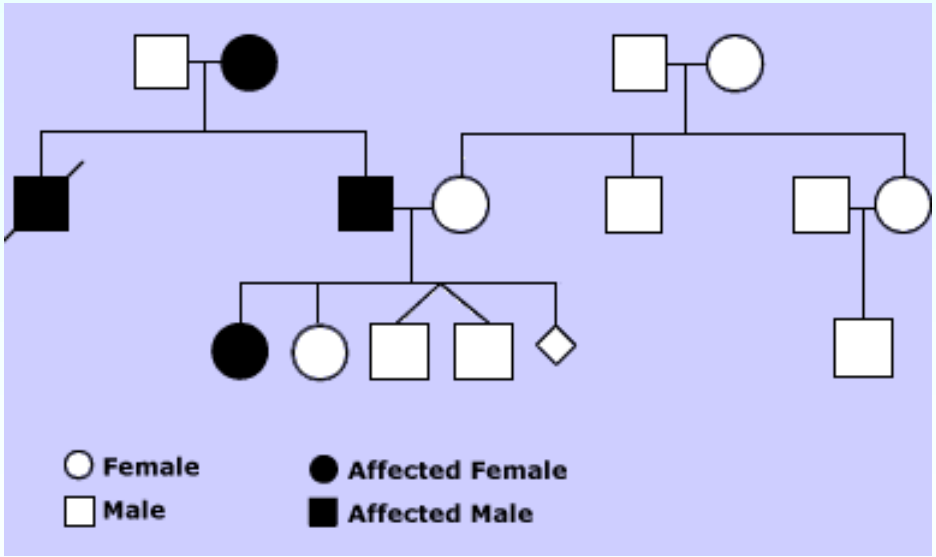
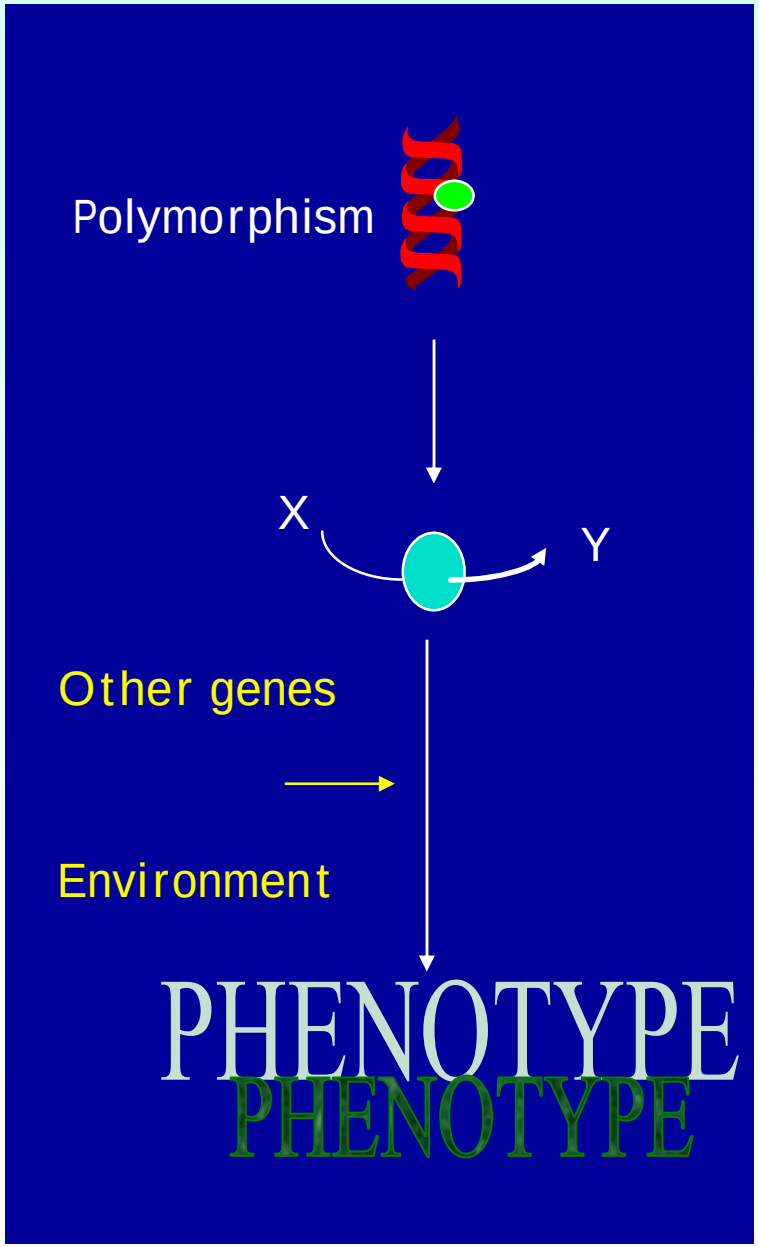
Why study the genetics of common disease?

- Predict risk, *and* intervene
- Identify genes and pathways in order to guide drug development
- Identify the genetic determinants of treatment response


Female
Male
Affected Female
Affected Male



There are 10 million common polymoprhisms in the human genome.

Physiological effects often subtle

Variants influence phenotypes of interest in combination with the genetic background and the environment

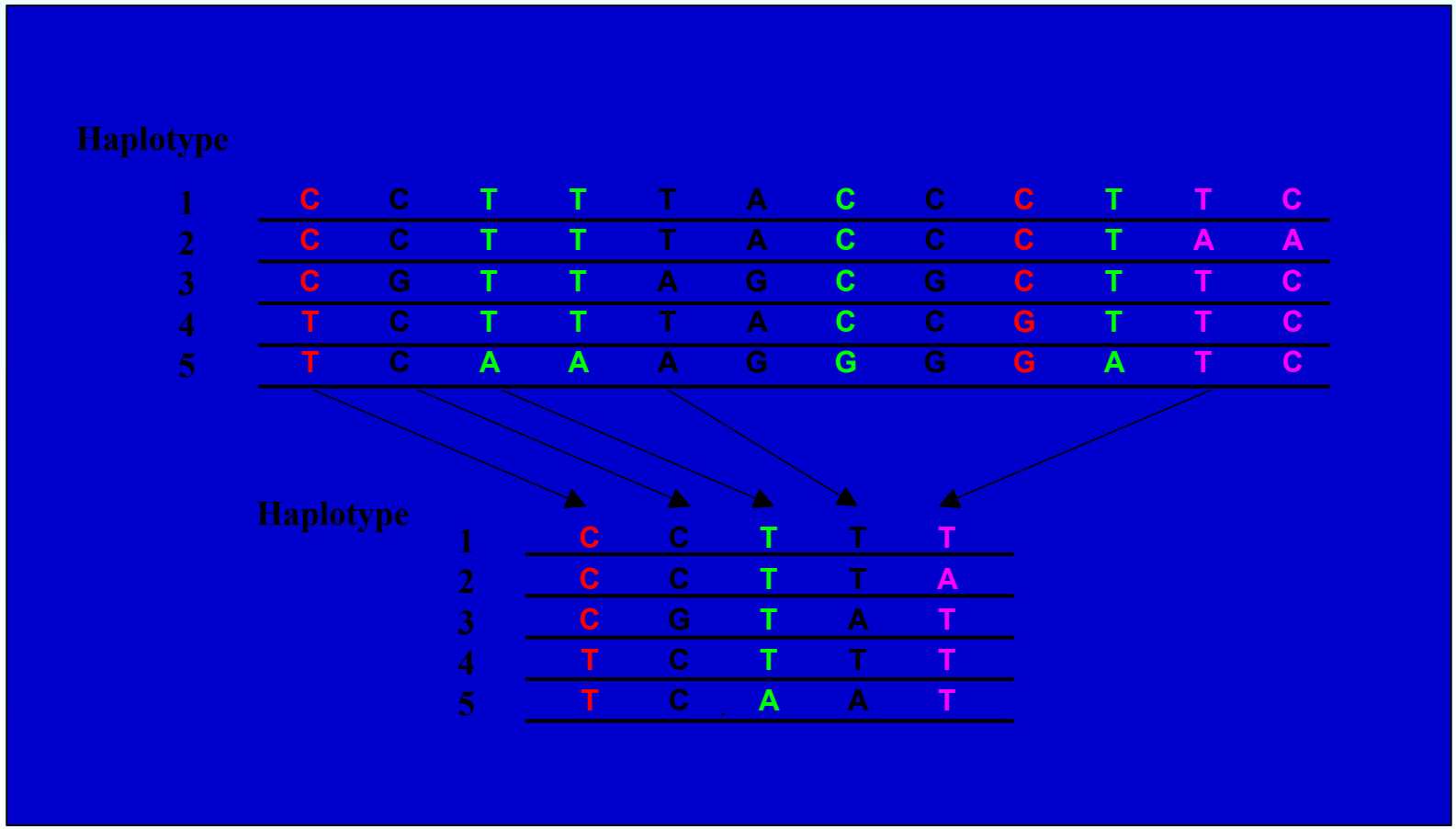
The distribution of phenotypes is influenced By the variant, NOT determined by the variant. It is not accurate to talk about "genes for" common disease.

Technical requirements

- Efficient representation of genetic variation
- Understanding of the phenotype
- Development of a framework for relating multiple forms of genomic and clinical information

Tagging SNPs

to represent common (known & unknown) variation

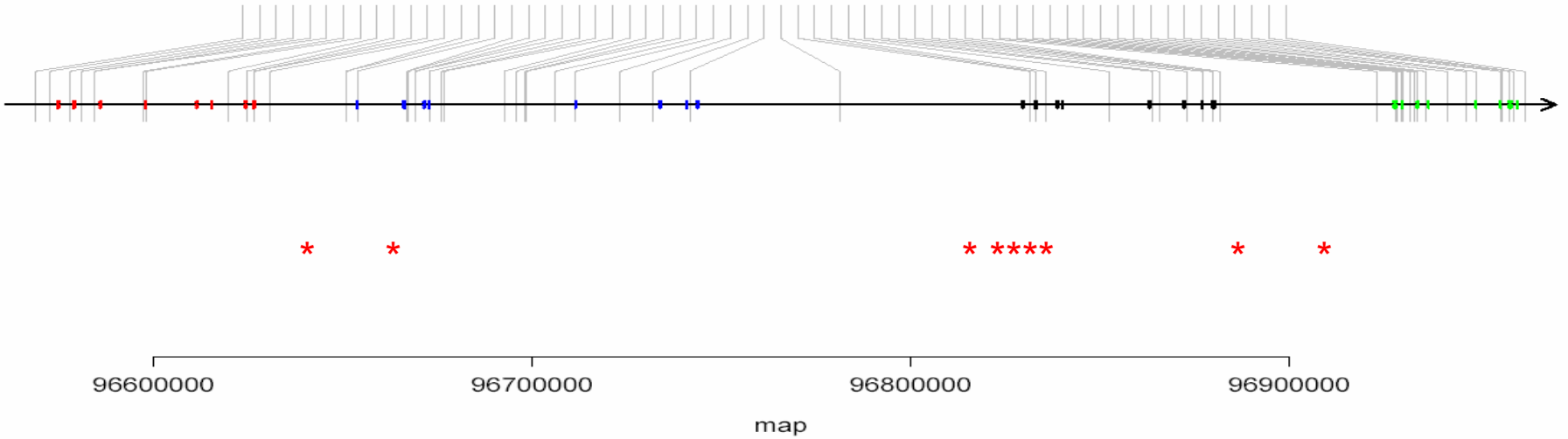


The data set …

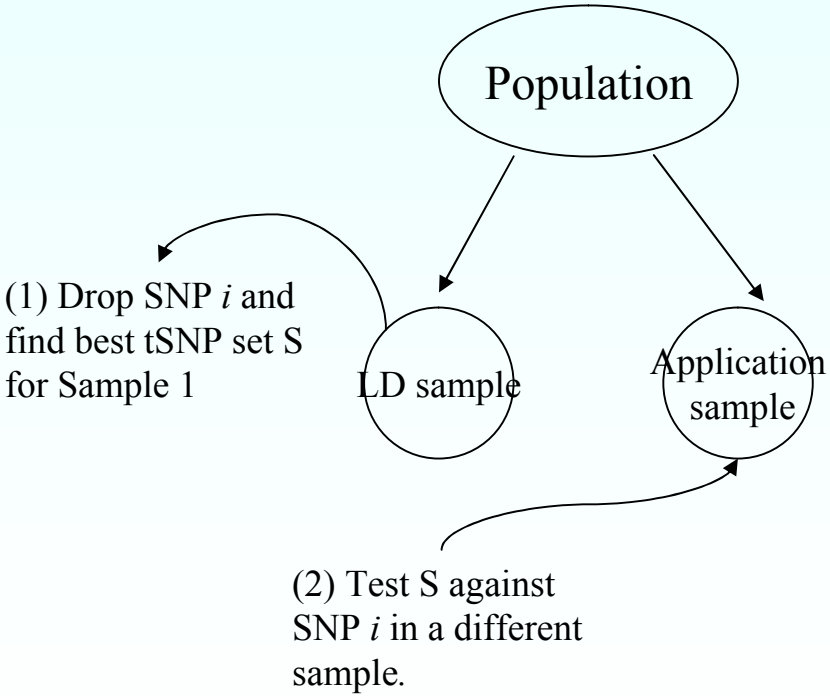
- 55 genes encoding most of the important DMEs

- Genotype approximately 1,000 SNPs in 64 CEPH and 64 Japanese individuals for a target density of one SNP / 2kb

-- GSK / UCL Collaboration --


* * * **** * *
96600000
96700000
96800000
96900000
map

Assessing the Performance of tSNPs

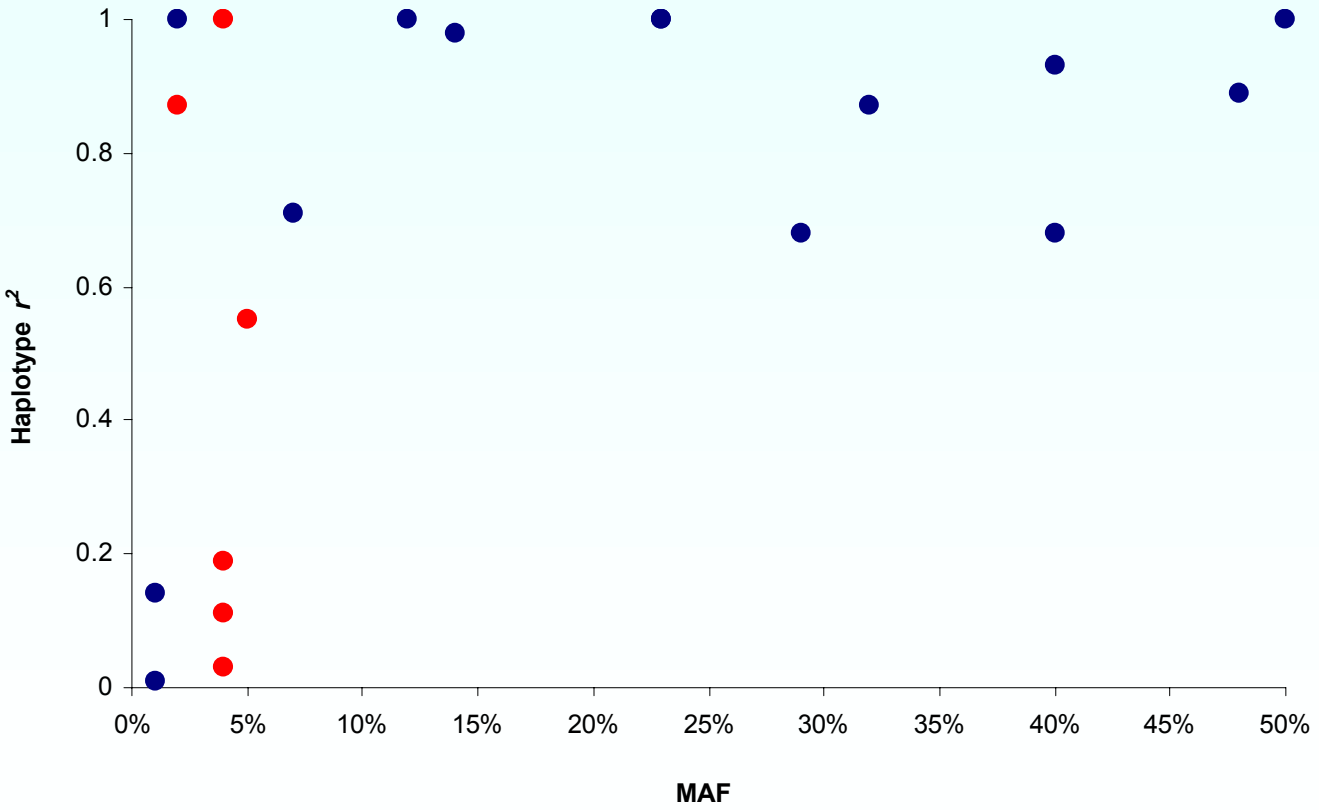


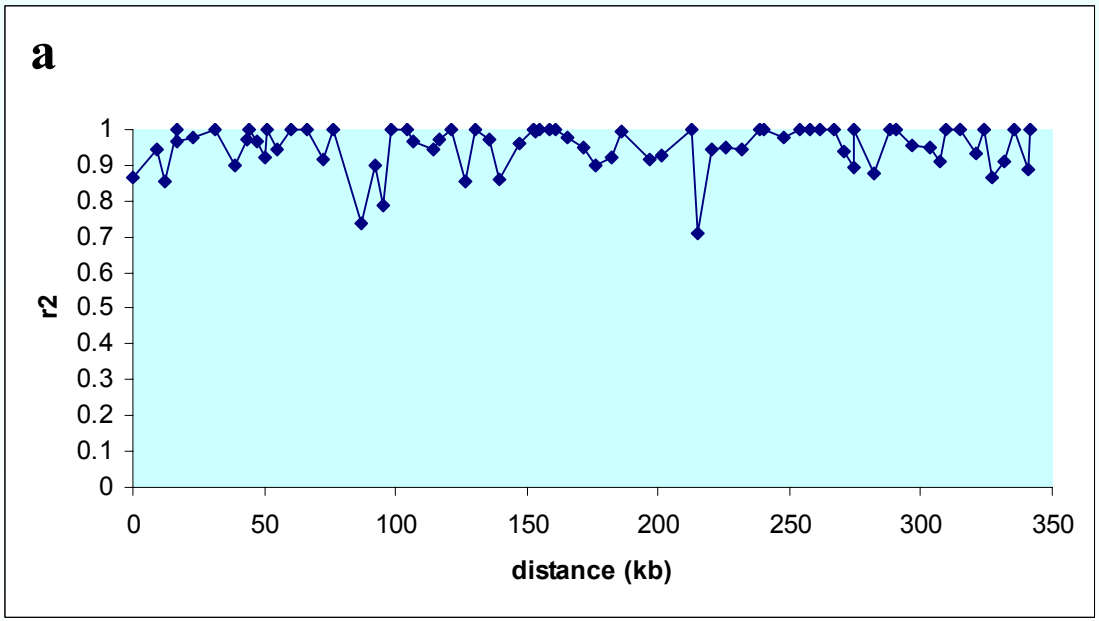
This experiment predicts the expected performance of tSNPs the way they will be used in the practise

Will tags hold in a different population?

- Tags defined in CEPH
- Genotyped in a large sample from Aberdeen
- And tested against the panel of functional variants

Application in a new population




a
r2
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
50
100
150
200
250
300
350
distance (kb)

Cosmopolitan SNPs

- Europe 196
- Japan 179

Cosmopolitan SNPs

- Europe 196
- Japan 179

- Europe and Japan 226

Tagging the major human DMEs

- **Approximately 200 SNPs are sufficient to represent the greater than 4,000 common polymorphisms in key genes regulating drug plasma levels**

(Ahmadi, Weale et al, 2005, Nature Genetics)

Representing variation

- Common variation can be efficiently represented
- It seems unlikely rare variation can be efficiently represented
  - Alternative methods required

What phenotypes should we measure?

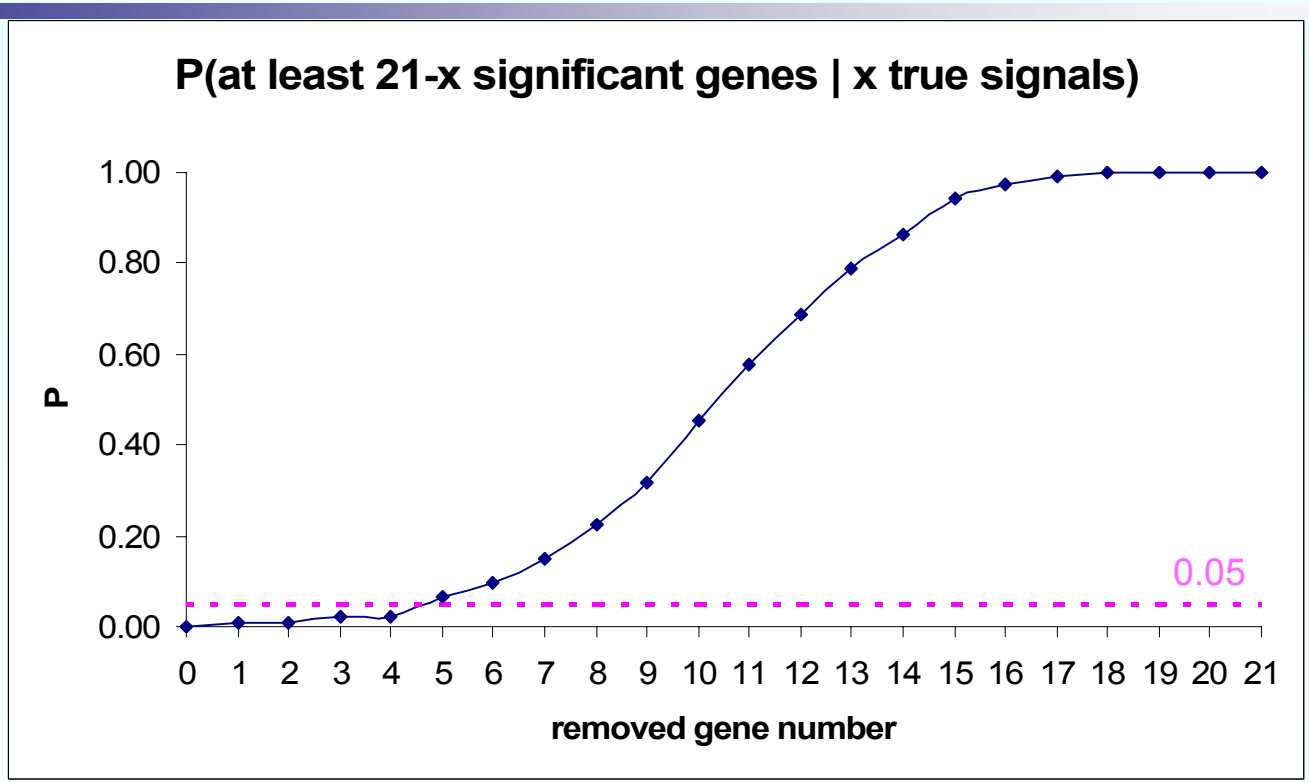
- What to measure at time of enrolment?
- What types of information most important
  - E.g. relevant tissue
  - Drug response
- Consider Managed health care providers

What are we trying to do?

HiTDIP Type 2 Diabetes Subjects

- Primary screen. All Caucasian
  - 401 cases selected from clinical trial data
    - Diagnosed diabetics with age at diagnosis between 30 – 70 years of age and BMI was < 35.
  - 400 controls selected from “Healthy Caucasian Controls”
    - Over 18 years of age free from clinical cardiac, pulmonary, gastrointestinal, hepatic, renal, haematological, neurological and psychiatric disease as determined by history, physical examination or screening investigations

Result: # true hits in primary + secondary



At least 5 hits are expected to be real at 0.05 level for T2D HiTDIP study.

Why Pharmacogenetics?

- Over 100,000 deaths from adverse drug effects in USA in

  1994

- 4^{th} / 5^{th} leading cause of death in US

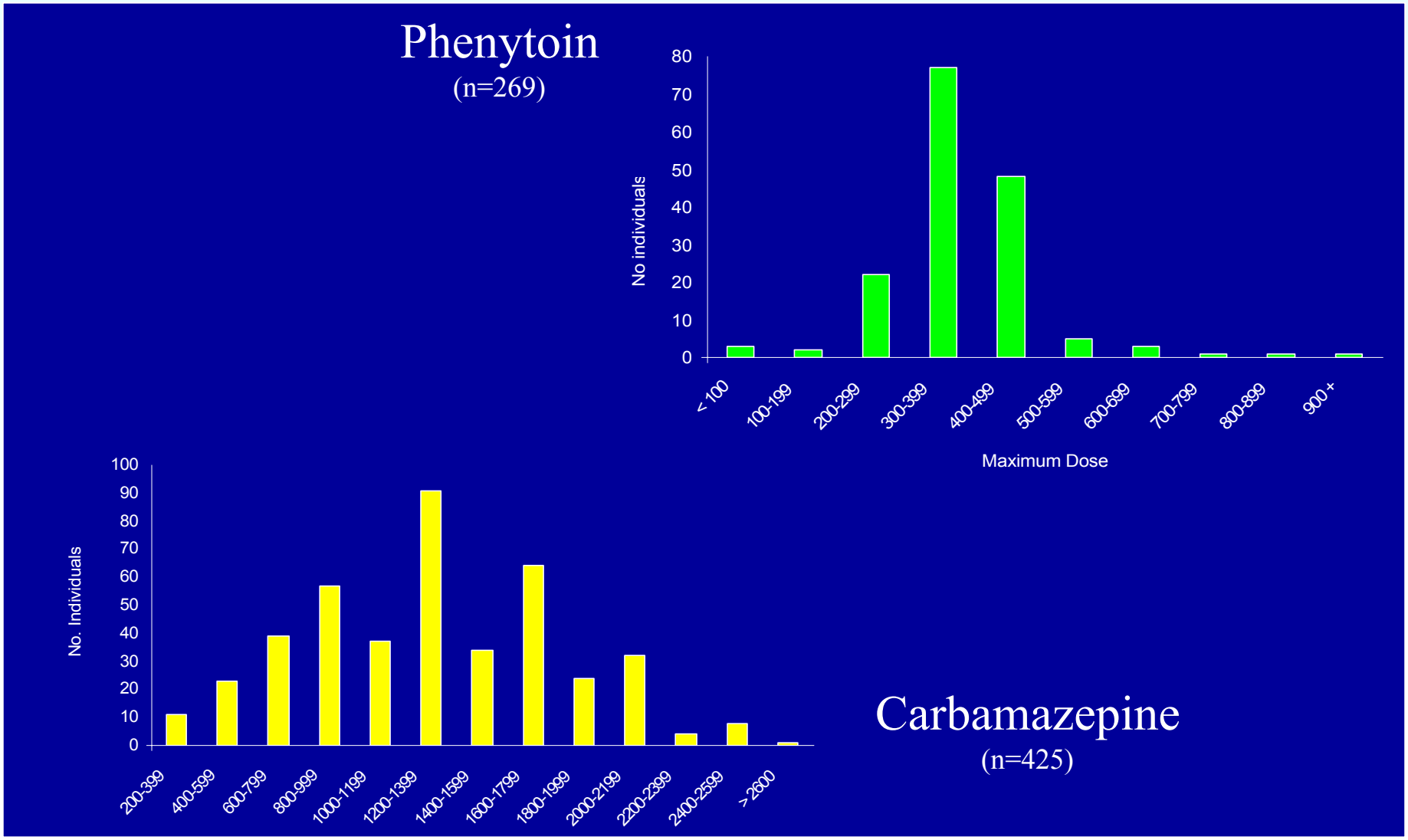
- Cost to health-care providers

Response rates of patients to a major drug for a selected group of therapeutic areas

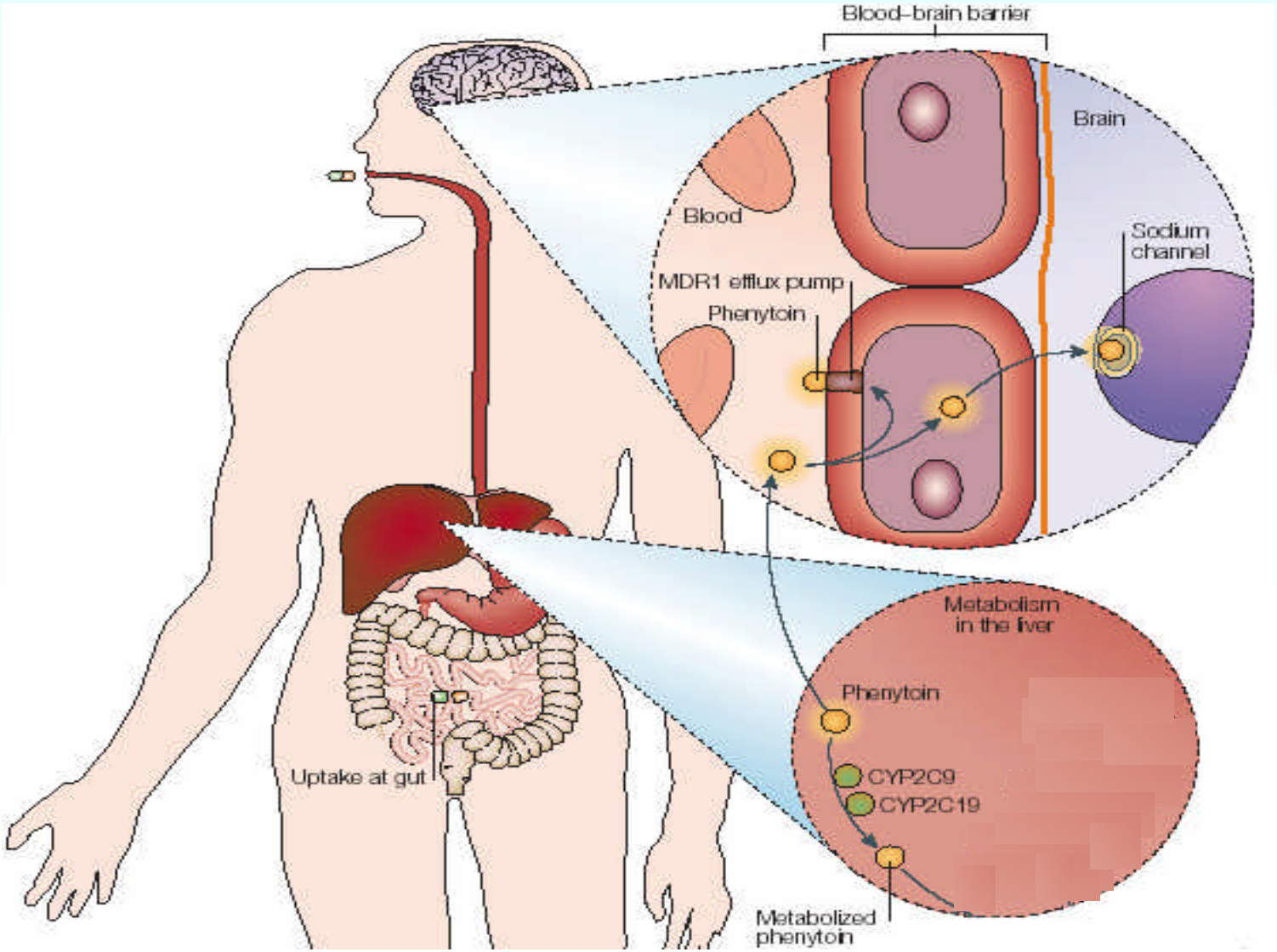
Therapeutic area	Efficacy rate (%)
Alzheimers	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrythmias	60
Depression (SSRI)	62
Diabetes	57
HCV	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Drug responses often simpler than diseases

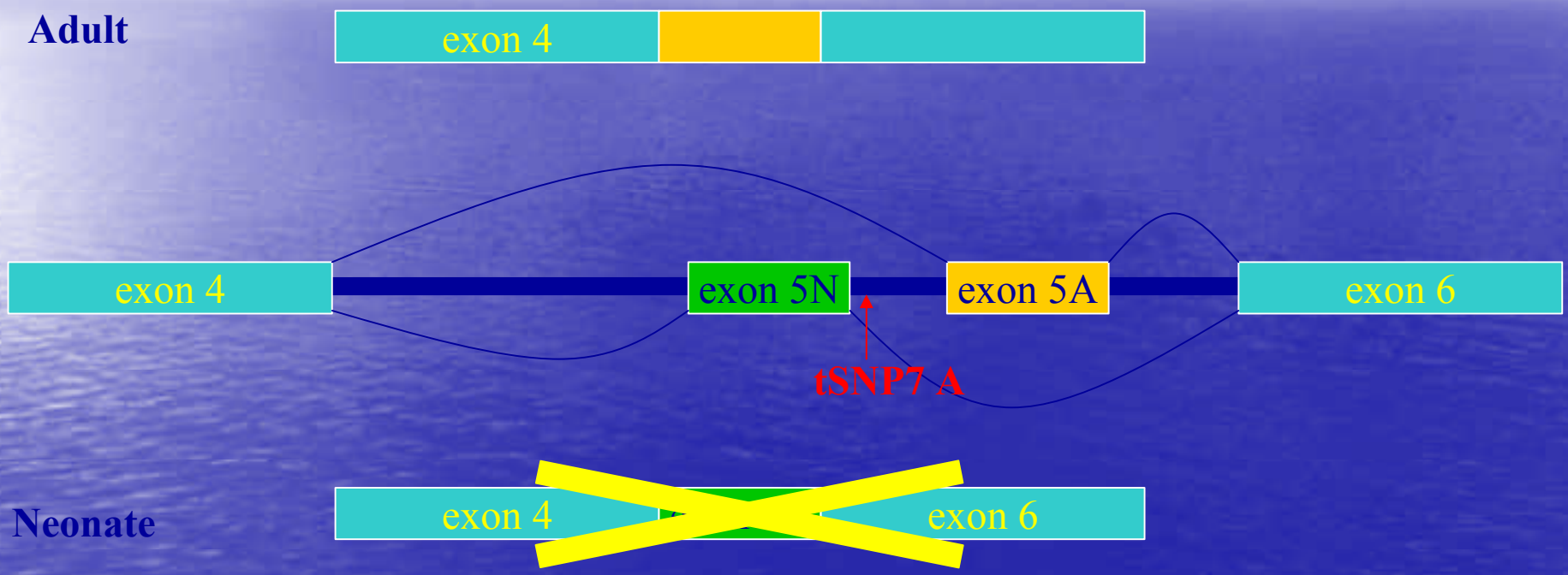
Distribution of maximum doses



Phenytoin Pathway



tSNP7 may affect SCN1A splicing in humans



tSNP7 A = splice site disrupted, expression of exon 5N altered altered 5A/5N ratio?

Clinical relevance?

- Rate at which AED dose can be safely increased

Clinical relevance?

- Rate at which AED dose can be safely increased
  - May be necessary to combine several polymorphisms that collectively offer sufficient predictive power

Pharmacogenetics is a *simpler complex trait*

- Obvious candidate genes often carry gene variants that influence drug response
- Many of the causal variants are common

Type	Total
drug target / pathway	**21**
drug transporter	**1**
metabolism	**13**
other	**7**
Total	*42*

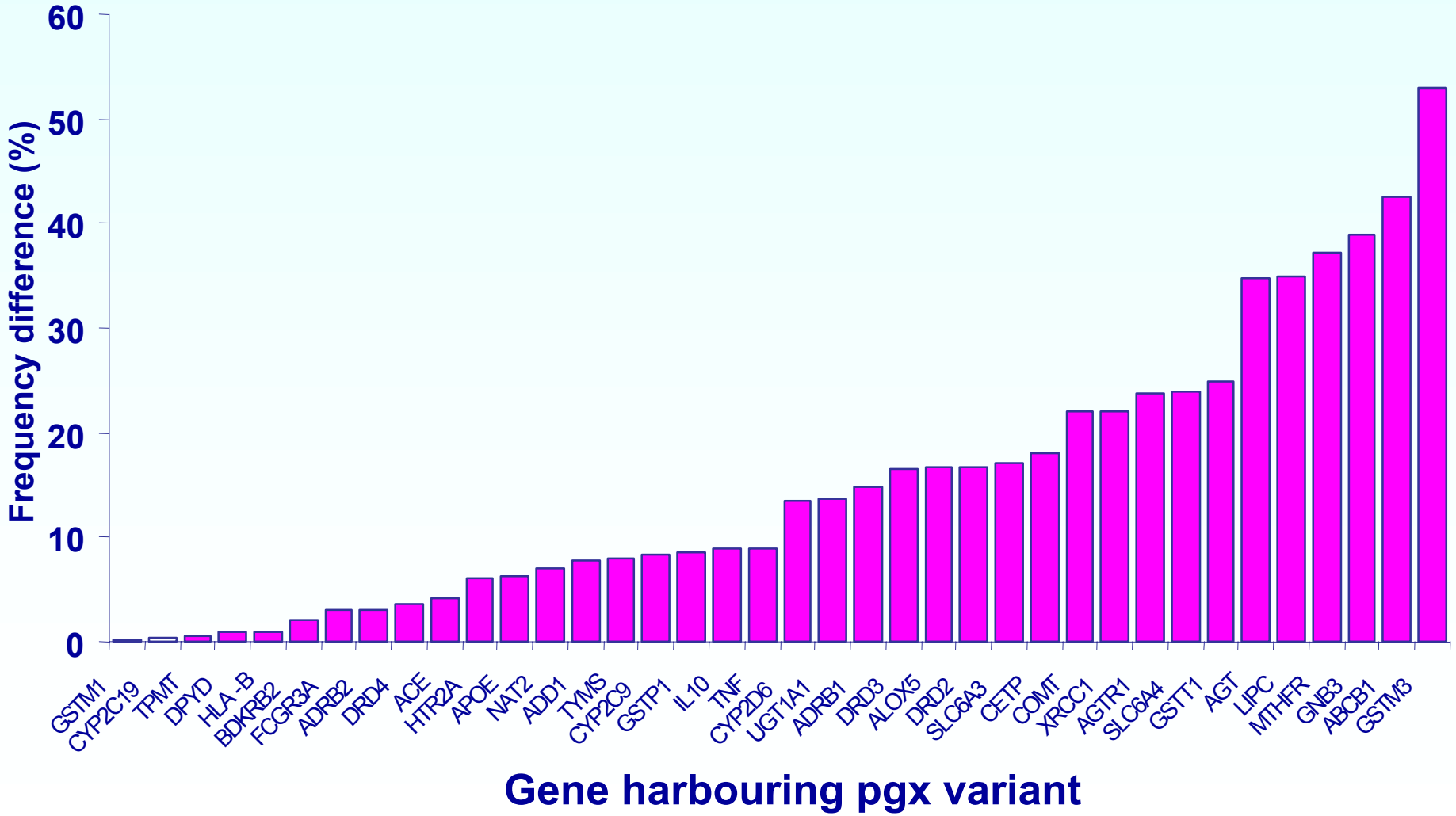
Pharmacogenetics is a *simpler complex trait*

- Obvious candidate genes often carry gene variants that influence drug response
- Many of the causal variants are common
- There is often the possibility of direct clinical relevance (change dose, select appropriate drug, etc)

A warning…

- PGx, in principle, has the potential to increase health care disparities, and this requires explicit consideration

Frequency Differences between CA and AA pgx variants (%)



Pharmacogenetics in society

- Your genome is used against you
  - Insurance, Employment, Privacy
- Your genome is not used for you

Will genetics create an information elite ?

- The genetics literature is replete with hints about what genetic differences might mean for health and drug response
- Translating these hints into practical advice requires professional help
- If national healthcare providers are unable to provide this service, only the elite will realize the benefits of genetic research in the near and medium term

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