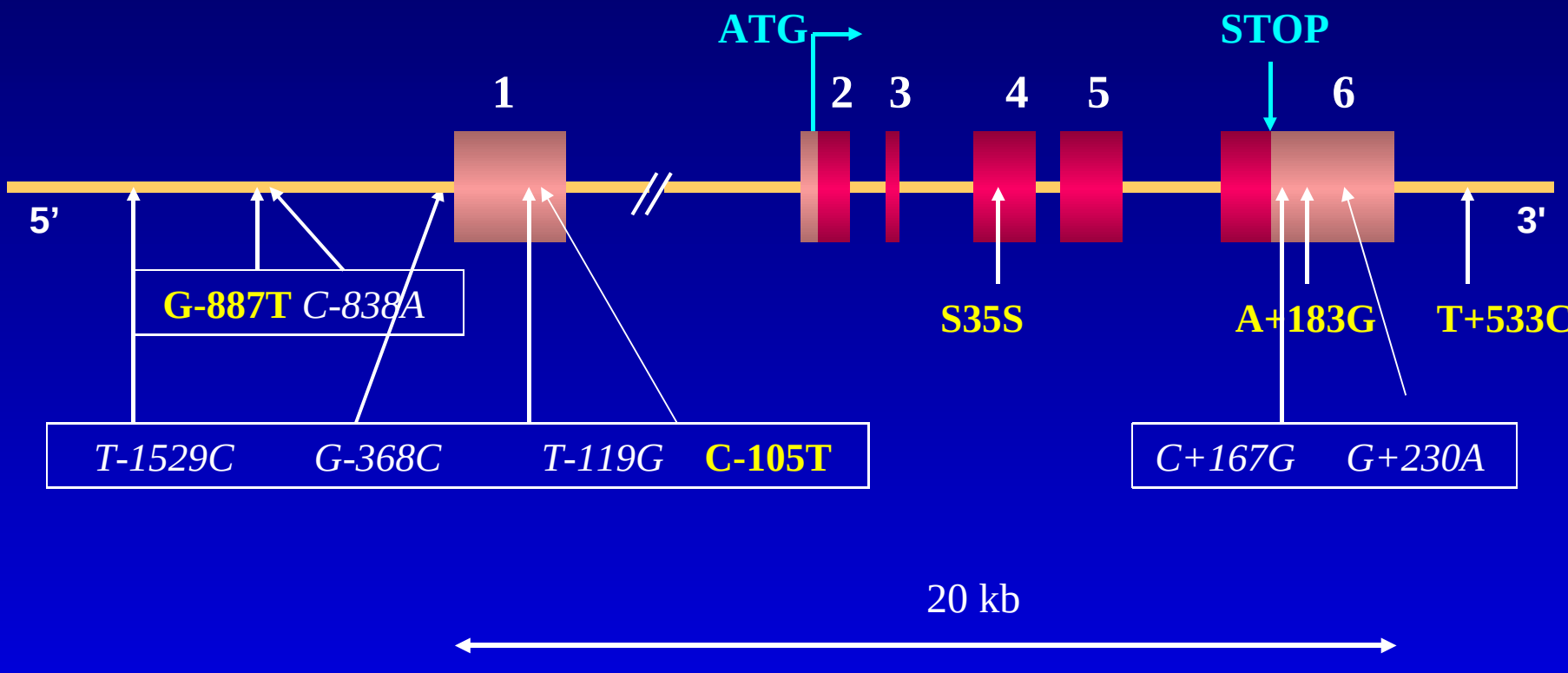
Genetic variability of the IL-18 system

Gene	Locus	Identified polymorphisms	Genotyped polymorphisms
*IL18**	11q22.2-q22.3	11	**5**
*IL18R1***	2q12	10	**9**
*IL18RAP***	2q12	8	**8**
*IL18BP***	11q13	1	**0**
Total		30	**22**

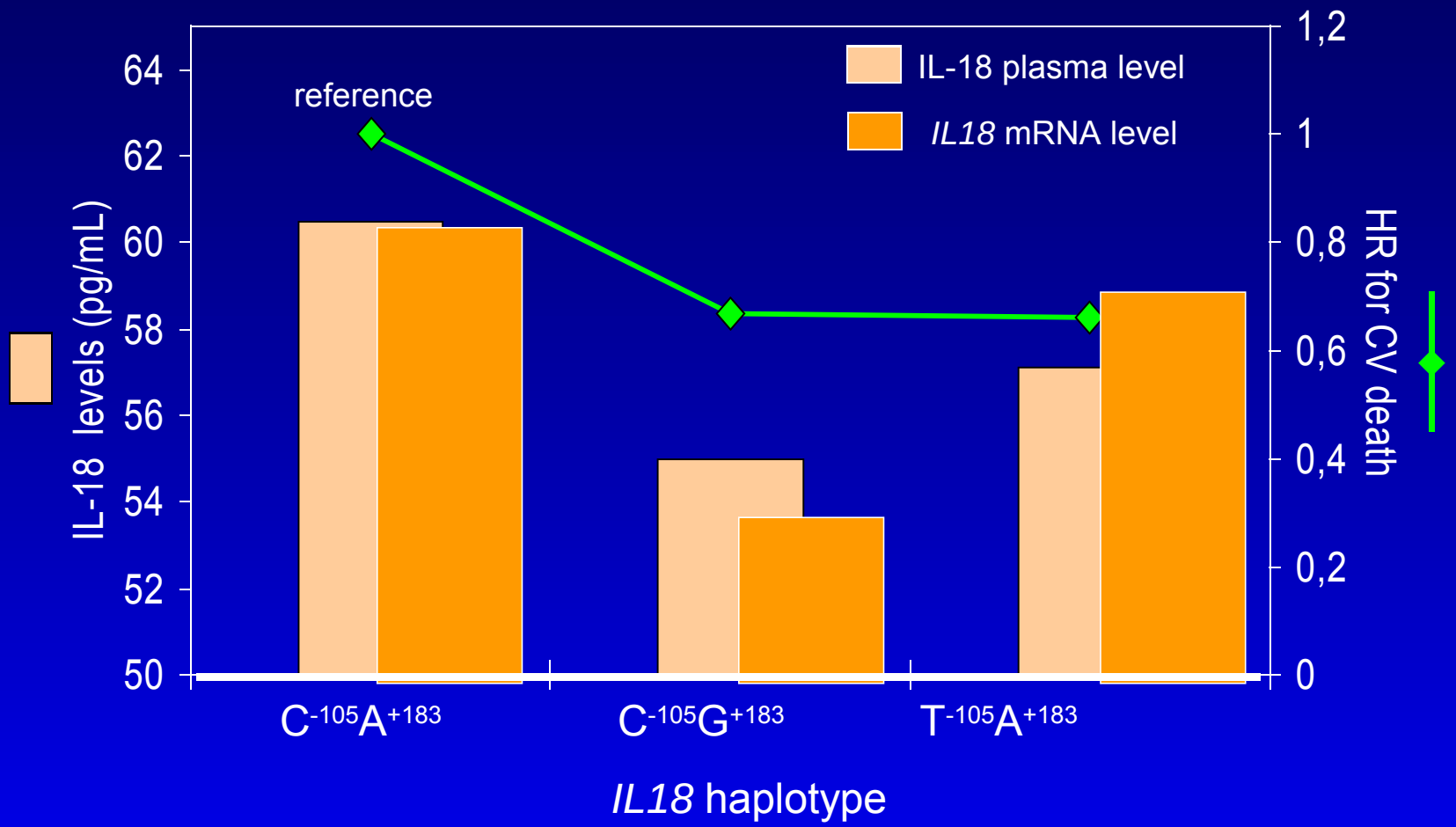
* Molecular screening at INSERM/U525

** Polymorphisms selected in Innate Immunity

IL18 gene (11q22.2-q22.3)



IL18 haplotypic effects on IL-18 plasma levels, mRNA levels and cardiovascular risk - The Athero*Gene* study

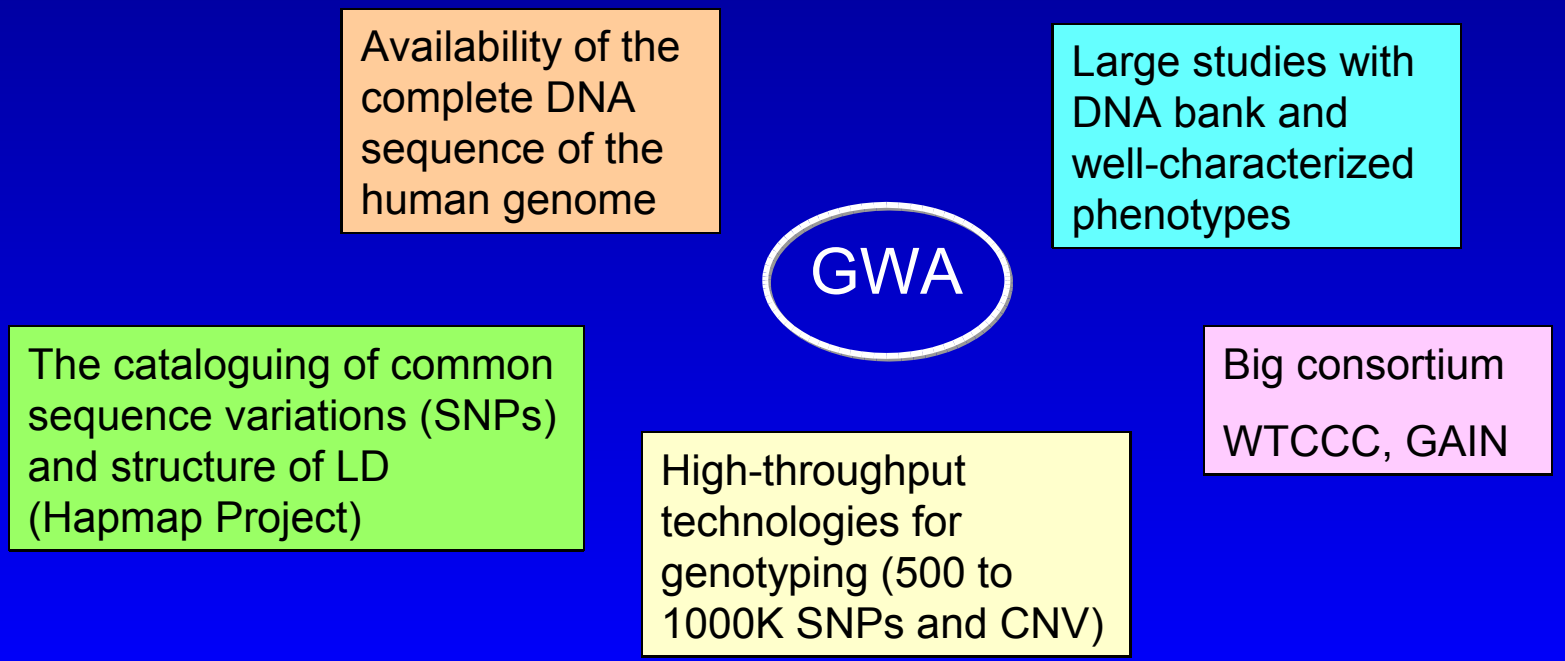


Tiret et al *Circulation* 2005

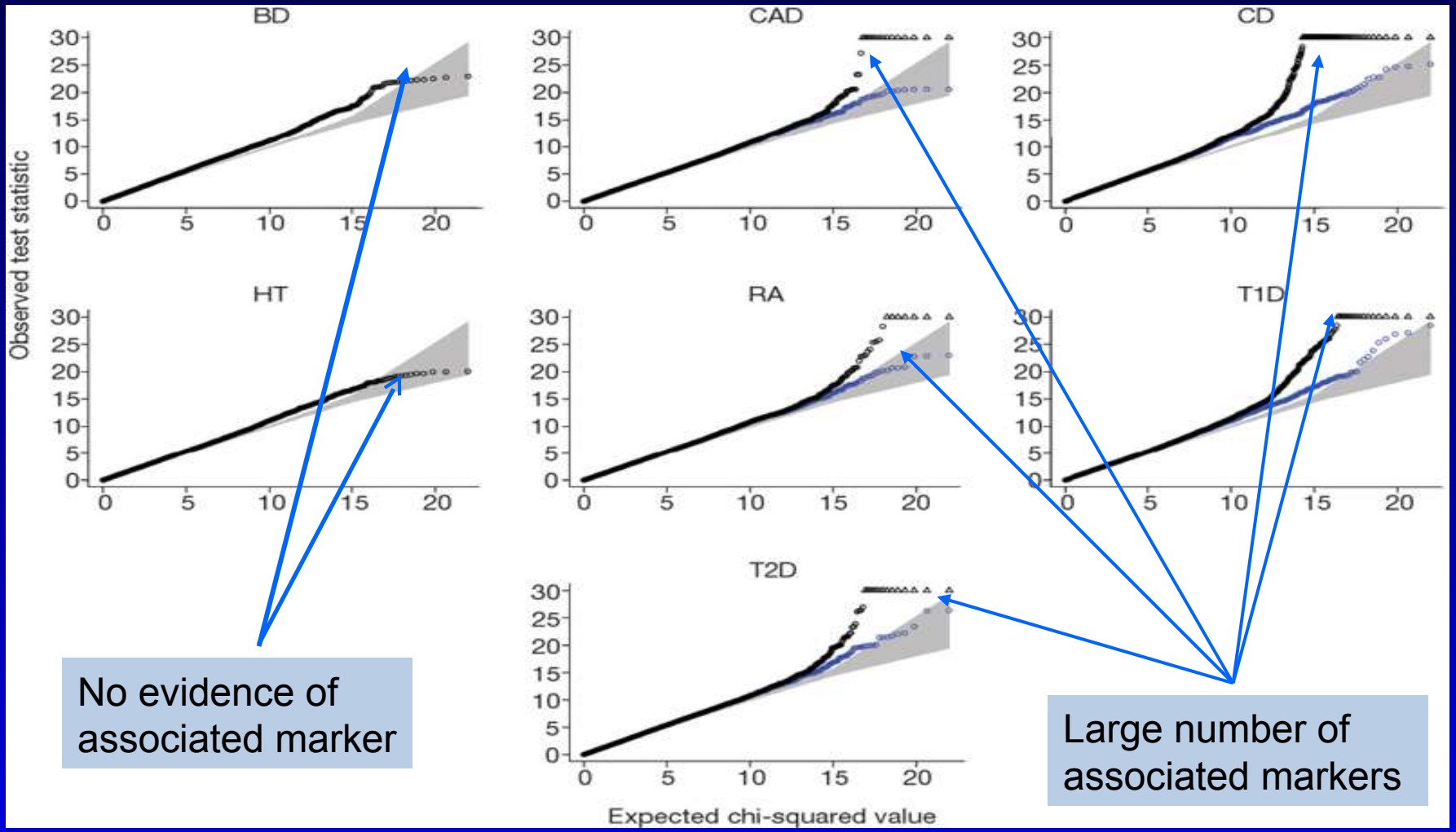
Barbaux et al *Eur J Hum Genet* 2007

Genome-wide association (GWA) studies

- Objective: to localize genomic regions harbouring susceptibility variants by linkage disequilibrium (LD) mapping
- No *a priori* hypothesis, global and independent of "traditional" biology
- Allows the identification of new or unsuspected genes
- True revolution in biomedical research

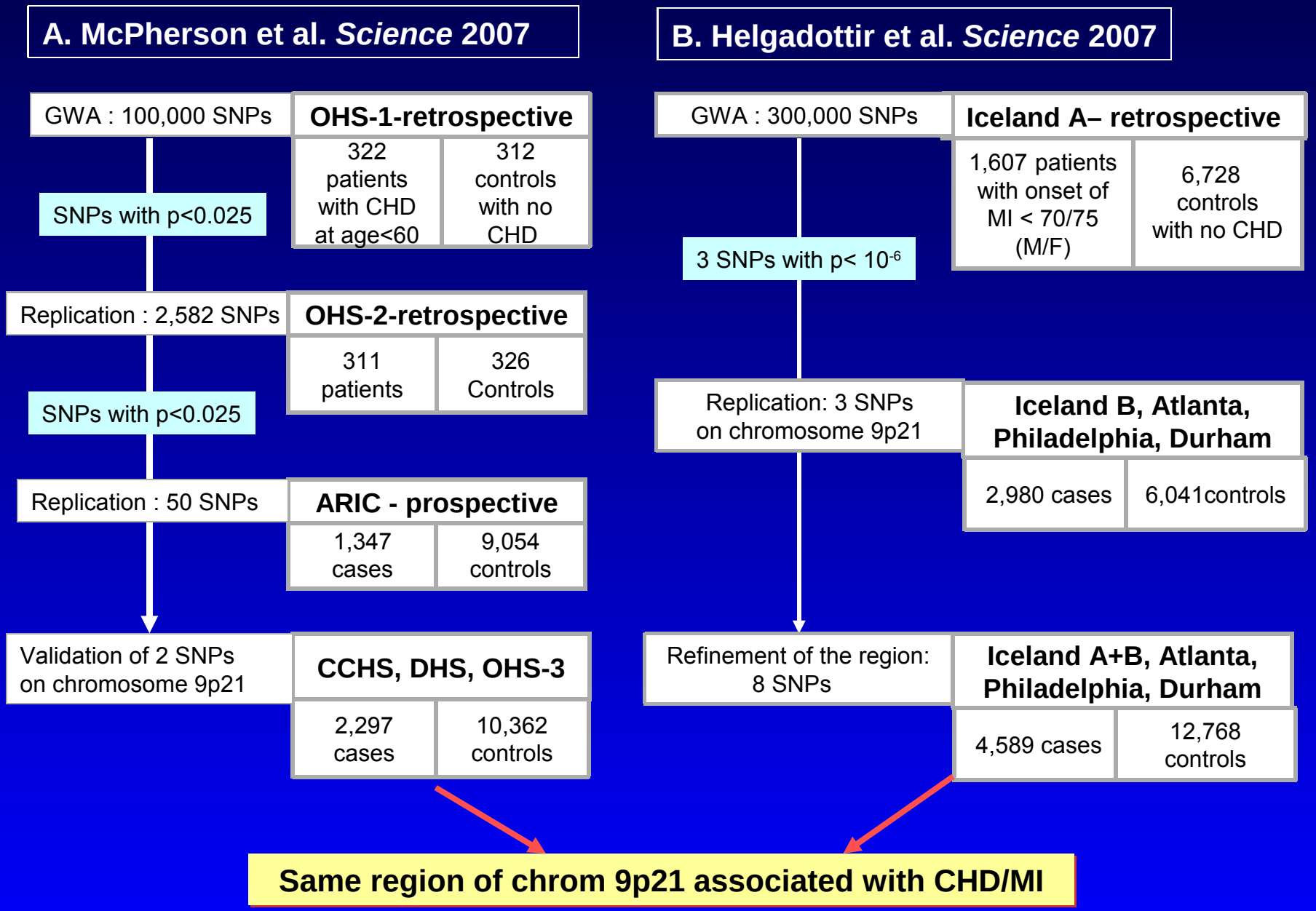


Quantile-Quantile (QQ) plots

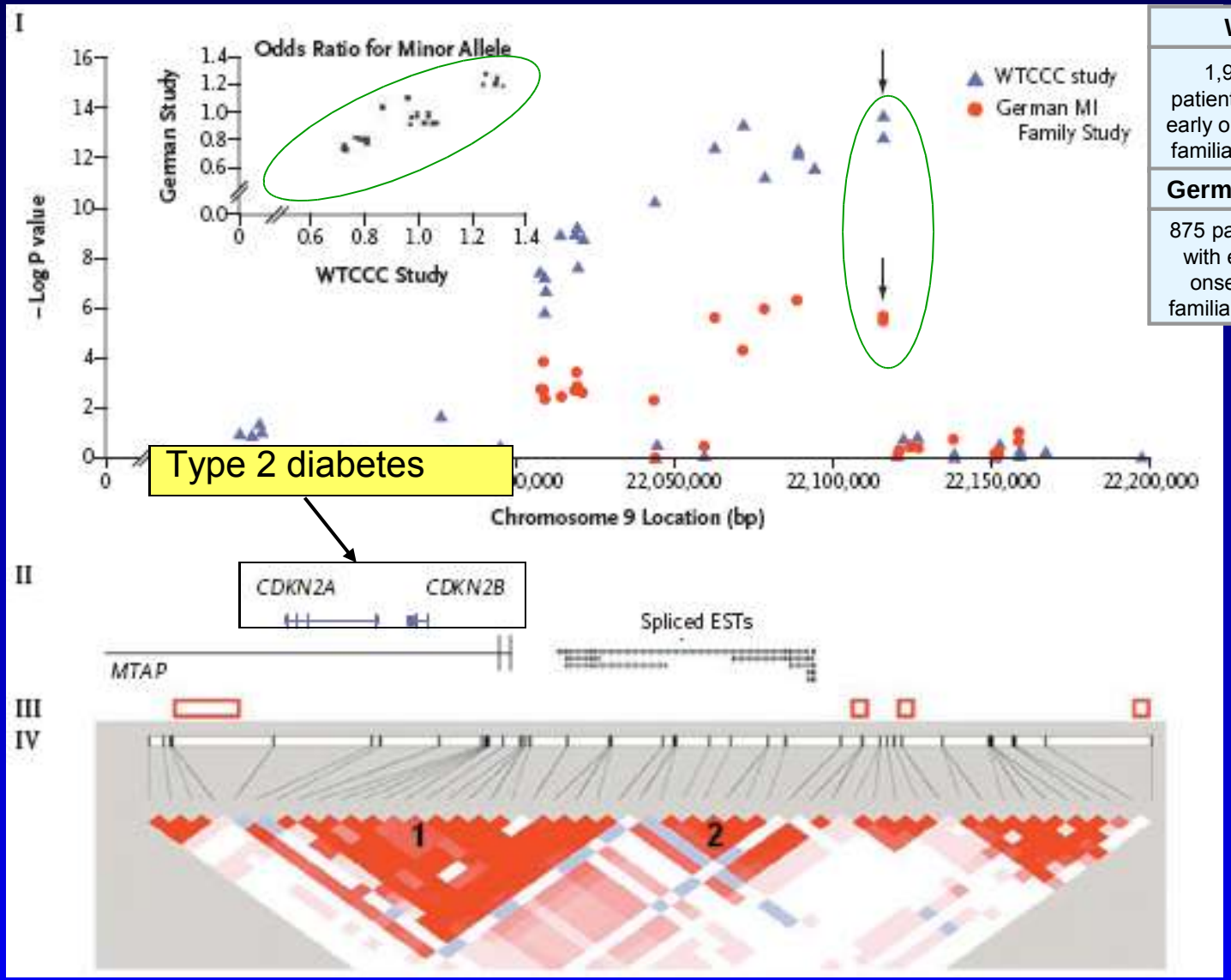


The Wellcome Trust Case-Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007
(BD=bipolar disorder, CAD=coronary artery disease, CD=Crohn disease, HT=hypertension, RA=rhumatoid arthritis , T1D=type 1 diabetes, T2D=type 2 diabetes)

GWA studies of CHD



GWA studies of CHD in Cardiogenics



WTCCC study	
1,926 patients with early onset of familial CHD	2,938 controls
German MI family study	
875 patients with early onset of familial CHD	1,644 controls

Samani et al. *NEJM* 2007

Still a long way…

- Refinement of the region (haplotype analyses)
- Fine mapping with denser maps
- Resequencing
- Identification of the functional variant(s)
- Understanding the molecular mechanisms (functional genomics)
- Clinically meaningful ?

Variants of “ intermediate ” to low frequency associated with non-mendelian traits

No evident familial pattern

Difficult to tag with common SNPs → no detectable by GWA

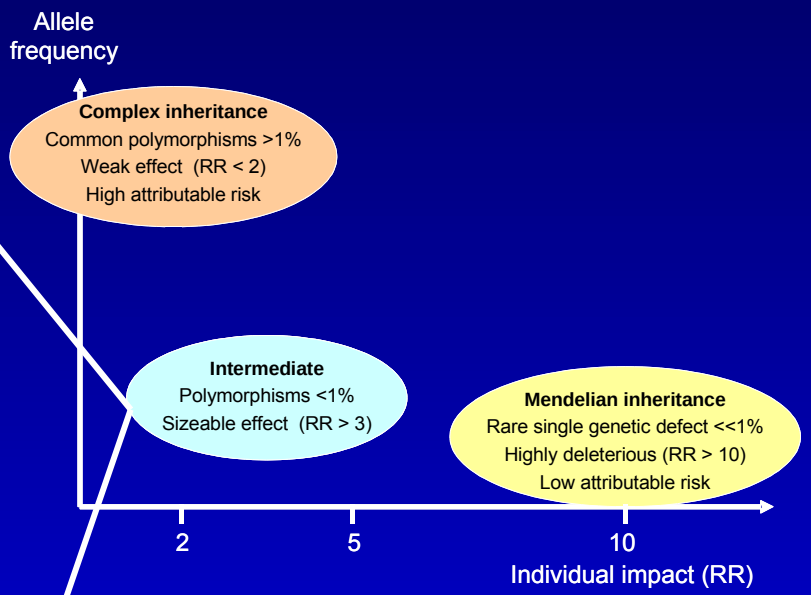
High-throughput sequencing

Large DNA banks

ABCA1 and HDL-cholesterol

PCSK9, LDL-cholesterol and CHD

ANGPTL4 and triglycerides



These results open completely new directions for fundamental and phamacological research

Conclusion

- ✓ In recent years, genetics has profoundly changed our understanding of several cardiovascular diseases
- ✓ The novel GWA strategy should further widen our understanding of the pathophysiology of these disorders
- ✓ Discovery of new susceptibility genes will provide a strong foundation for systems biology-style analyses
- ✓ Discovery of new drug targets as a consequence of genetic research may considerably modify the therapeutic approaches of cardiovascular diseases in the near future
- ✓ From a clinical perspective, phenotypic biomarkers that naturally integrate multiple genetic and nongenetic influences are likely to be preferred to genetic biomarkers, because the integration of genotypic information and its translation into medical decision will be very challenging