Pharmacogenomics: an important step in the quest for biomarkers of drug response

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PHARMACOGENOMICS

- Development drugs/biologicals against completely new drug targets
- Studying genetic variants as effect modifier of response to currently marketed drugs (pharmacogenetics)

Pharmacogenetics: Why ?

- To utilize drugs more effectively and safely by using biomarkers (*markers of biological response*)
- To gain scientific insight into biological effects and pathways

AND

- ***The step from clinical trial to real-life can not be solved by pooling of halthcare databases and other forms of 'big data'***

DRUG EFFECTS

- 30% NO beneficial effects — ***WHY ?***
- 30% beneficial effects
- 10% only adverse effects — ***WHY ?***
- 30% non-compliant

Biomarkers might facilitate population-based Pk/Pd modelling as well as tailored pharmacotherapy

Are genetic variants confounders or effect modifiers ?

The magic of confounding

MI	OC +	OC -
+	39	114
-	24	154

OR: 39*154/24*114 = 2.2

MI	OC +	OC -
+	21	26
-	17	59

MI	OC +	OC -
+	18	88
-	7	95

Young women: OR: 21*59/17*26 = 2.8 Old women: OR: 18*95/7*88 = 2.8

The *CLINICAL* reality of effect modification

GI – blood loss	NSAID +	NSAID -
+	39	114
-	24	154

OR: 39*154/24*114 = 2.2

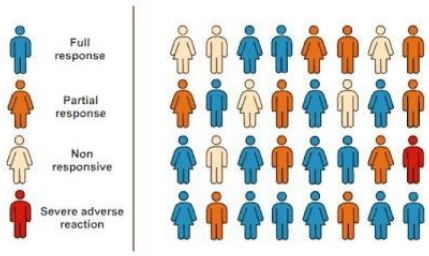
GI	NSAID +	NSAID -
+	9	26
-	17	59

Young women: OR: 9*59/17*26 = 1.2

GI	NSAID +	NSAID -
+	30	88
-	7	95

Old women: OR: 30*95/7*88 = 4.6

GENES ARE (MOSTLY) EFFECT MODIFIERS OF DRUG RESPONSE

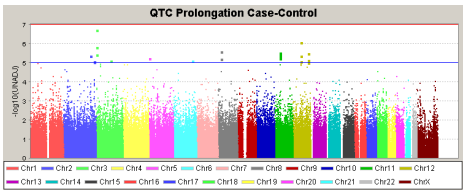


NEED FOR DETAILED POPULATON-BASED STUDIES: ROTTERDAM STUDY COHORT

- 15,000 study participants
- 5 cross-sectional interviews plus extensive physical examinations and imaging
- Complete coverage of medication and 5 drug interviews [including adherence and OTC]
- DNA available
- GWAs, exome sequencing, metabolomics, proteomics

Pharmacogenetics: mostly 2 scientific approaches

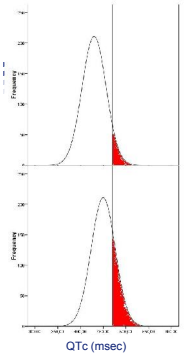
- Candidate gene studies, e.g. CYP2C9, CYP2D6
- Genome-wide analysis



Results: QT interval (msec) duration

- Difference in QT interval duration by NOS1AP genotype

	Genotypic model			Allelic model
rs10494366	Genotype			Per G-allele
	TT	TG	GG	
Subjects	2100	2334	704	5138
RR adjusted	Ref	3.2 (2.3-4.1)	7.0 (5.7-8.3)	3.4 (2.8-4.0)
RR, age, sex adjusted	Ref	3.3 (2.4-4.2)	7.1 (5.8-8.4)	3.5 (2.9-4.1)



'shift' of QTc in persons with risk genotype

Results: NOS1AP and SCD risk

rs10494366

	Genotype (cases)		
All SCD	TT (90)	TG (95)	GG (36)
Crude	Ref	1.0 (0.7-1.3)	1.3 (0.9-1.9)
Full model	Ref	1.0 (0.7-1.3)	1.3 (0.9-1.9)
Witnessed SCD	TT (47)	TG (43)	GG (26)
Crude	Ref	0.8 (0.5-1.2)	1.7 (1.0-2.7)
Full model	Ref	0.8 (0.6-1.3)	1.7 (1.0-1.8)

- HR (95% CI)
- Full model: adjusted for age, sex, BMI, smoking, hypertension, diabetes, heart failure and myocardial infarction

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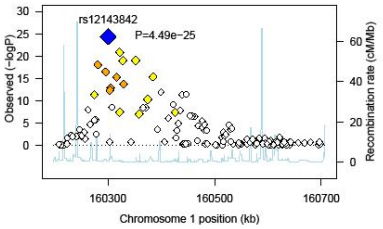
NOS1AP region, genotyped Illumina 550k SNPs



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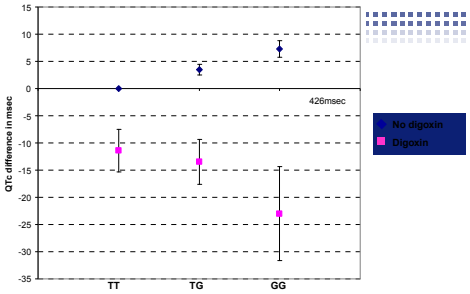
Results: Effect of digoxin and *NOS1AP* on QTc



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Genes are probably very important effect modifiers

- Absorption & distribution
  - ATP Binding Cassette (ABC)-transport proteins, e.g. P-glycoprotein
  - Solute Carrier (SLC)-transporters
  - Organic anion transporters (OCT)
- Metabolism
  - Cytochrome P450 isoenzymes, e.g. 3A4, 2C9
- Receptors

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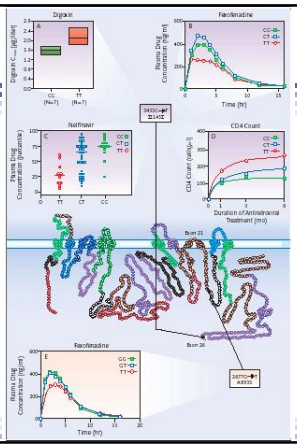

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Neuropsychiatric Adverse Reactions to mefloquine and ABCB1-gene

Haplotype	Non-cases	Cases	OR	OR*	95 % CI*
3435-2677-1236					
CGC-CGC	13	5	1.0	1.0	Ref.
CGC-TTT	25	9	0.9	0.8	(0.2 – 3.1)
TTT-TTT	5	7	3.6	3.7	(0.7 – 17.8)
TTT-TTT versus CGC carriers			3.8	4.1	(1.1 – 15.7)

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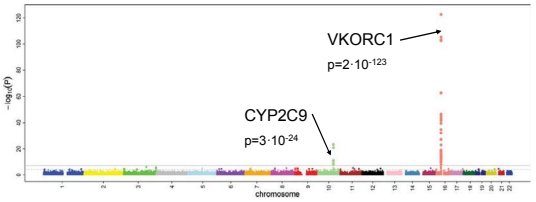
Genome wide association study acenocoumarol



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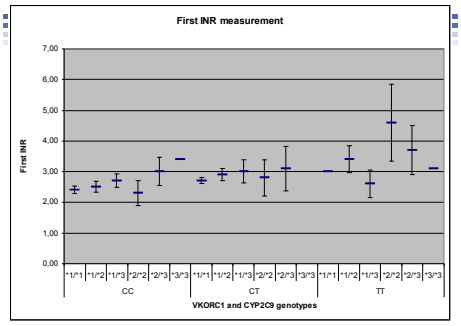
CYP2C9 & VKORC1 variants and overanticoagulation



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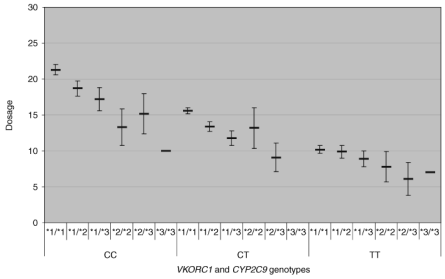
Example 1 CYP2C9, VKORC1 and coumarin dose



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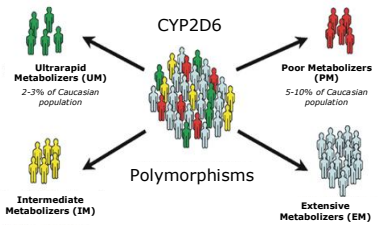
Teichert M, et al. CPT 2009;85:379-86

CYP2D6 phenotype



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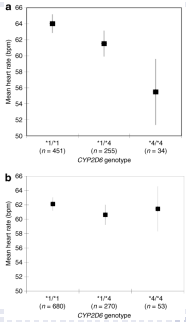
CYP2D6, ß-blockers and heart rate



metoprolol

atenolol

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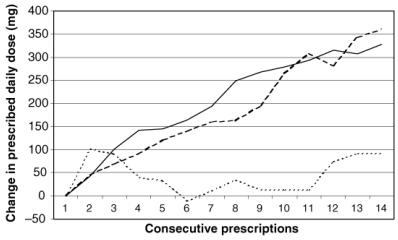
Bijl MJ, et al. CPT 2009;85:45-50

CYP2C9 and tolbutamide dose

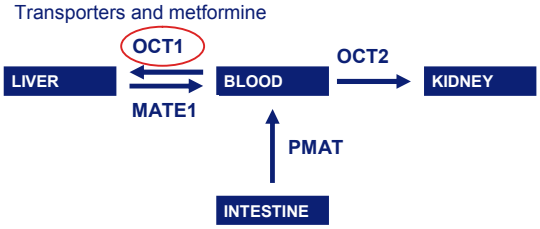


Straight line: *CYP2C9*1/*1* genotype (*n*=200).
Striped line: *CYP2C9*1/*2* and **2/*2* genotypes (*n*=61).
Dotted line: *CYP2C9*1/*3*, **2/*3*, and **3/*3* genotypes (*n*=35).

Becker ML, et al. CPT 2008;83:288-92.

Metformine & OCT1

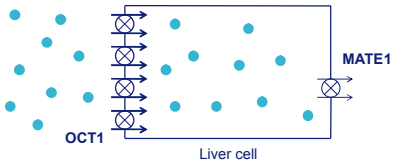
Transporters and metformine



Metformine, OCT1 & MATE1

Sufficient transport inside (OCT1); poor transport outside (MATE1)

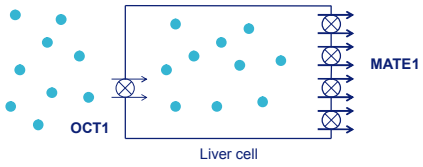
liver cell



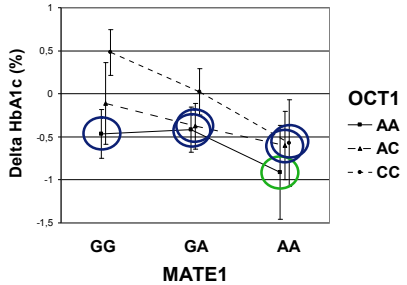
Metformine, OCT1 & MATE1

Poor transport inside (OCT1); sufficient transport outside (MATE1)

liver cell



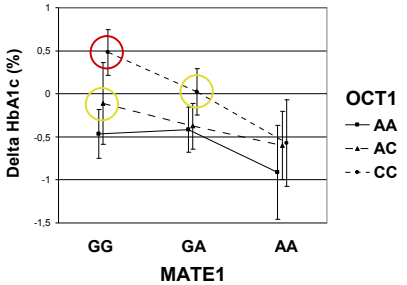
Metformine, interaction OCT1 & MATE1



68% good response to metformine

8% very good response to metformine

Metformine, interactie OCT1 & MATE1

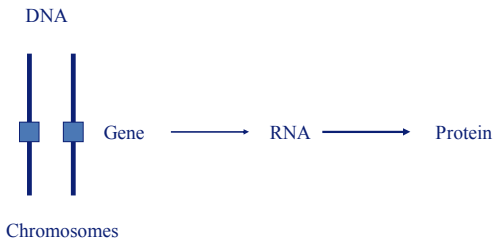


9% poor response to metformine

15% moderate response to metformine

DESPITE A 99.9% SIMILARITY IN GENES, WE ARE REMARKABLY DIFFERENT

From gene to protein



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From protein to event ?

Protein → ?????? → Event

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Conclusions

- Genetic determinants are important effect modifiers (metabolism, receptors)
- However, pharmacogenetics is only one group of potential biomarkers
- We need more knowledge about biomarkers for safe and effective drug response from detailed population-based studies
- The limitations of clinical trials can never be resolved by 'big data' only

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