FDA Workshop on Drug Metabolizing Enzymes and Pharmacogenomics

September 13th, 2004

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First Description of a Defect in Debrisoquine Metabolism

Mahgoub A, Idle JR, Dring LG, Lancaster R, Smith RL. Lancet ,1977

94 healthy staff and students from St. Mary's Hospital Medical School each took debrisoquine orally (declinax, 10 mg

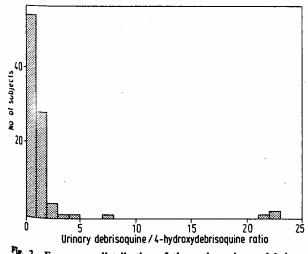


Fig. 2.—Frequency distribution of the ratio, urinary debrisoquine/4-hydroxydebrisoquine, in 94 human volunteers.

The Population Distribution of Sparteine Metabolism is Polymorphic: Eichelbaum et al: 1977.

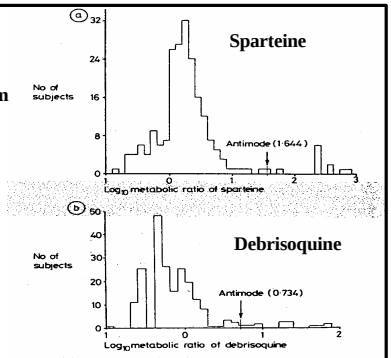


FIG 1 *(a) Frequency distribution histogram of log_{10} metabolic ratio for sparteine in 215 unrelated white British subjects. (b) Frequency distribution histogram of log_{10} metabolic ratio for debrisoquine in 215 unrelated white British subjects.*

CYP2D6 genotype can Significantly Alter the Pharmacokinetics of Multiple Drugs:

e.g. Metoprolol.

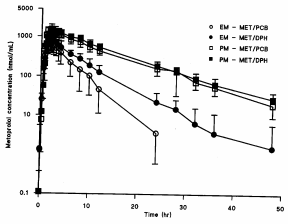


Fig 2. Pharmacokinetic profile of metoprolol in 10 extensive metabolizers and six poor metabolizers after single oral dose of metoprolol with and without concomitant administration of diphenhydramine or placebo.

CYP2D6 genotype Effect on Pharmacokinetics sometimes translates to a Pharmacodynamic effect

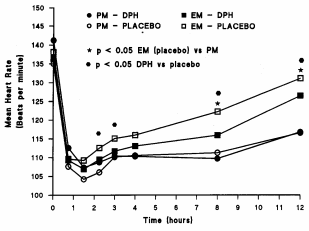
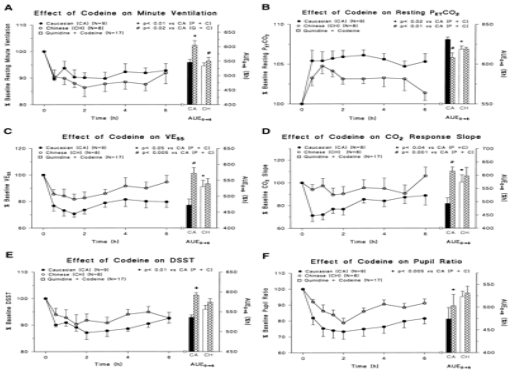


Fig 3. Changes of mean heart rate during exercise in 10 extensive metabolizers and six poor metabolizers after a single oral dose of metoprolol with and without concomitant administration of diphenhydramine or placebo.

Turgeon et al: Clin Pharmacol Ther: 2000:466-477

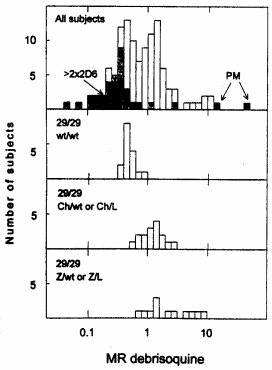


CARACO ET AL JPET,1999. CAUCASIAN AND CHINESE SUBJECTS,OPIATE RESPONSIVENESS

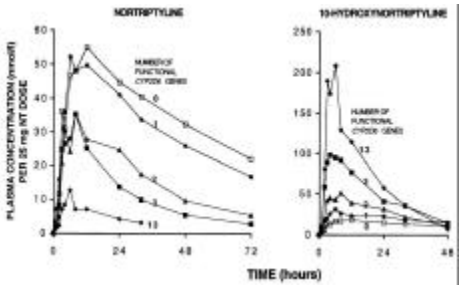
CYP2D6 Substrates: www.drug-interactions.com

- Atomoxetine
- Fluoxetine
- Paroxetine
- Dextromethorphan
- Flecainide
- Ondansetron
- Bufarol
- Metoprolol
- Propafenone
- Propranolol
- Codeine
- Tamoxifen
- Tramodol

1996: Description of ultrarapid CYP2D6 metabolism of debrisoquine caused by multiple copies of the CYP2D6 gene



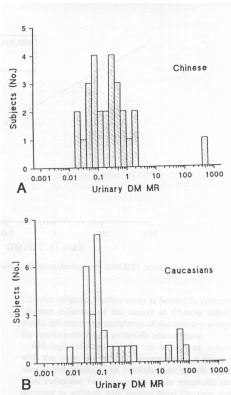
Aklillu et al: JPET 1996:278:441-446.



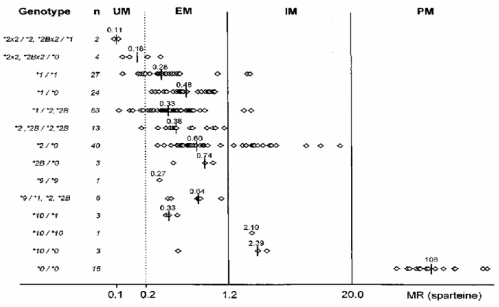
Population Distribution of CYP2D6 phenotype using Dextromethorphan in Chinese and Caucasians

From Woosley *et al*:

Clin Pharmacol Ther 1991;49:410-419

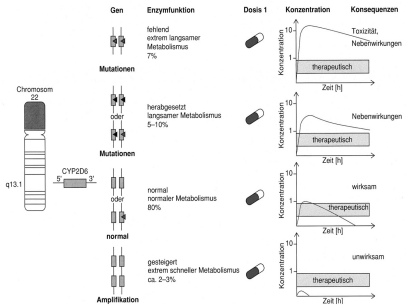


1997: CYP2D6 Genotype Can be Used to Predict 4 Phenotypes in the Sparteine Metabolic Ratio



From: Eichelbaum *et al*: Pharmacogenetics 1997;8:15-26.

Auswirkungen von CYP2D6-Polymorphismen

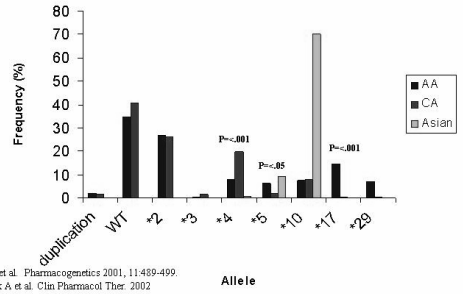


Forth, Henschler, Rummel: Allgemeine und spezielle Pharmkakologie und Toxikologie, 8.Auflage, 2001, Seite 50

CYP2D6 Alleles

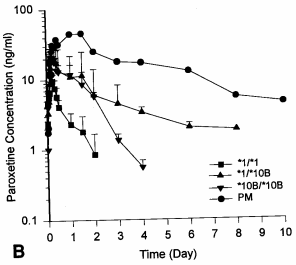
- Multiple alleles Suggests a Large Number of Genotypes need to be Tested for in Every Case
- Not so

Allelic Frequencies of CYP2D6 in African-American and Caucasians



Wan Y et al. Pharmacogenetics 2001, 11:489-499.
Gaedigk A et al. Clin Pharmacol Ther. 2002 Jul;72(1):76-89.

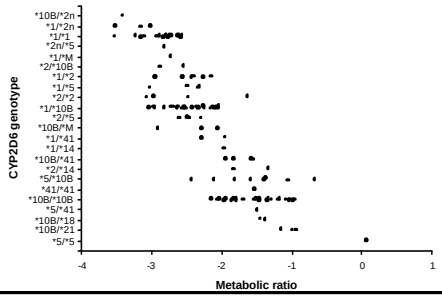
2000: The *10 allele Alters Paroxetine Pharmacokinetics



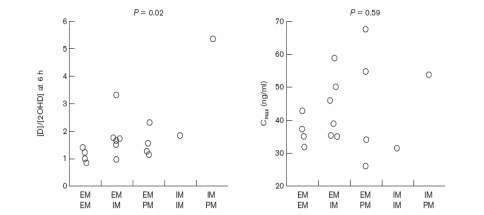
Shin J-G et al: CPT 2000;67:567-576.

Correlation between CYP2D6 genotype and dextromethorphan MR phenotype

: Distribution of metabolic ratios (MR) relative to their CYP2D6 genotypes in 131 Koreans **Shin J-G et al. 2004**.



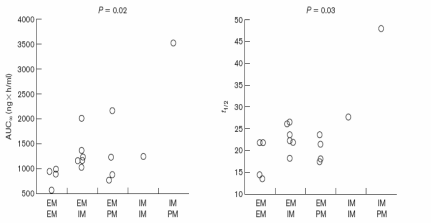
2004: A Scoring System for CYP2D6 Genotype e.g. Desipramine



Relationship of CYP2D6 phenotypes to desipramine pharmacokinetic parameters following a single 100 mg dose. AUC_{∞} is the extrapolated total plasma desipramine exposure. $t_{1/2}$ is the plasma desipramine elimination half-life. [D]/[2OHD] is the metabolic ratio of plasma desipramine/2-hydroxydesipramine concentrations. C_{max} is the maximum measured plasma desipramine concentration.

Katz DA et al:
Pharmacogenetics 2004, 14:279–284

Fig. 1



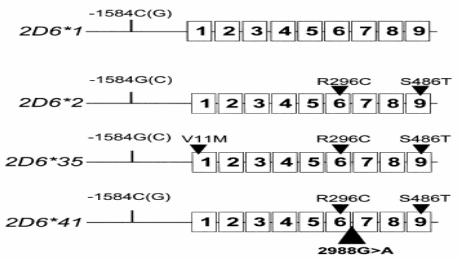
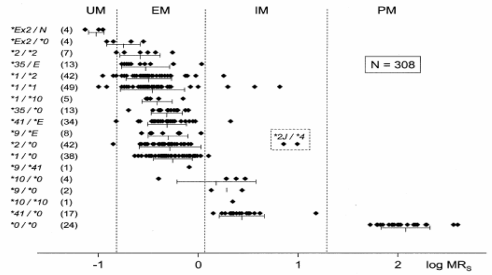


Fig 1. Schematic representation of characteristic sequence differences between investigated *CYP2D6* alleles. For the −1584C>G polymorphism, major and minor (in parentheses) allele variants observed for **1* and **2* are indicated. Additional sequence differences between the alleles are not shown.

Zanger U et al: Clin Pharmacol Ther 2004;76:128-38.

2004: CYP2D6 genotypes' prediction of sparteine metabolic ratio



Zanger U et al: Clin Pharmacol Ther 2004;76:128-38.

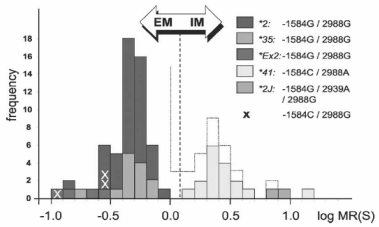
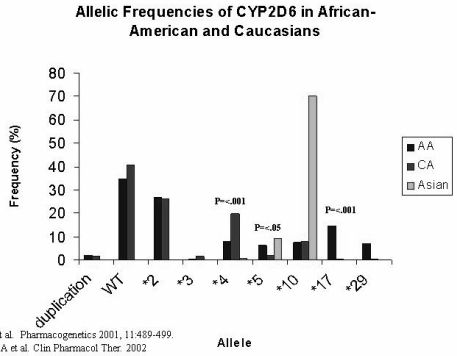


Fig 4. Frequency histogram for selected genotypes. Only individuals who carry 1 functional allele of the indicated type together with 1 nonfunctional allele are shown. The *dotted line* represents the course of the histogram for the entire population.

Zanger U et al: Clin Pharmacol Ther 2004;76:128-38.



Wan Y et al. Pharmacogenetics 2001, 11:489-499.
Gaedigk A et al. Clin Pharmacol Ther. 2002 Jul;72(1):76-89.

CYP2D6 Genotyping in Caucasian or Hispanic Populations

- Include the *3, *4, *5, *6, *8 null alleles
- Consider *2 multiple copy genotyping
- Consider *41 genotyping

CYP2D6 Genotyping in Asian Populations

- Include the *10 allele
- *21?

CYP2D6 Genotyping in West African or African American Populations

- Include *17
- Include *29
- Consider *2 multiple copy genotyping