Pharmacogenetics PGx

How far have we come and what can we expect?

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Outline of presentation

- *Key definitions in Pharmacogentics (PGx)*
  What do we expect form PGx?
  What kind of genes are we interested in?

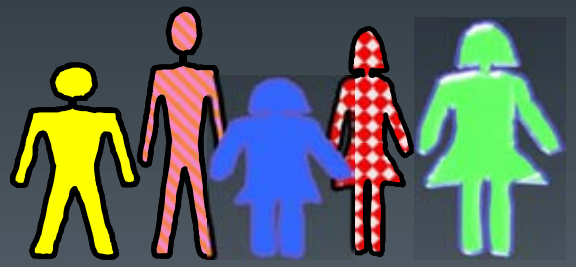
- *Examples of clinicially relevant achievements in PGx*

- *Obstacles and Outlook*

Pharmacogenetics definition

- *Pharmacogenetics (PGX) studies:*
  *…**how genetic differences between individuals affect their individual reaction to drugs.***

- *The ultimate goal:*
  *… **personalised drug therapy***



Our wish list

PGx should help in predicting…

- … how effective a drug will be
- … the correct dose
  (dose related side-effects)
- …idiosyncratic side effects
- …development of new drugs

Genes of interest in PGx

Pharmacokinetics

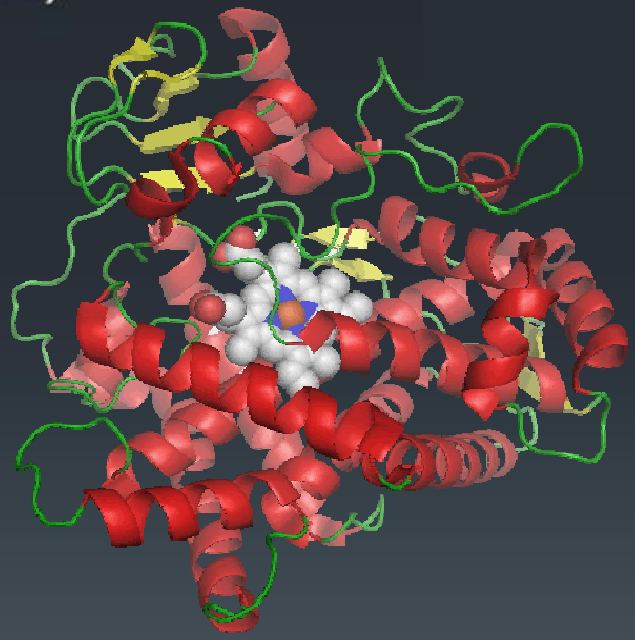
*How the body affects a drug over a period of time as a function of **absorption, distribution, metabolism and excretion**.*

Pharmacodynamics

The desired or adverse biological (for example, biochemical or physiological) effect of a drug on the body.

Pharmacokinetics: Variability in metabolizing enzymes

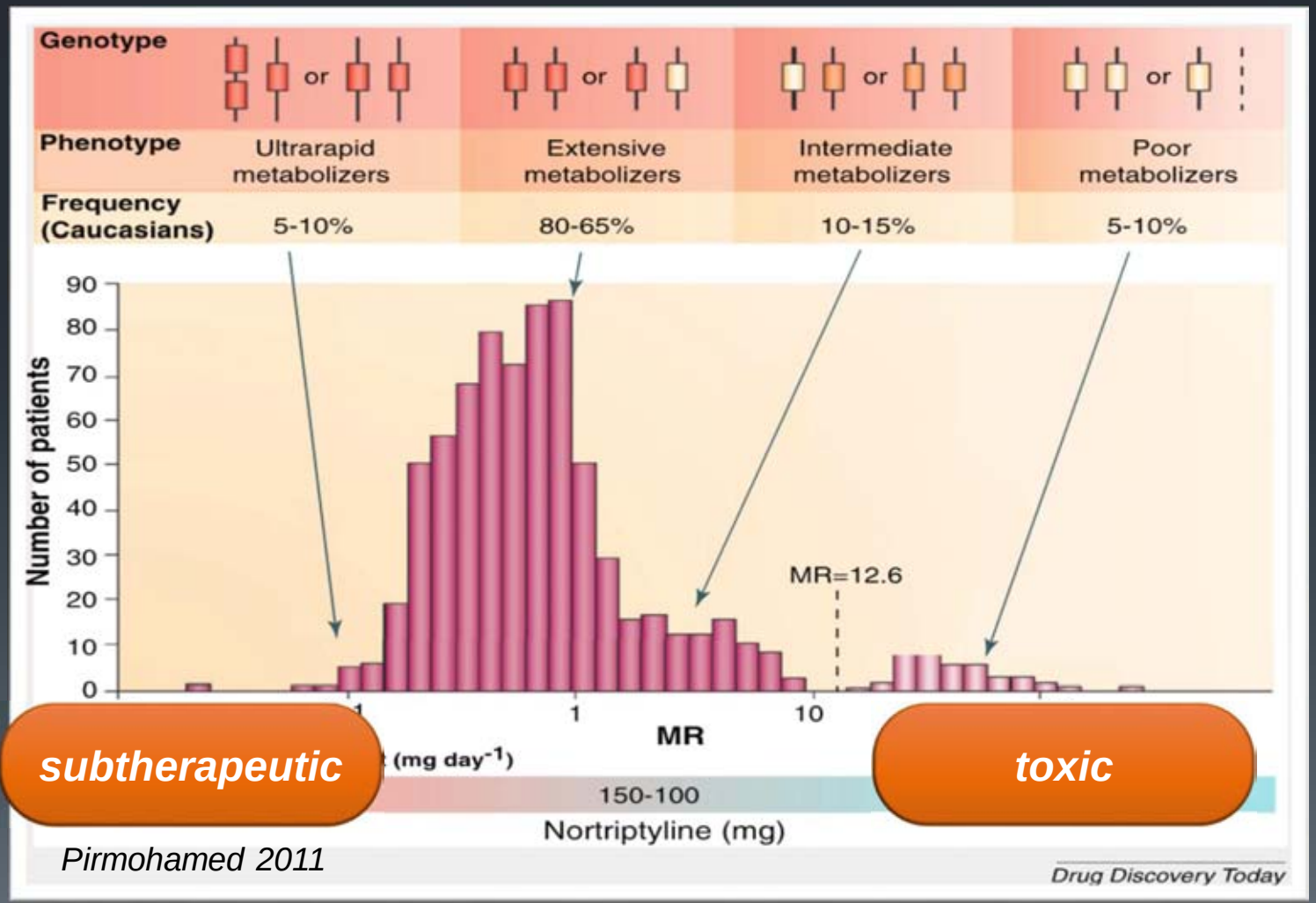
- *Cytochrome P450 family (57 genes)*
- *30-50 % of all drugs metabolized by CYP450-family*
- ***Highly polymorphic genes***
  - *alleles with reduced function/ loss of function*
  - *alleles with gain-of-function*



CYP2D6
80 different alleles

Pharmacokinetics: Variability in metabolizing enzymes

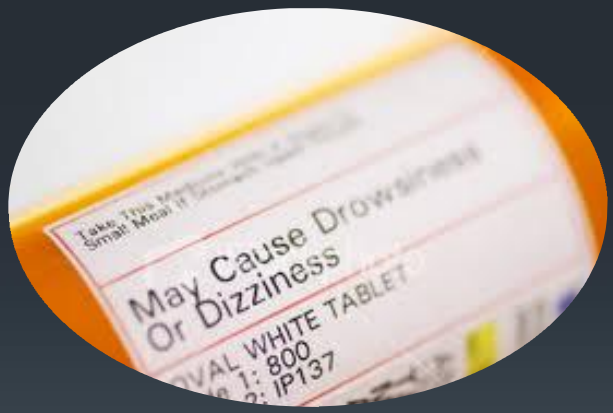
CYP2D6 metabolizers in Caucasians



Pirmohamed 2011

Case report: Phenytoin toxicity
(Kidd et al., 2001)

- *64 yr. woman, Stat. epilept.*
  -> 300 mg PHT
- *2 wks later ->*
  severe PHT intoxication
  (49,5 µg/ml)
- *Only 17% of clearance capacity*
- ***Half-life of 13 days***
  (normal 6 -24 hrs)
- *CYP2C9: 90% of PHT metabolism*
- *Patient **homozygous***
  *for **CYP2C9 *6 allele***
  (loss of function)

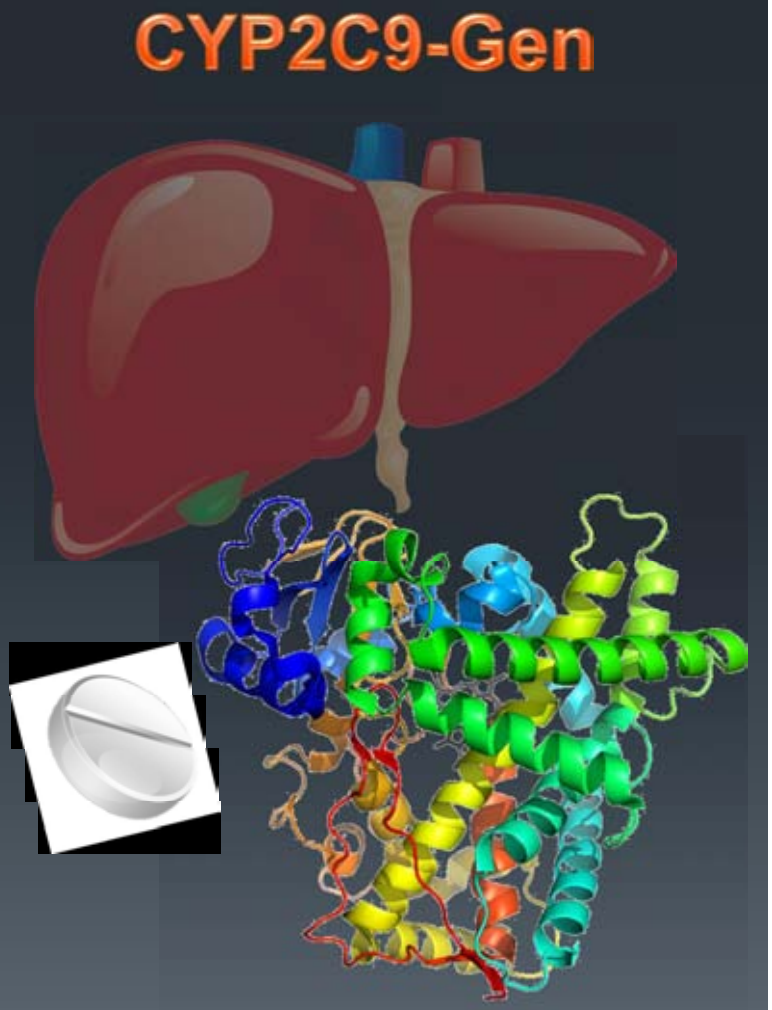


CYP2C9 alleles and PHT in population

- ***Several CYP2C9 alleles*** *(*2, *3, promoter variants) associated* ***with reduced*** *enzymatic activity*

- ***Multivariate models*** *explain 47% of PHT maintenance dose (Chaudhry, 2010)*

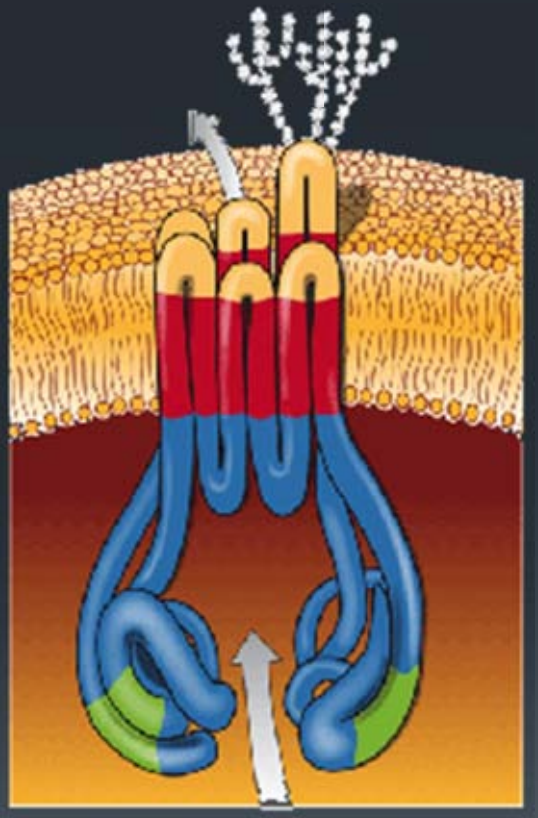
- *not in clinical use*



Pharmakokinetics – Variability in the distribution of drugs

Multi-drug resistance proteins

- *P-glycoprotein implicated in phenomenon of pharmacoresistance in epilepsy* ***(AED – Efflux)***
- *Do genetic variants in MDR-proteins play a role?*



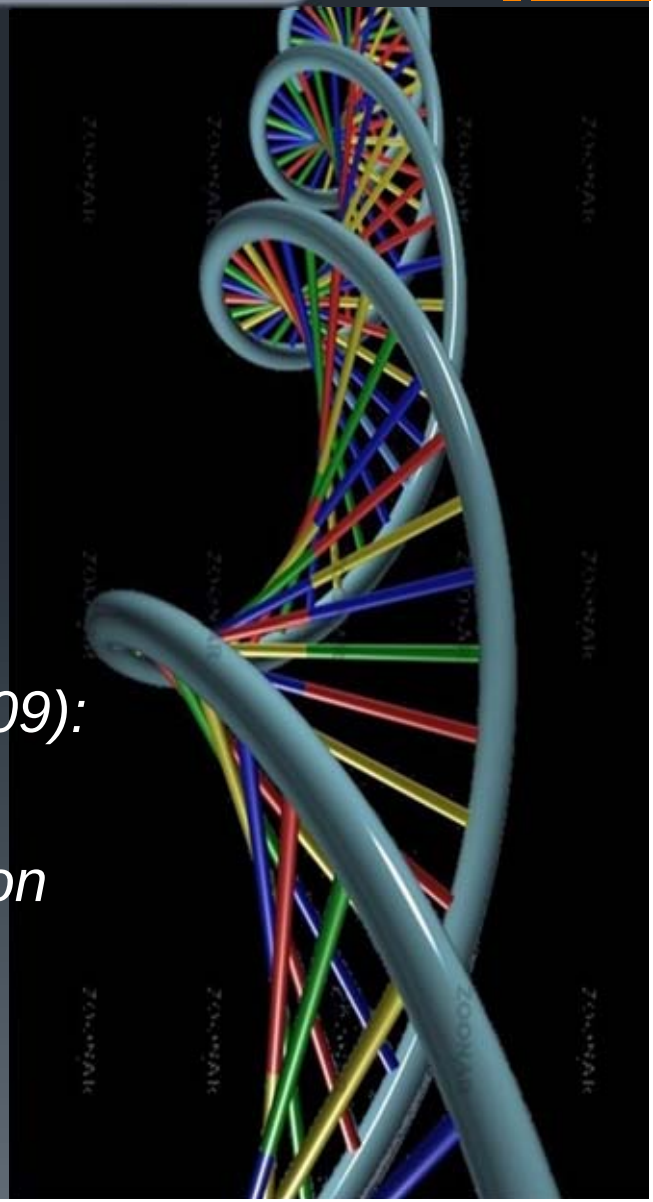
P-gylcoprotein (PGP)

PGx and pharmakoresistence

ABCB1-gene (P-glycoprotein)

- *Numerous studies of* ***C3435T-genotype with pharmacoresistance in epilepsy*** *-> results contradictory*
- ***metaanalysis negative*** *(Bournissen, 2009):*

  but heterotgeneous phenotype/ medication

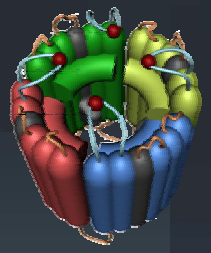


PGX and pharmacodynamics

- *focus on genes of drug targets*

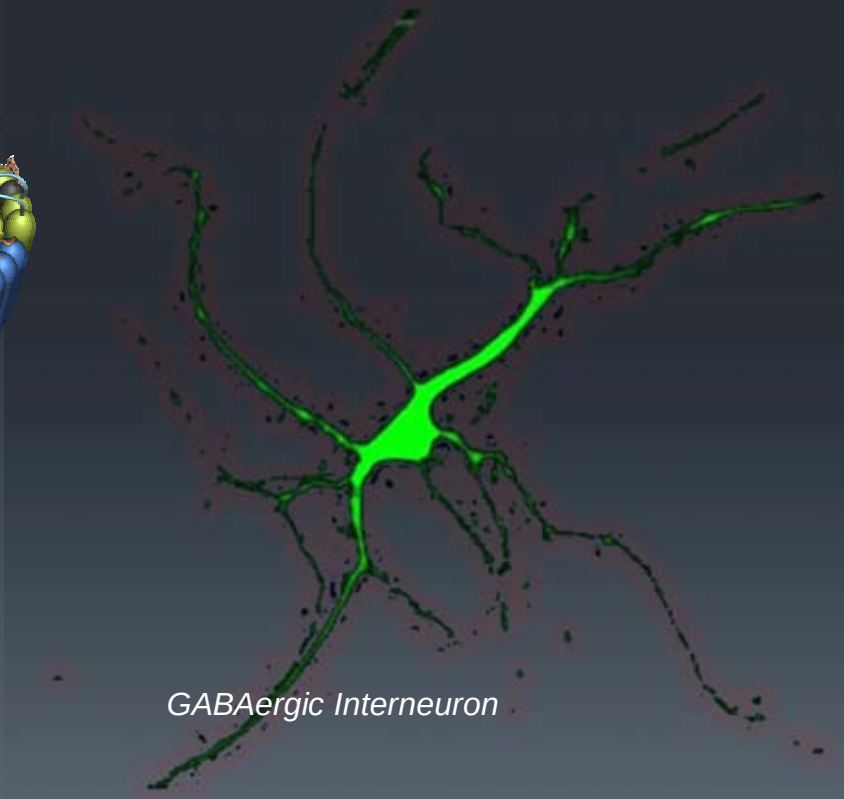
Example:

Sodium channel gene SCN1A – Dravet Syndrom



- *Genetics helps in rationalizing AED therapy*

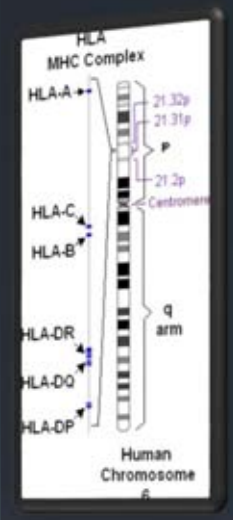
---> *no Na-channel AEDs*



GABAergic Interneuron

PGx: clinical examples

- *Idiosyncratic cutaneous reaction on carbamazepine and HLA-genes*



- *Clopidogrel efficacy and CYP2C19 genotypes*

AEDs and cutaneous side-effects

Maculopapular exanthema (MPE)

- *in **4%-10% of all AEDs***
- *mild and transient after discont.*

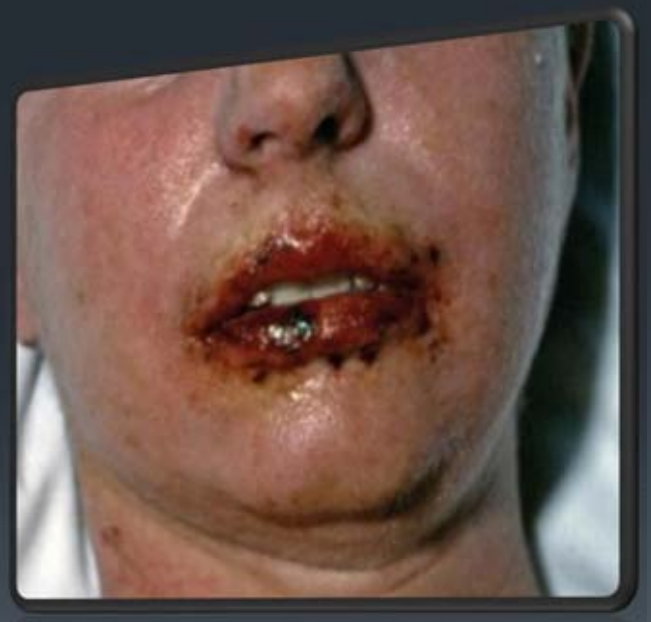
Hypersensitivity syndrome (HSS)

- *eosinophilia, systemic symptoms,*
- *lethality 10 %*

AEDs and cutaneous side-effects

Stevens–Johnson syndrome (SJS)
toxic epidermal necrolysis (TEN)

- *generalized vesicular exanthema (mucous membranes)*
- *fever and system. reactions*
- ***lethality** 5% (SJS) - **30%** (TEN)*
- *risk with aromatic AEDs 0,2% nach CBZ*



SJS / TEN & carbamazepine
(in Han-Chinese)

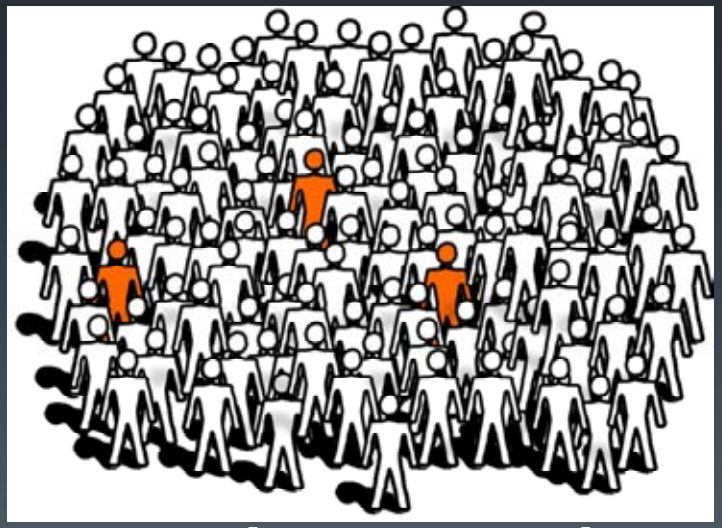
- *Chung 2004: HLA-genotypes in Han Chinese with **SJS/TEN** on **CBZ***

- *Near perfect association with*

HLA-B*1502

SJS/TEN-patients (n=44)

100% HLA-B*1502

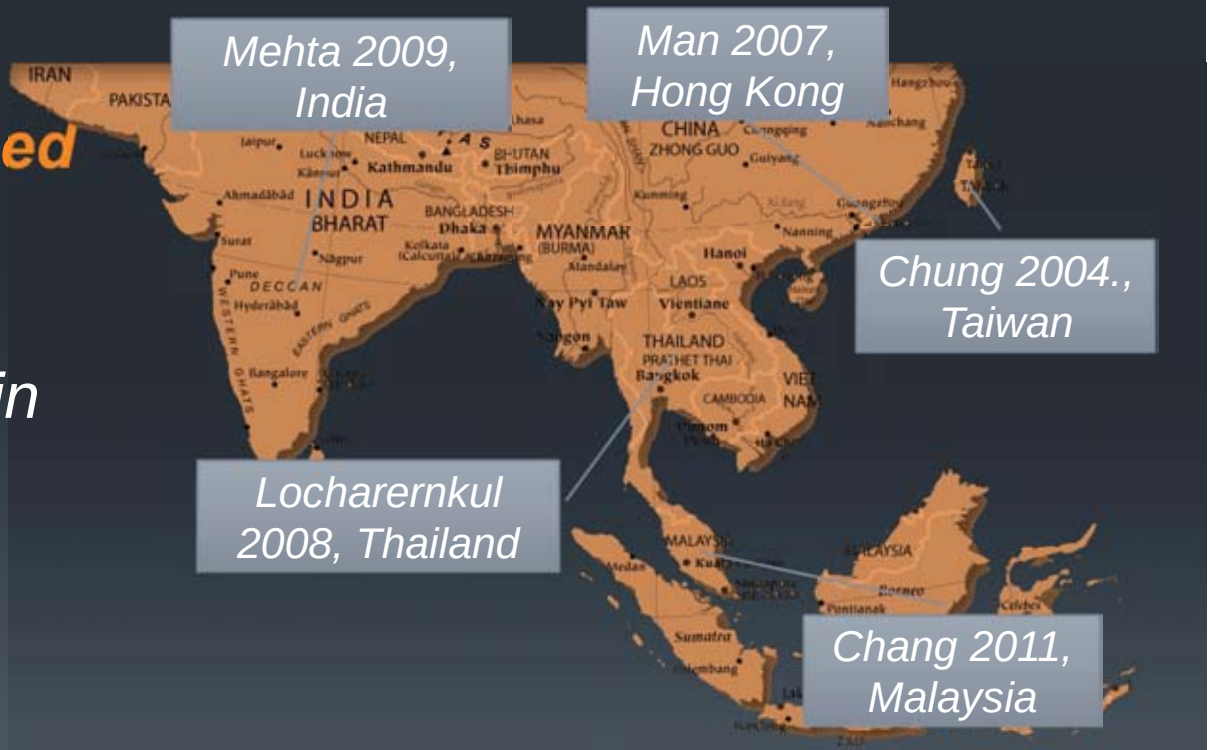


CBZ-tolerant pat. (n=101)

3% HLA-B*1502

Ethnicity and HLA-B*1502 / SJS / CBZ

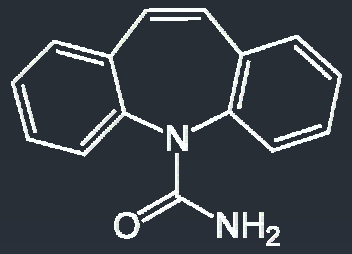
- *Association repeat. **confirmed** in **SO-Asia***
- ***No** association in **Europeans, Japanese***
  Lonjou 2006
  Ozeki, 2011
- *Allele-frequencies:* *8% in Asia*
  0,1% in Japan/Europa



HLA-B*1502 and other AEDs

HLA-B*1502 association…

- *…extends to other* ***aromatic AEDs*** *(Hung, 2010 He, 2012)*



- ***…specific for SJS/TEN*** *i.e.* ***no*** *association with (MPE or HSS)*

Mechanism of HLA-B*1502 effect

- ***direct HLA-B - CBZ interaction***

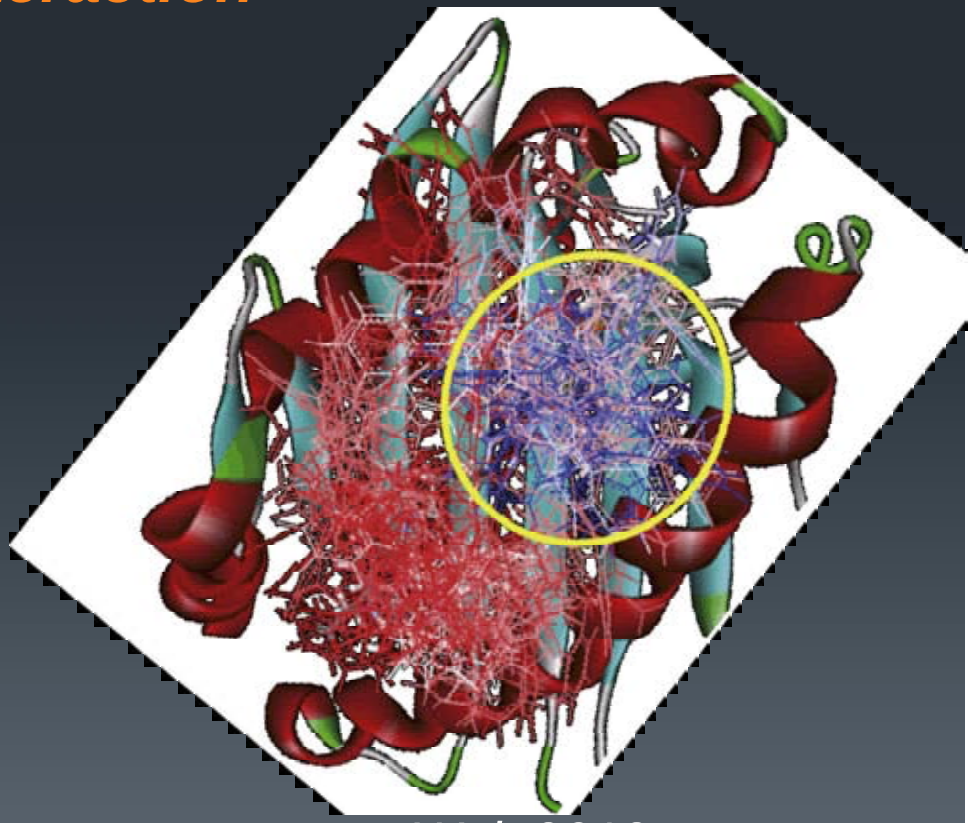
  …no need for CBZ-metabolism

- ***robust immunologial synapse***

  *HLA-B*1502*

  CBZ

  TCR



Wei, 2012

HLA-B*1502 as a biomarker
for SJS/Ten in Han-Chinese

- *sensitivity < 98.3%,*
  specificity 95.8%
  (OR: 113,4)
- *Negative predictve value : 99.9%*
  Positive predictive value: 5.6%.

FDA-Alert:

- *: … "Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine." (2007)*

HLA-B*1502 in clinical practice
in prevention of SJS/Ten in Han-Chinese

Chen, NEJM, 2011
Prospektive multicentric study, Taiwan, 2007–10

4855 patients before CBZ-therapy

testing for HLA-B*1502

7,7% positive
ê
alternat. medication

92,3% negative
ê
CBZ

follow up: 2 months

NO case of SJS/TEN (10 expected)

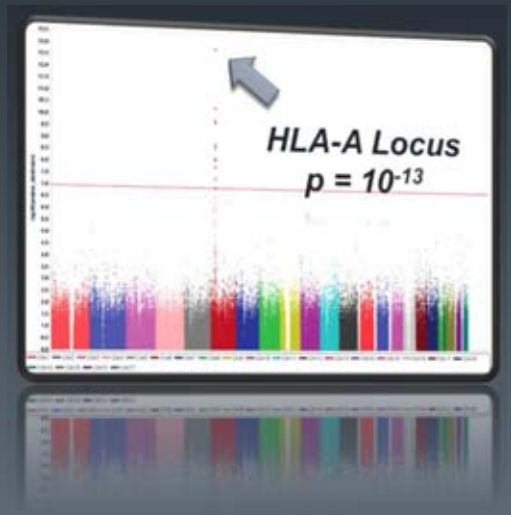
Number needed to screen: 461
(to prevent on case of SJS) (Yip, 2012)

Are other HLA-genes associated with AED induced cutaneous SE?

HLA-A*3101

- *associated with whole spectrum of **cutaneous SE** (MPE - HSS - SJS/TEN) after **CBZ –treatment***
- *global occurence (2% -9%)*
- *example of **successful GWAS***

?á-chain of MHC class I



HLA-A*3101: a biomarker for CBZ-associated cutaneous SE

	Ozeki 2011	McCormack 2011
Sensitivity	*60.7%*	*26%*
Specificity	*87.5%*	*96%*
Odds Ratio	*10.8*	*9,1*
Pos. predictive value	*12.7%*	*26%*

Number needed to screen: 47-67

Clopidogrel pharmacogenetics

- *Clopidogrel widely used antiplatelet agent with interpatient varia*
  *- **30% do NOT respond** eff*
- *Clopidogrel is a prodrug – **converted** by **CYP2C19** into **active metabolite***
- ***CYP2C19*2**: a common **loss of function** allele (>12*
- **2-allele carriers show reduced clopidogrel platelet inhibition*

Clopidogrel pharmacogenetics

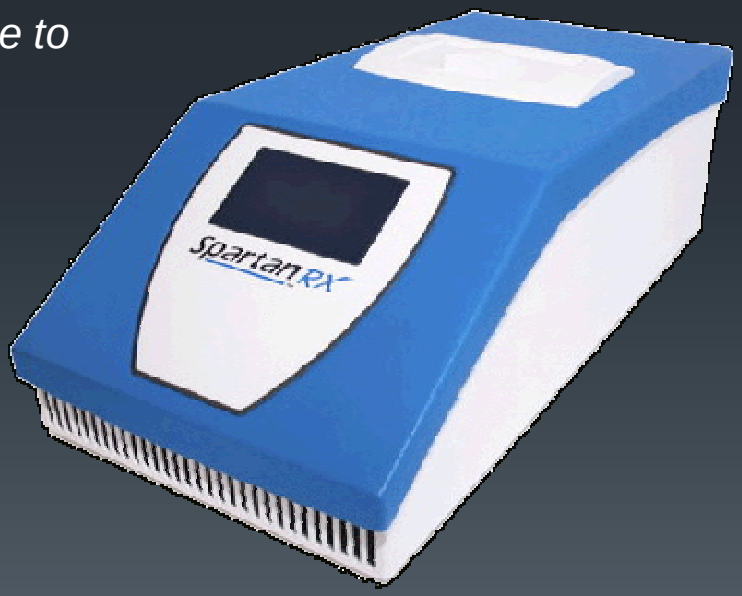
- ***CYP2C19*2-allele carriers*** *show increased* ***risk*** *for* ***clopidogrel treatment failure*** *(cardiovascular events)*
- ***Meta-analysis*** *(Mega et al. 2010)*
  9685 patients with coronary artery disease

RISK INCREASE *(for cardiovascular events under clopidogrel)*	***Allel *2 heterozygotes***	***Allel *2 homozygotes***
Stent thrombosis	***2,67***	***3,97***

Clopidogrel pharmacogenetics

- *2010: boxed **FDA warning**:*

  It is estimated that 2 to 14%of the U.S. population are poor metabolizers. The FDA recommends that health care professionals consider alternative dosing of Plavix for these patients, or consider using other anti-platelet medications. Tests are available to assess CYP2C19 genotype to determine if a patient is a poor metabolizer.



- *Development of point of care **genotyping devices** and **clinical guidelines***

- *Prospective **radomized trials** underway to test clinical utility.*

The most significant genetic predictors of drug response

Organ or system involved	Associated gene/allele	Drug/drug response phenotype
Blood		
Red blood cells	*G6PD*	Primaquine and others
Neutrophils	*TPMT*2*	Azathioprine/6MP-induced neutropenia
	*UGT1A1*28*	Irintotecan-induced neutropenia
Platelets	*CYP2C19*2*	Stent thrombosis
Coagulation	*CYP2C9*2, *3, VKORC1*	Warfarin dose-requirement
Brain and peripheral nervous system		
CNS depression	*CYP2D6*N*	Codeine-related sedation and respiratory depression
Anaesthesia	*Butyrylcholinesterase*	Prolonged apnoea
Peripheral nerves	*NAT-2*	Isoniazid-induced peripheral neuropathy
Drug hypersensitivity	*HLA-B*5701*	Abacavir hypersensitivity
	*HLA-B*1502*	Carbamazepine-induced Stevens Johnson syndrome (in some Asian groups)
	*HLA-A*3101*	Carbamazepine-induced hypersensitivity in Caucasians and Japanese
	*HLA-B*5801*	Allopurinol-induced serious cutaneous reactions
Drug-induced liver injury	*HLA-B*5701*	Flucloxacillin
	*HLA-DRB1*1501-DQB1*0602*	Co-amoxiclav
	*HLA-DRB1*1501-DQB1*0602*	Lumiracoxib
	*HLA-DRB1*07-DQA1*02*	Ximelagatran
	*HLA-DQA1*0201*	Lapatinib
Infection		
HIV-1 infection	*CCR5*	Maraviroc efficacy
Hepatitis C infection	*IL28B*	Interferon-alpha efficacy
Malignancy		
Breast cancer	*CYP2D6*	Response to tamoxifen
Chronic myeloid leukaemia	*BCR-ABL*	Imatinib and other tyrosine kinase inhibitors
Colon cancer	*KRAS*	Cetuximab efficacy
GI stromal tumours	*c-kit*	Imatinib efficacy
Lung cancer	*EGFR*	Gefitinib efficacy
	EML4-ALK	Crizotinib efficacy
Malignant melanoma	*BRAF V600E*	Vemurafenib efficacy
Muscle		
General anaesthetics	*Ryanodine receptor*	Malignant hyperthermia
Statins	*SLCO1B1*	Myopathy/rhabdomyolysis

Pirmohamed, 2011

Pharmacogenetics – Challenges and Obstacles in Clinical Application

1. ***Need to discover more PGx phenotype/genotype associations***

   - *Maximise patient numbers (collaborative studies)*
   - *Improve phenotyping (endophenotypes)*
   - *Prefer genome-wide studies (GWAS, NGS)*

Pharmacogenetics – Challenges and Obstacles in Clinical Application

2. *What level of evidence is necessary?*

- *Where possible* ***prospective/randomized trials*** *to demonstrate utility of PGx-test*
- *… but randomized trials* ***not always feasible*** *as little incentive for established drugs.*
- ***Principle of Noninferiority*** *of genetic test (prescribing practice with genetic test not worse for patients than without test)*

Pharmacogenetics – Challenges and Obstacles in Clinical Application

2. How to bridge the translational gap?

- *PGx-tests must become affordable and fast.*
  - *Point of care devices*
  - *preemptive genotyping*

- *Facilitate interpretation of test results (Teaching, guidelines and clinical pathways)*

Future of pharmacogenetics

In spite of many obstacles
PGx has the potential to transform medical care in the not too distant future