UNIVERSITY OF NEWCASTLE

Psychobiology Research Group

Pharmacogenetics: Any relevance to clinical practice?

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Knowledge of the literature

Hamish - Training Center

File Edit View User Help

History | Workouts

December 2005

Mon	Tue	Wed	Thu	Fri	Sat	Sun
28	29	30	1	2	3	4
5	6	7	8	9	10	11
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Today: 12/02/2006

- 31/12/2005 09:26:37
- 29/12/2005 09:06:58
- 28/12/2005 08:48:03
- 26/12/2005 11:24:18
- 25/12/2005 09:03:13
- 18/12/2005 - 24/12/2005
  - 24/12/2005 11:07:21
  - 23/12/2005 07:41:49
  - 22/12/2005 17:50:52
  - 21/12/2005 19:51:59
  - 21/12/2005 19:30:56
  - 21/12/2005 19:13:37
  - 19/12/2005 19:45:00
  - 18/12/2005 10:36:27
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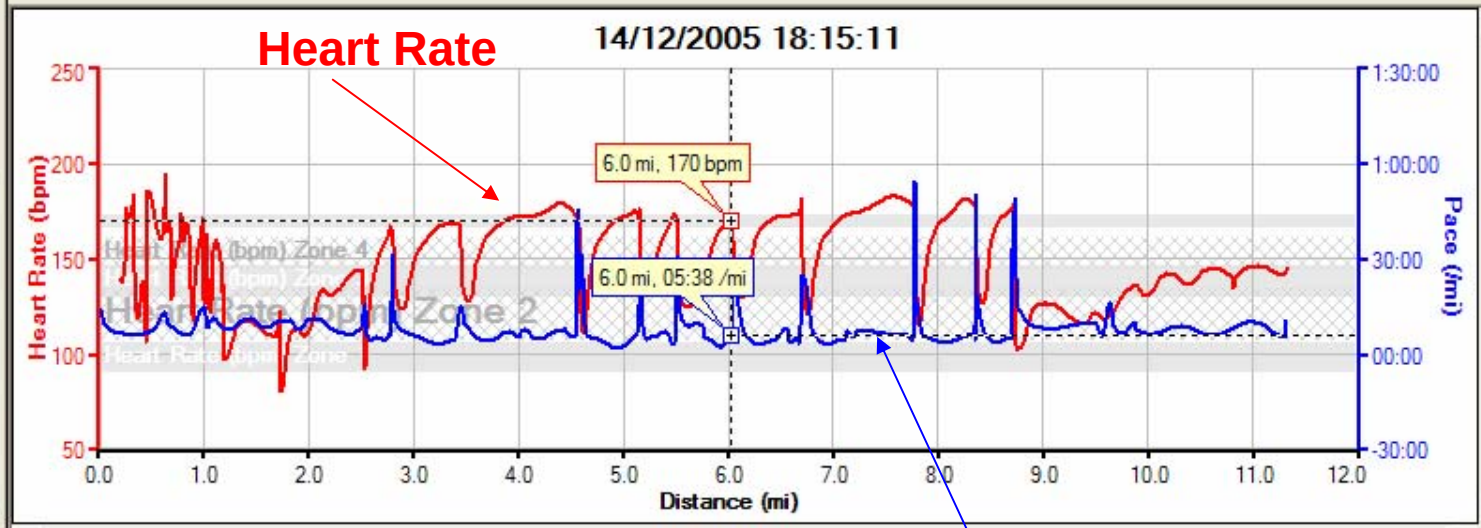
- 11/12/2005 - 17/12/2005
  - 17/12/2005 09:17:04
  - 16/12/2005 07:00:01
  - 15/12/2005 18:32:53
  - 14/12/2005 18:15:11
  - 12/12/2005 19:31:43
  - 11/12/2005 09:10:30
- 04/12/2005 - 10/12/2005
  - 07/12/2005 18:34:07
  - 07/12/2005 07:07:31
  - 05/12/2005 19:31:34
  - 05/12/2005 18:50:21
- Biking

Map | Totals | Notes

Name	Total Distance	Total Time	Avg Pace	Avg Speed	Total Calories	Avg Heart Rate
14/12/2005 18:15:11	11.39 mi	1:29:53	07:53 /mi	7.6 mph	1454 cal	144 bpm
Lap 1 - 18:15:11	2.53 mi	21:26	08:28 /mi	7.1 mph	295 cal	133 bpm
Lap 2 - 18:44:09	0.24 mi	01:30	06:07 /mi	9.8 mph	30 cal	145 bpm
Lap 3 - 18:45:39	0.14 mi	01:30	10:37 /mi	5.6 mph	53 cal	136 bpm
Lap 4 - 18:47:09	0.50 mi	03:00	05:58 /mi	10.0 mph	59 cal	157 bpm
Lap 5 - 18:50:09	0.15 mi	01:30	10:07 /mi	5.9 mph	23 cal	143 bpm
Lap 6 - 18:51:39	1.01 mi	06:00	05:55 /mi	10.1 mph	135 cal	166 bpm

Item	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Zone 8	Zone 9	Zone 10
Heart Rate (Time)	02:03	29:55	26:35	14:48	15:02					
Heart Rate (Distance)	0.2 mi	3.2 mi	3.3 mi	1.9 mi	2.3 mi					
Speed (Time)	10:52	-1:-32	05:07	04:52	04:41	06:18	08:40	15:59	08:17	01:29
Speed (Distance)	1.0 mi	-0.2 mi	0.7 mi	0.7 mi	0.7 mi	1.0 mi	1.4 mi	2.8 mi	1.6 mi	0.3 mi



Heart Rate (bpm) | Distance | Pace

Pace

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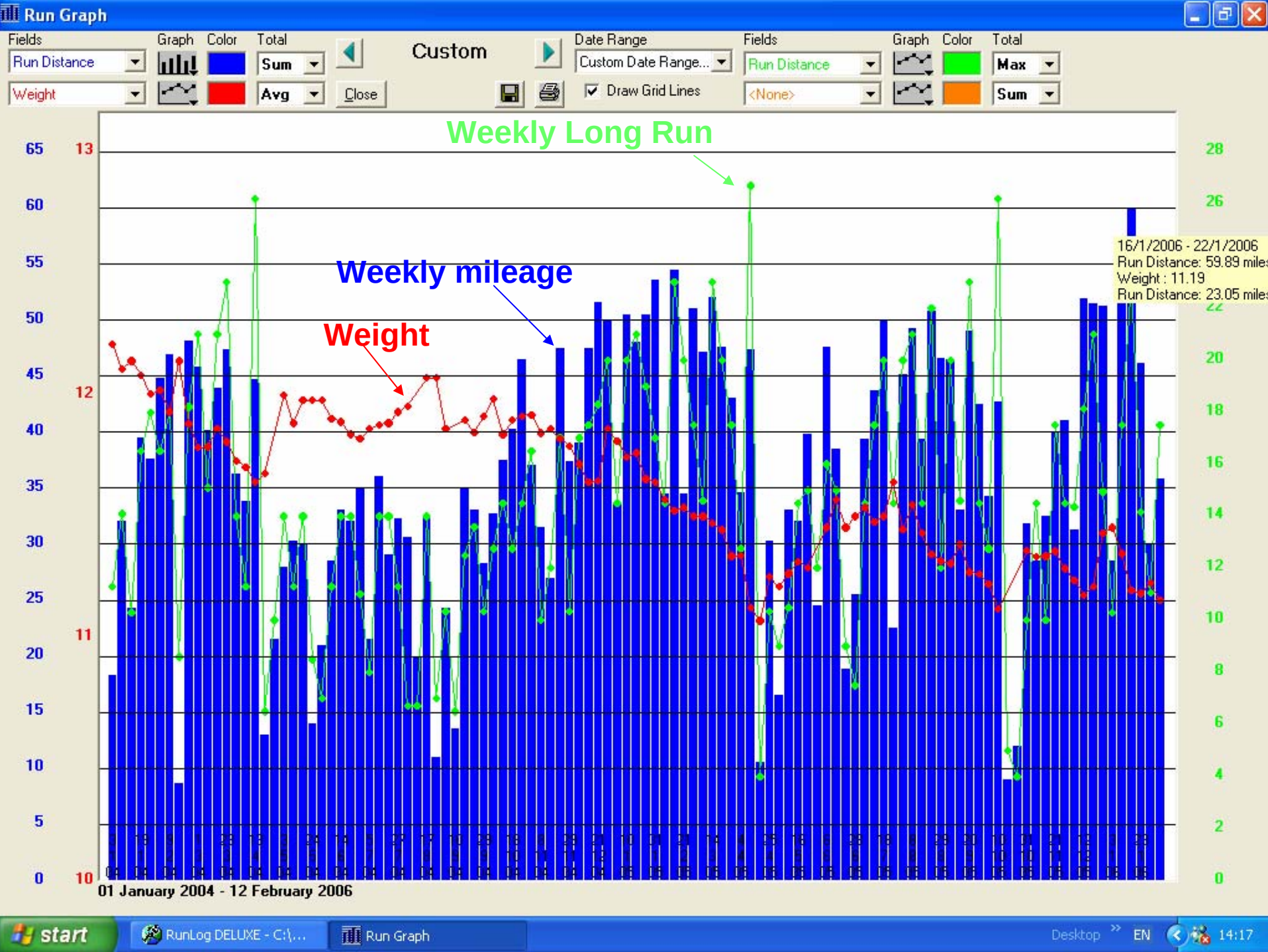
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Experience

London 2004 **London 2005** **Amsterdam 2005**

Plan

- What is pharmacogenetics and why might it be of interest in psychiatry?
- What are some of the findings in pharmacogenetics esp. relating to antidepressants and antipsychotics?
- Do these have any current or future clinical relevance?

Why Pharmacogenetics?

- Traditional use of medication in psychiatry
  - Complex poorly understood aetiology of illness
  - Trial and error
  - Restricted knowledge of drug action
  - Can take significant periods of time before it is known if a response will occur or whether side effects will be a problem
    - Biological predictors not come through to date: too great a variability between individuals?
  - Lowers compliance and affects prognosis (Black et al. 2001)

Pharmacogenetics

- Hypothesis
  - Variability in response, toxicity and adverse effects following drug treatment is influenced by genetic variation
- Advantages
  - Genotyping can be done any time
  - Not influenced by current treatment
  - Can be measured very reliably
  - Genome fully sequenced
  - Easy to do – peripheral blood sample

Potential clinical place for pharmacogenetics

1. **Narrow Therapeutic Window**
   - Accurate drug level critical
   - May be in connection with Therapeutic Drug Monitoring
2. **Significant Side Effects**
   - Side effects may cause major harm
   - Side effects may lead to significant treatment cost
3. **Efficacy Issues**
   - Difficult to determine effectiveness of drug quickly
   - The consequences of non-response are great
4. **Non-emergency Applications (initially)**
   - Sufficient turnaround time to conduct test has to be allowed
   - Need eliminated if prospective genotyping becomes standard

Heritability – a starting point

- FHx of response or side effects
  - Poor man's pharmacogenetics?
- Antidepressants
  - 38 family pairs concordant for response to Imipramine (Angst, 1964)
  - 12/12 and 10/12 concordance of first degree relatives (Pare et al. 1962; Pare & Mack, 1971)
  - Retrospective study in 4 families who responded to tranylcypromine but not other ADs (O'Reilly et al. 1994)
  - 67% of 1° rels of fluvoxamine responders responded (Franchini et al. 1998)
- Antipsychotics
  - Afro-Caribbean greater acute response than Caucasians (Emsley et al. 2002)
  - Little other supportive data

Definition of some terms

- Pharmacogenetics
  - The study of candidate genes that may influence drug effects and metabolism
- Pharmacogenomics
  - The study of all genes (and their expression) in the genome that may influence drug effects and metabolism
  - Needs large-scale high-through put techniques to screen the genome

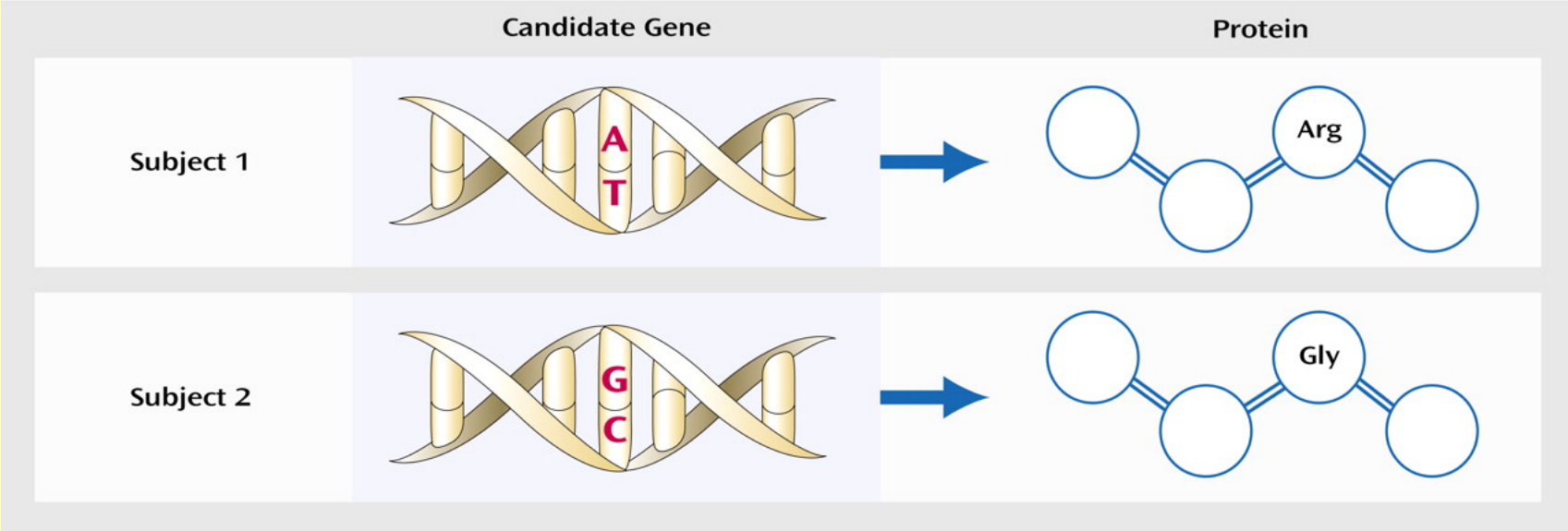
The origins of pharmacogenetics

- Isoniazid (Kalow, 1962)
  - Can lead to neurological problems in some patients
  - Due to being poor metabolisers of isoniazid due to reduced activity of N-acetyltransferase
  - Subsequently shown to be due to genetic variation in this gene

Genetic Variation

- Polymorphism
  - Genetic variation that occurs with a frequency ≥ 1% in the population
  - Various types
    - SNPs (Single nucleotide polymorphisms)
    - Repetitive DNA sequences
  - Must be functional (?)
    - Alter the expression levels or conformation of a drug-related protein

Single Nucleotide Polymorphism (SNP) in the Coding Region of a Gene



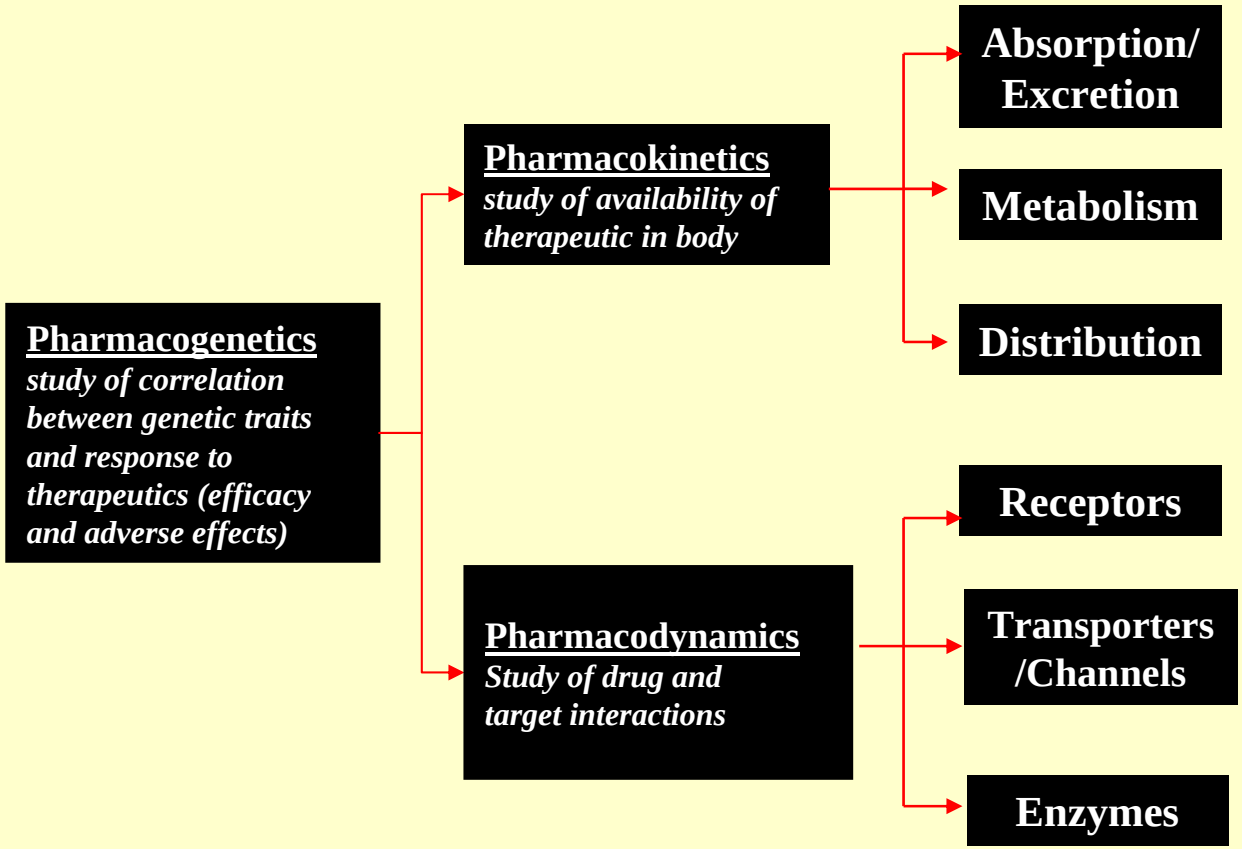
- SNP results in alteration of the amino acid sequence of the corresponding protein
  - arginine (Arg) substituted for glycine (Gly)
  - Distinct protein structures could result in phenotypic differences between the subjects, such as variation in response to medication.

Taken from Malhotra et al. 2004 Am.J.Psych.

Pharmacogenetics: Association studies

- Association of polymorphisms of candidate genes in individuals with different responses to treatment
- Useful for identifying genes of major effect
- Problems
  - Definition of phenotype
    - Diagnostic heterogeneity
    - Response assessment
    - Placebo response
    - Effects of previous treatments
  - Sample size
  - Duration of treatment
  - Ethnicity
  - Comorbid illness and concomitant medication
  - Response probably determined by multiple genes of small effect

Pharmacogenetic tree



CYP450:

- **76%** of ADRs are dose dependent
- **CYP450** is one of the best characterized metabolic protein complexes

Pharmacokinetics: CYP450

- CYP450 enzymes polymorphic with e.g. 70+ variants of CYP2D6 gene
  - Some of these affect functionality
  - Reduced activity
    - CYP1A2*1C, CYP2D6*10B, CYP2C9*2
  - Increased activity
    - CYP1A2*1F, CYP2D6*2xn

Drug Concentrations by Genotype

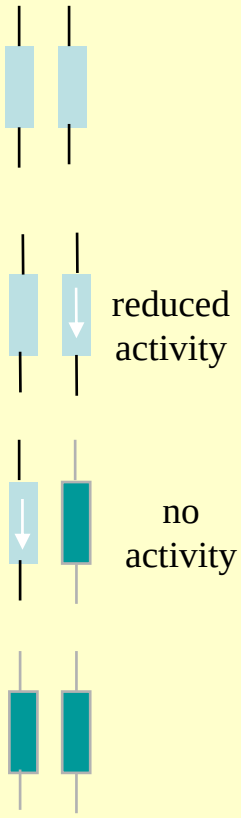
Metabolizer Status	Genotype	Response to average daily dose

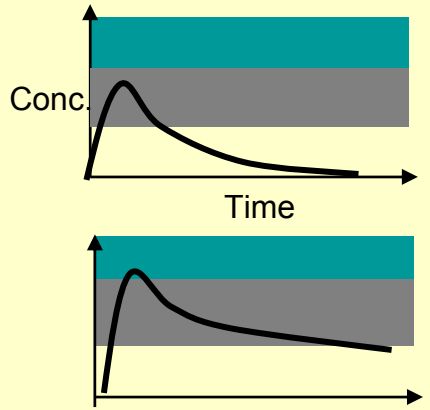
Ultrarapid

Extensive

Intermediate

Poor



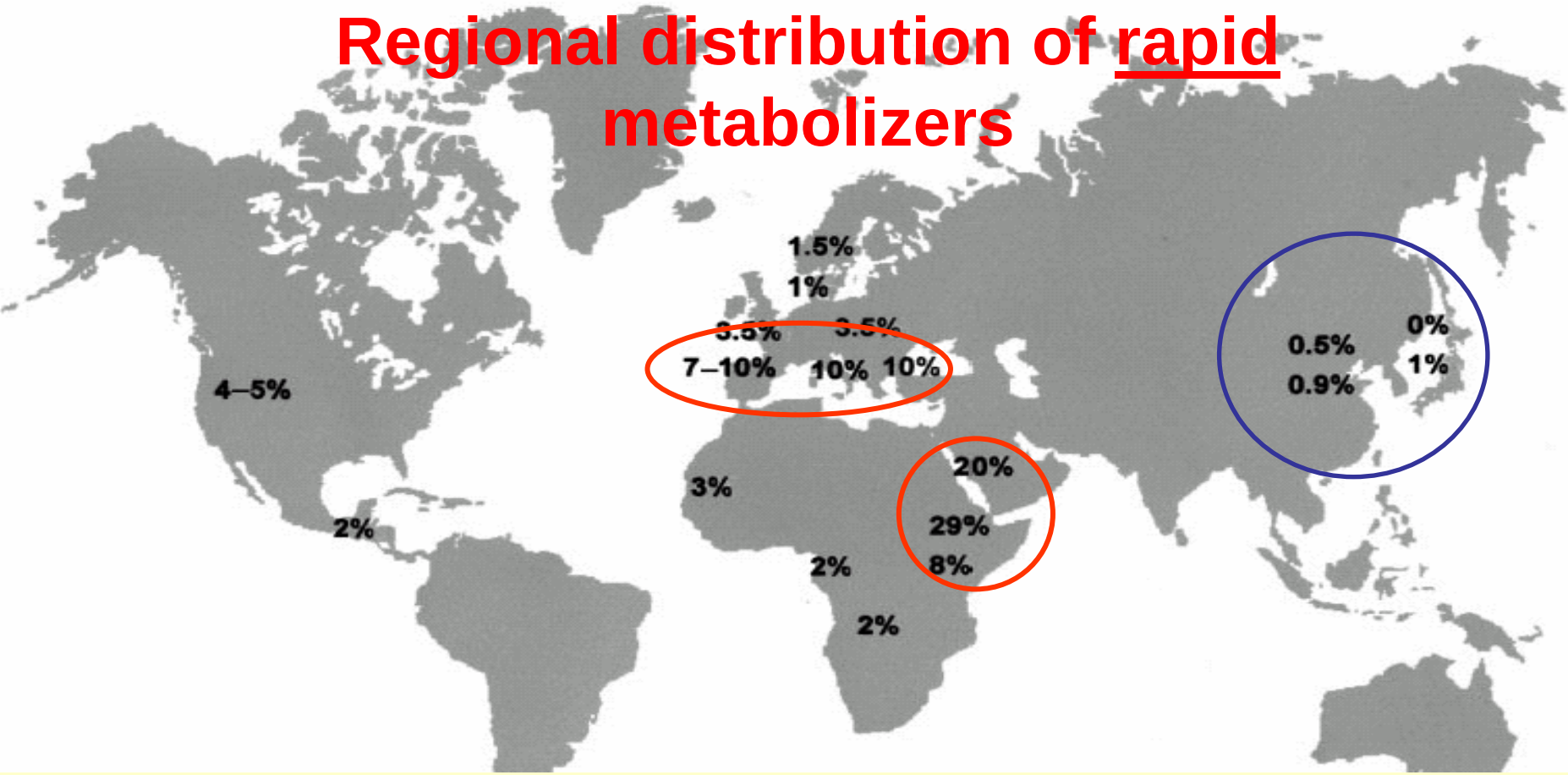


= Adverse Events

= Therapeutic Window

= Ineffective

Regional distribution of rapid metabolizers



Ingelman-Sundberg (2001) Journal of Internal Medicine 250: 186

CYP2D6 and dosing of antidepressants

Genetic analysis may allow for appropriate dosing:

	Percent of normal dose			
Drug	UM	EM	IM	PM
Venlafaxine	-	130%	80%	20%
Desipramine	260%	130%	80%	20%
Fluoxatine	-	120%	-	60%
Mianserin	300%	110%	-	70%

Source: Kirchheiner et al., Acta Psychiatr. Scand 2001: 104: 173-192

CYP450 Polymorphism Findings

- No association between CYP450 polymorphisms and response to antipsychotics or antidepressants identified to date
- CYP2D6 and CYP1A2 associated with increased side effects of antipsychotics (TD and PSx)(Basile et al. 2000; Lam et al. 2001)
- CYP2D6 and CYP2C19 associated with increased side effects with sertraline (Wang et al. 2001)
  - N.B. wide therapeutic index with SSRIs

Roche

Diagnostics

AMPLICHIP

Powered by Affymetrix

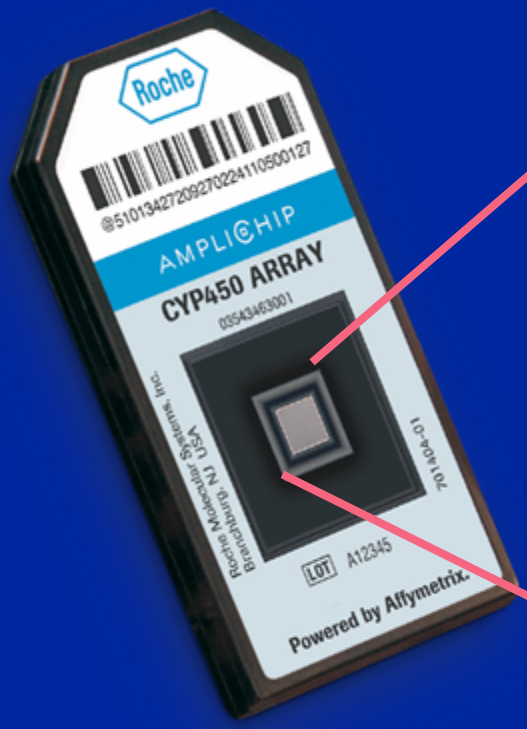
The Way Ahead™

The AmpliChip tests are based on Affymetrix microarray technology

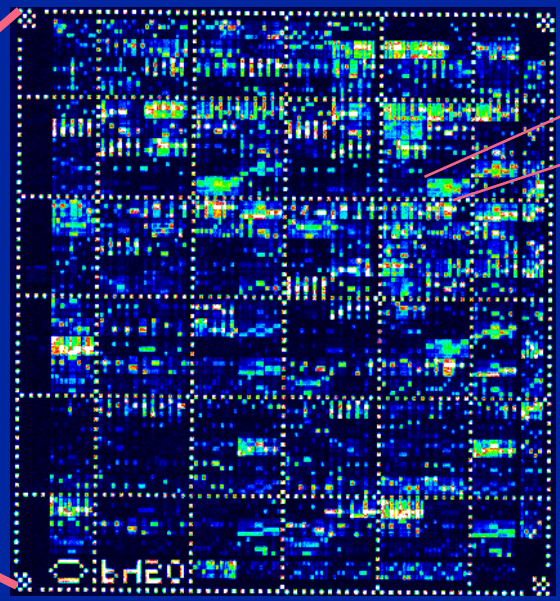
AmpliChip CYP450 CE-IVD

Roche

Diagnostics

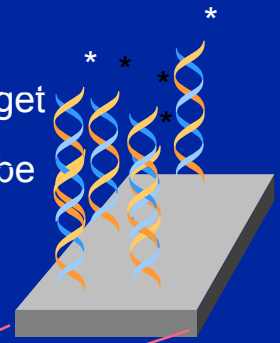


CYP450 *2D6 & 2C19*



labeled DNA target

Oligonucleotide probe



To address the relevant genetic variations, each array contains over 15,000 different probes complementary to sense and anti-sense P450 genomic DNA. Probes range in length from 18mer to 22mer

AMPLICHIP

Pharmacodynamics

- The interaction of a drug with a target molecule
  - Receptors, enzymes, transporters, ion channels
- Leads to therapeutic effects
- Can lead to side effects

Dopamine receptors and antipsychotics

- DRD2 polymorphisms
  - Associated with early response to HDL and Risperidone (Malhotra et al. 1999; Schafer et al. 2001; Mata et al. 2002)
  - **Not** long-term clozapine response (Arranz et al. 1998)
  - **Not** TD (Kaiser et al. 2002)
  - BUT N.B. largest DRD gene with many polymorphisms
- DRD3 polymorphisms
  - Associated with clozapine response (Scharfetter et al. 1998)
  - Effect of olanzapine on +ve symptoms (Staddon et al. 2002)
  - Meta-analysis shows small risk of TD (Lerer et al. 2002)
- DRD4 polymorphisms
  - No consistent association with clozapine response (Malhotra et al. 2004)

DRD3 and antipsychotic induced TD

- DRD3 S9G polymorphism associated with TD shown in meta-analysis (Lerer et al. 2002)
  - G allele has higher affinity for DA (Lundstrom et al. 1996)
  - PET study before and after HDL (Potkin et al. 2002)
    - G/G genotype have greater metabolism in striatum
    - Greatest activity in striatum associated with greatest TD

5-HT Receptors and antipsychotics

- 5-HT_{2A} polymorphisms
  - 2 different ones associated with clozapine non-response in European and American populations (Arranz et al. 1995; Masellis et al. 1998)
  - 1 associated with risperidone and clozapine response in Chinese populations (Lane et al. 2002)
  - Increased risk of TD (Tan et al. 2001)
- 5-HT_{2C} polymorphisms
  - Meta-analysis suggests role in clozapine response (Sodhi et al. 1999)
  - Risk of TD (Segman et al. 2000)
  - Risk of weight gain (Reynolds et al. 2003)
- 5-HT_{6}
  - ?Clozapine response (Yu et al. 1999; Masellis et al. 2001)

5-HT Receptors and antipsychotics:
The case of the non-functional polymorphism

- Association of 5-HT_{2A} T102C polymorphism with response to clozapine (Arranz et al. 1995)
- However…..
  - Not replicated by several (smaller) studies (Malhotra et al. 1996; Nothen et al. 1995; Lin et al. 1999; Masellis et al. 1998)
  - T102C does NOT result in amino acid substitution and does NOT effect function of 5-HT_{2A} receptor (Masellis et al. 1995)
- BUT….
  - Strong linkage disequilibrium with polymorphism in the promotor region of the gene (Arranz et al. 1998)
  - Meta-analysis confirms association (Arranz et al. 1998)
  - Opposite association in Chinese (Lane et al. 2002)

5-HT Receptors and antidepressants

- 5-HT_{2A} polymorphisms
  - Marginal association with SSRI response (Cusin et al. 2002)
- 5-HT_{1A} polymorphism
  - Functional
  - Associated with alterations in expression of 5-HT_{1A} receptors (Lemonde et al. 2003)
  - Associated with response to TCAs and SSRIs (Serretti et al. 2004; Lemonde et al. 2004)

5-HT Transporter

- Polymorphism in the 5-HTT promoter region (5-HTTLPR) – s and l forms
  - s/s associated with an stress X genetic interaction in vulnerability for depression (Wilhelm et al. 2006)
  - l/l associated with SSRI greater response in Caucasians (Smeraldi et al. 1998)
    - Response also faster (Pollock et al. 2000; Zanardi et al. 2000)
    - ? Effect in Asians - non-response (Kim et al. 2000) but response in Chinese (Yu et al. 2002)
  - s/s associated with antidepressant induced mania (Mundo et al. 2001)

Other proteins

- Tryptophan Hydroxylase polymorphism
  - Poor response to fluvoxamine and paroxetine (Serretti et al. 2001)
  - N.B. non-functional
- MAO-A polymorphism
  - No association with antidepressant response (Serretti et al. 2004)
- G-protein polymorphisms
  - Association with depression and antidepressant response (Zill et al. 2000; Exton et al. 2003)
- BDNF polymorphism
  - Trend for association with SSRI response (Tsai et al. 2003)
- Inositol phosphate polymorphism
  - Inconsistent data with lithium (Steen et al. 1998)

Lithium

- Which candidate genes to look at??
- No association between lithium response and polymorphisms of:
  - DRD2, DRD3, DRD4, $GABA_A$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, COMT, MAO-A, G-protein
  - Trend for association with tryptophan hydroxlyase
  - Association with 5-HTTLPR (Serretti et al. 2001)
- Genomic scan of lithium responders in a number of families (Turecki et al. 2001)
  - Association with markers on chromosomes 15 and 7

Combinations of genes

- Combining information from key response-related genes
  - Can constantly refine predictions by adding additional genes
  - Will need adjustments for ethnic mix
- Examples:
  - DRD3 and 5-HT_{2C} polymorphisms have additive effects on risk of TD (Segman & Lerer 2002)
  - DRD3 and CYP1A2 polymorphisms additive effects on risk of TD (Basile et al. 2000)
  - Response in Alzheimers predicted by combination of polymorphisms of APOE, PS1 and PS2 (Cacabelos et al. 2000)
- Problems
  - What statistical methods should be used?
  - Disequilibrium
  - Effects additive or synergistic?

Prediction of Clozapine response (Arranz et al. 2000)

- 200 schizophrenia patients (all white Caucasians of British origin) treated with clozapine (133 responded)
- 19 polymorphisms analysed
- 6 with strongest association with response (5-HT_{2A} X 2, 5-HT_{2C} X 2, 5-HTT, H_2) combined
  - PPV: 0.76 ± 0.08
  - NPV: 0.82 ± 0.16
  - Sensitivity 95.9% ± 0.04% (for identifying “satisfactory” responders)
  - Specificity 38.3 % ± 0.14% (for identifying poor responders)
- Utility?
  - “benefit of persevering with treatment in poor responders”
  - “more patients will benefit from clozapine if a positive response is predicted”
  - Other drugs
    - Olanz 70% correct predictions; add in DRD3 increases to 76%

Clozapine pharmacogenetic testing

- LGC (formerly the Laboratory of the Government Chemist, privatised in 1996)
  - DNA testing to identify patients with treatment resistant schizophrenia who may potentially respond to Clozapine
  - Based on Kerwin and Arranz findings
  - Cost of test = £150
  - Not recommended by D&T (see Newsletter Dec 2005)
  - Replication in prospective studies required (Malhotra et al. 2004)

Where to next?

- Independent replication of results needed
- Clarification of ethnic differences
- DNA micro-arrays for high through put analysis for a wider search of the genome
- Newer candidates
  - Genes who's expression is altered by disease
  - Signal transduction proteins

Conclusions

Pharmacogenetics:
Any relevance to clinical practice?

Possibly….

- CYP450 chip technology may be helpful for a minority of patients
  - A pragmatic trial is about to start
- Use of pharmacogenetics for efficacy predictions (e.g. for clozapine) less clear

- The future (5-10 years) does potentially look very interesting

Reviews

- General
  - Bolonna et al. (2004) Int Rev Psychiatry 16(4), 311-319
  - Malhotra et al. (2004) Am J Psychiatry 161(5), 780-796
- Antidepressants
  - Serretti & Artioli, (2004) Psychopharmacology 174, 490-503
- Antipsychotic induced weight gain
  - Correll & Malhotra (2004) Psychopharmacology 174, 477-489