3er Curso de Genética Humana

Valencia, 26 Enero 2008

SEG Sociedad Española de Genética,
Instituto de Biomedicina de Valencia y CIBER de Enfermedades Raras

"Aplicación de la Farmacogenética al tratamiento de pacientes psiquiátricos".

Adrián LLerena MD PhD.

allerena@unex.es

Univ. of Extremadura. CiCAB. Extremadura University Hospital. Spain.
University of Beira Interior, Faculty of Health Sciences, Covilhã, Portugal.

Variabilidad Interindividual en la respuesta a los fármacos

¿Respondemos todas las personas de la misma forma a los medicamentos?

¿Respondemos todas las personas de la misma forma a los medicamentos?

¿ Somos los seres humanos idénticos ?

¿ Debe ser la respuesta a los medicamentos igual en todas las personas ?

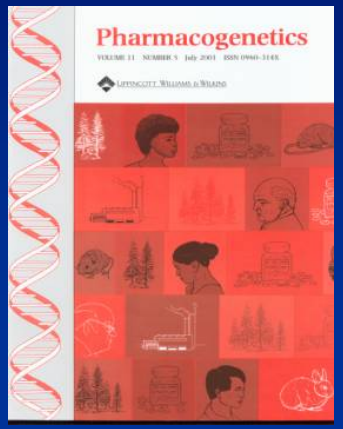
Aunque se administre la misma dosis de un medicamento, cada persona puede responder de una manera diferente

Dosis → Concentración Plasmática → Efecto Terapéutico

Dosis → ↑ Concentración Plasmática → Reacción Adversa

Dosis → ↓ Concentración Plasmática → Fallo Terapéutico

Variabilidad Metabolismo	Variabilidad Mec. Acción
Fase I: CYPs Fase II…	Receptores, Transportadores etc



The Journal of Pharmacogenomics

Personalized Medicine


The Next New Thing

A revolution in genetic research is targeting treatments to patients' unique characteristics. It can mean the difference between life and death. By Sharon Begley

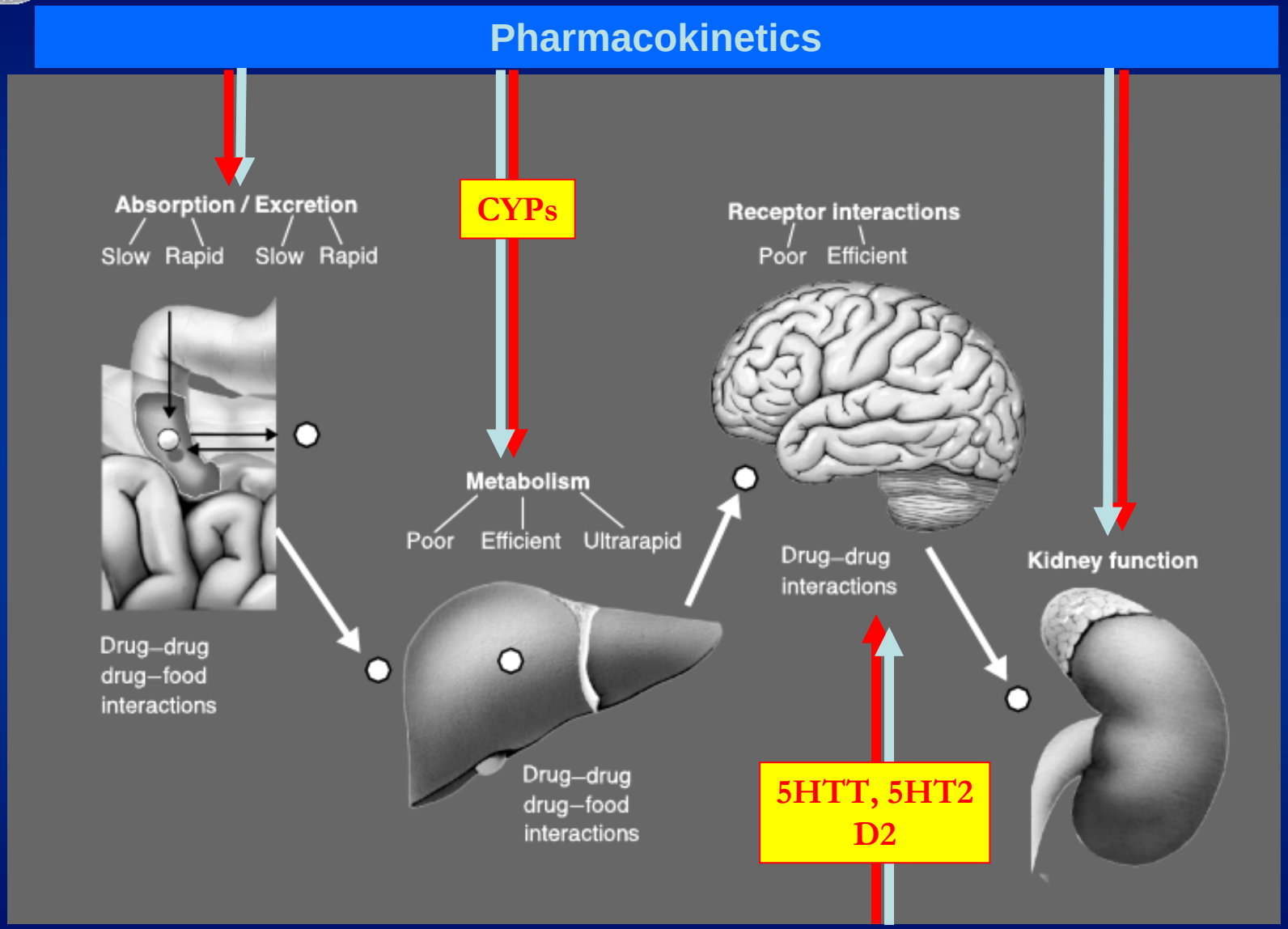
Made-to-Order Medicine

JILL WAS ONLY 2 WHEN the diagnosis came: acute lymphoblastic leukemia (ALL). The rare childhood cancer, the doctors assured her parents, is highly curable with a cocktail of four chemotherapy drugs. But from the very beginning the chemo made Jill acutely ill: her white-cell, red-cell and platelet counts plummeted, and even with biweekly transfusions "her counts kept going lower and lower," says Dr. Mary Relling of St. Jude Children's Research Hospital in Memphis, where Jill was treated. Doctors didn't know whether the leukemia was knocking out her blood production—or whether the chemo itself was. But they had a way to find out. Researchers at St. Jude and at the Mayo Clinic in Rochester, Minn., had recently discovered that patients with a single mistake in a gene called TPMT fail to produce the enzyme that metabolizes the chemo drug, 6-mercaptopurine. As a result, the drug builds up in the body to toxic levels. Jill belonged to the 0.3 percent of the population—one person in 300—that carries two copies of the misspelled TPMT

SPECIAL TREATMENT Herceptin, a drug developed by Dr. Dennis Slamon, targets a receptor found in only 30 percent of breast cancers

1. Genetic polymorphism of CYP2D6 (Pheno/genotyping)
2. Interthnic variability
3. Endogeous metabolism: Psychological functions in healthy volunteeers
4. Vulnerability to psychiatric disorders: Depression / Schizophrenia
5. **Pheno and genotypes in psychiatric patients**
6. Clinical implications : Plasma concentration and QTc interval lenghtening

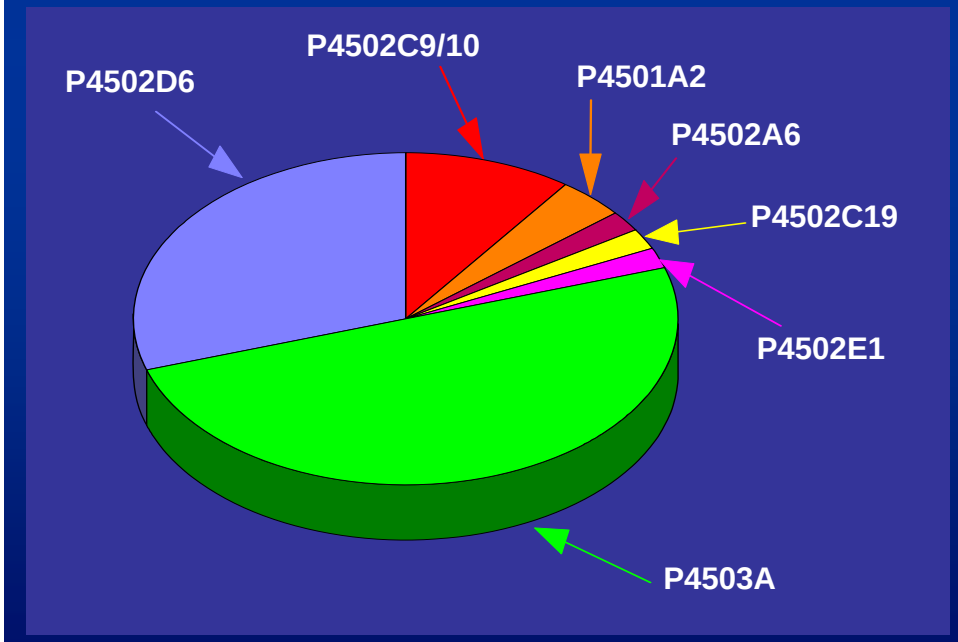
VARIABILITY IN DRUG RESPONSE



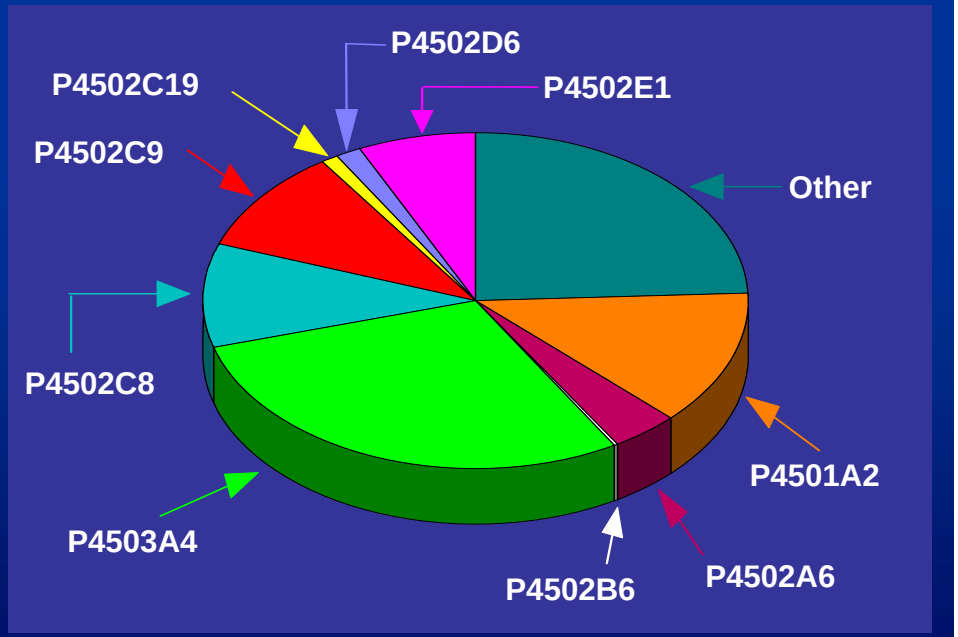
Drug Oxidation - Major Route of Drug Metabolism

Family of enzymes (CYPs) in liver

Proportion of Pharmaceuticals Metabolized by Individual Cytochrome P450's

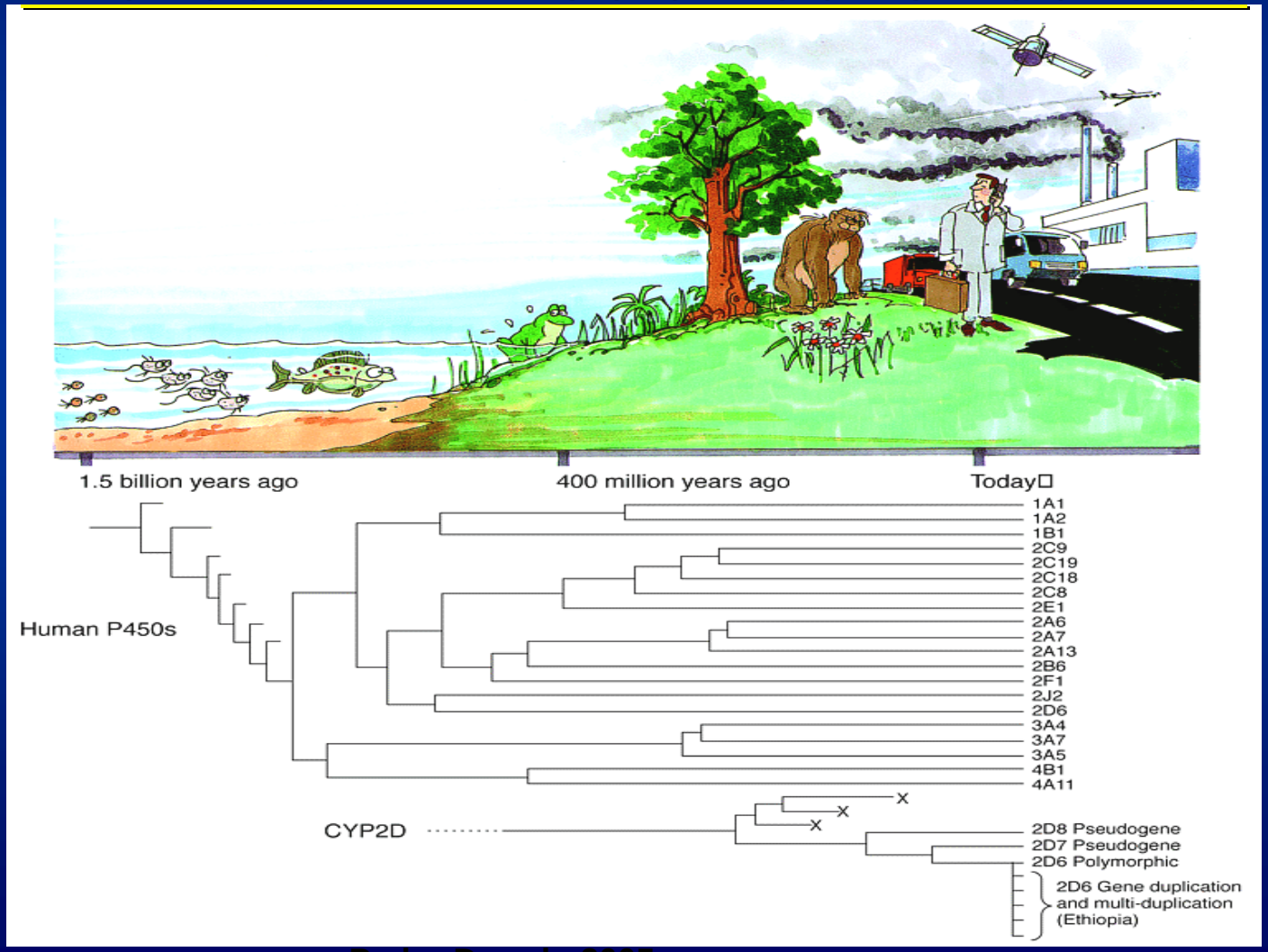


Major P450 Content of Human Liver



Shimada *et al.*, 1994

EVOLUCIÓN DE LOS CITOCROMOS P450



Factores implicados en la variabilidad en la respuesta farmacológica

FACTORES AMBIENTALES
tabaco, alcohol, etc.

FACTORES ENDÓGENOS

FACTORES FISIOLÓGICOS
edad

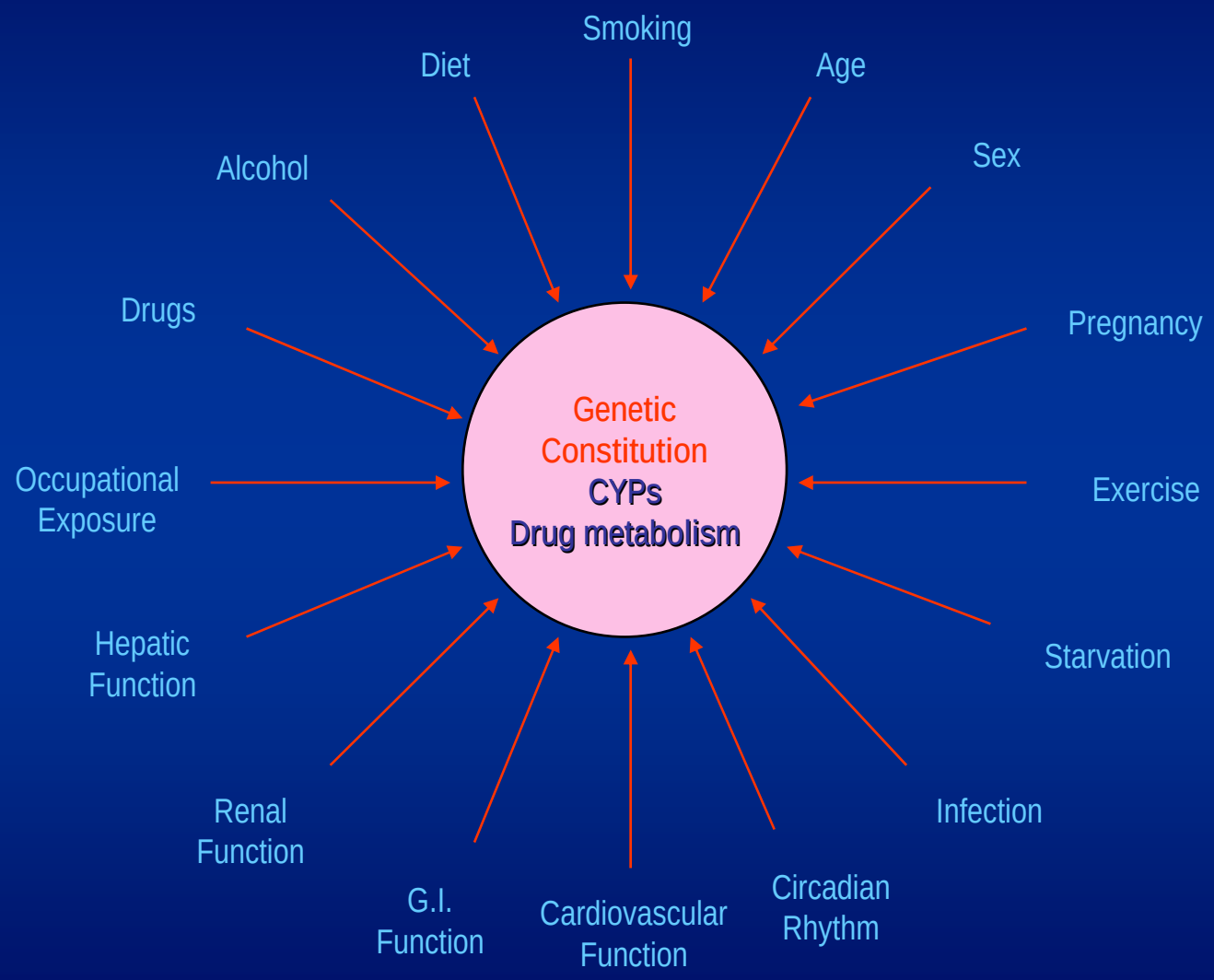
DIFERENCIAS INDIVIDUALES EN LA RESPUESTA A FÁRMACOS

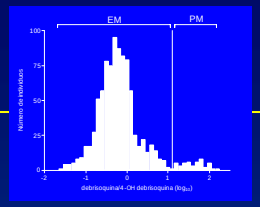
FACTORES GENÉTICOS

XENOBIÓTICOS
fármacos

FACTORES PATOLÓGICOS
enfermedad

VARIABILITY IN DRUG RESPONSE: GENE-ENVIRONMENTAL INTERACTION





Gene-environmental interaction: CYP2D6 Pheno/ genotype

Gender/tobacco
Tobacco abstinence
Menstrual cycle
Ovariectomy
Alcohol intake

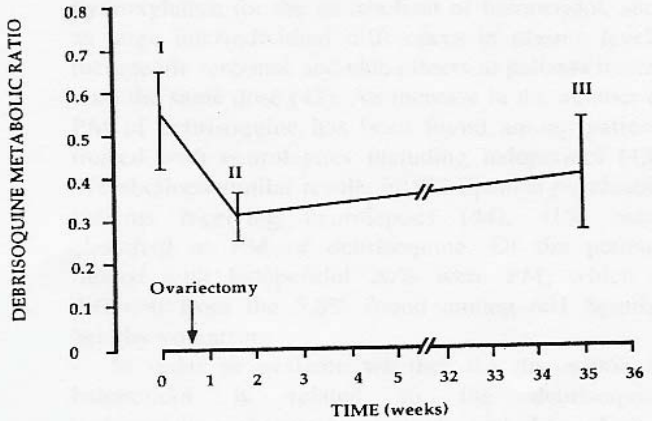


Fig. 3 : Debrisoquine metabolic ratio (mean ± SD) of 11 extensive metabolizer women determined the week before (I: 2.8 ± 2.5 days; mean ± SD), during the second week after (II: 7.9 ± 1.4 days), and 5–14 months after (7.8 ± 3.2 months) ovariectomy.

(LLerena et al, 1995))

NEWS

Gender in the Pharmacy: Does It Matter?

Studies of how women's and men's bodies process drugs have turned up mostly minor differences. But some drugs may be less or more effective in women or cause more side effects, and other variations may await discovery

Selected Medications and Possible Sex Differences

DRUG CLASS	WOMEN COMPARED TO MEN	STRENGTH OF EVIDENCE	MECHANISM
Certain antibiotics, antihistamines, antiarrhythmics, antipsychotics	Higher risk for drug-induced arrhythmias	Strong	Longer QT interval in women; drugs block cardiac ion channels
Opioids	May respond better to kappa-receptor opiates with fewer side effects	Mixed	Estrogen's effects on receptor density, binding, signaling
Antidepressants	May respond better to selective seratonin reuptake inhibitors	Mixed	Estrogen may enhance seratoninic effects
Anticoagulants (warfarin, heparin)	Bleeding more common	Strong	Doses too high for body size, possible pharmacodynamic effects
Antipsychotics	Respond better but more side effects	Strong	Fat-soluble so remain in women's bodies longer; estradiol may act on same receptors
Verapamil (hypertension)	Blood levels higher for oral drug, lower for intravenous drug	Strong	Activity of metabolizing enzyme (CYP3A4) and P-glycoprotein drug transporter

10 JUNE 2005 VOL 308 SCIENCE www.sciencemag.org

Debrisoquine hydroxylation phenotype (CYP2D6) in the Spanish Population (n=633) (LLerena et al 1988)

CYP2D6 phenotype

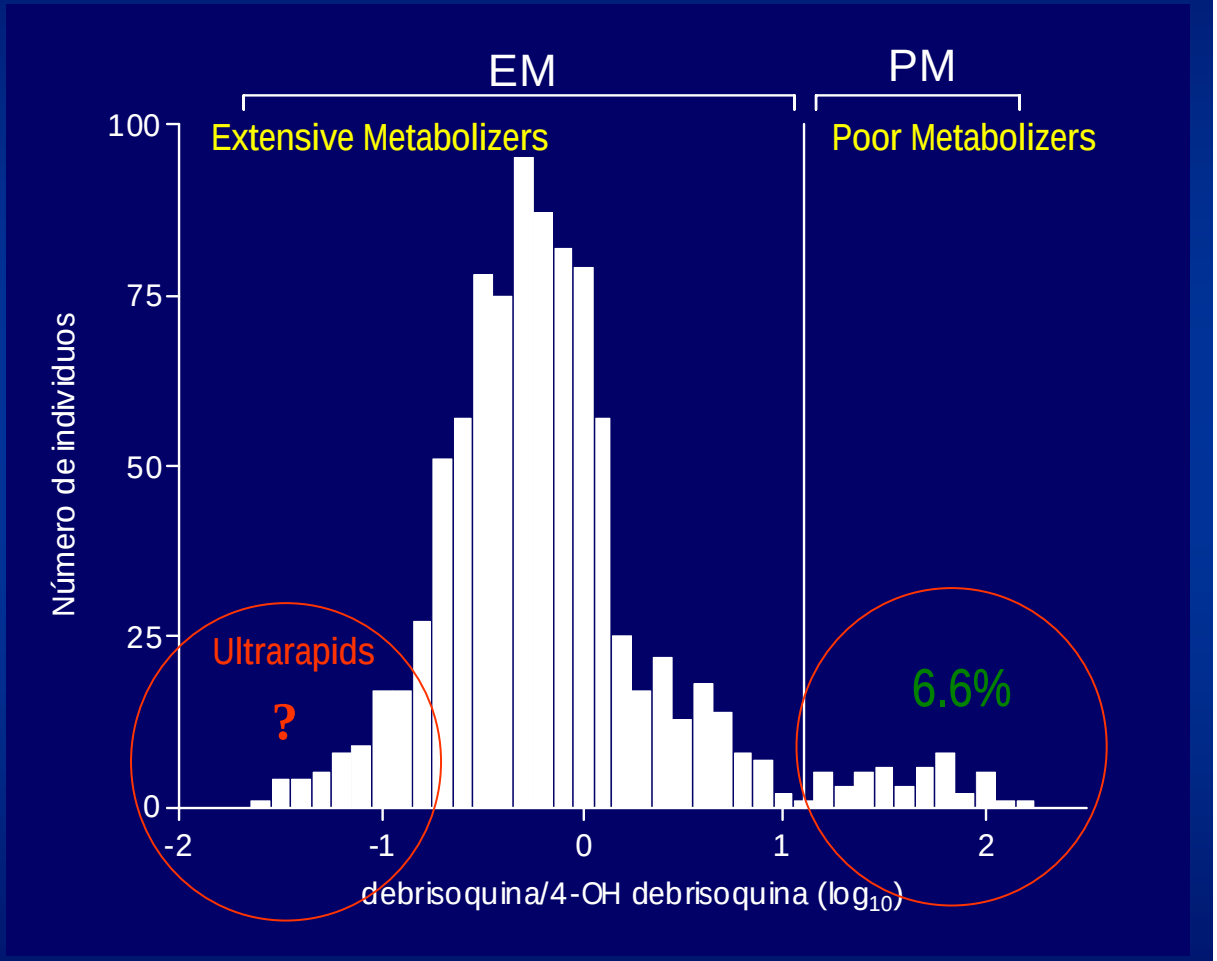
Test sbstrate: DBQ

CYP2D6

4-OH-debrisoquine

Metabolic ratio

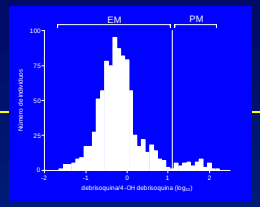
$$\frac{\%\ \text{debrisoquine}}{\%\ \text{4-OH-debrisoquine}}$$



Eliminación de los fármacos del organismo

METABOLIZADORES LENTOS	
Personas que tardan mas	Efecto mas duradero

Personas que tardan menos	Efecto menos duradero
METABOLIZADORES RAPIDOS	



Gene-environmental interaction: CYP2D6 Pheno/ genotype

Ultrarrapids: DBQ Phenotypes

(LLerena et al, 1993)

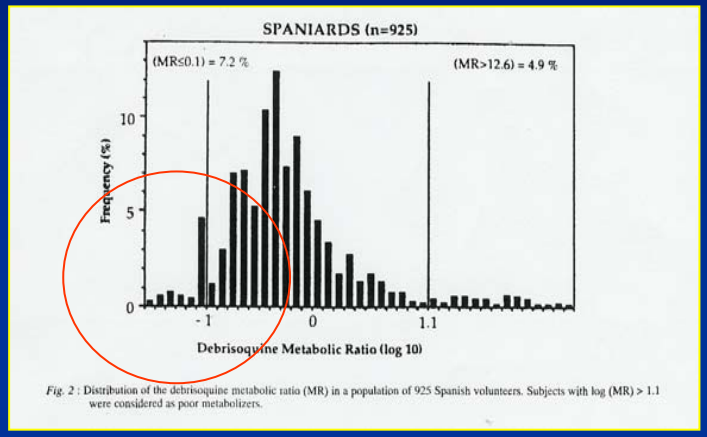
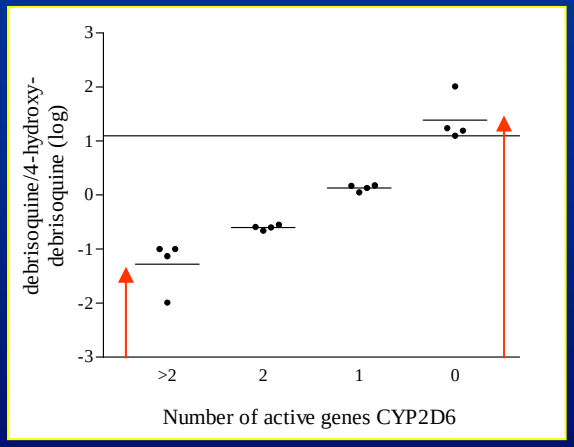
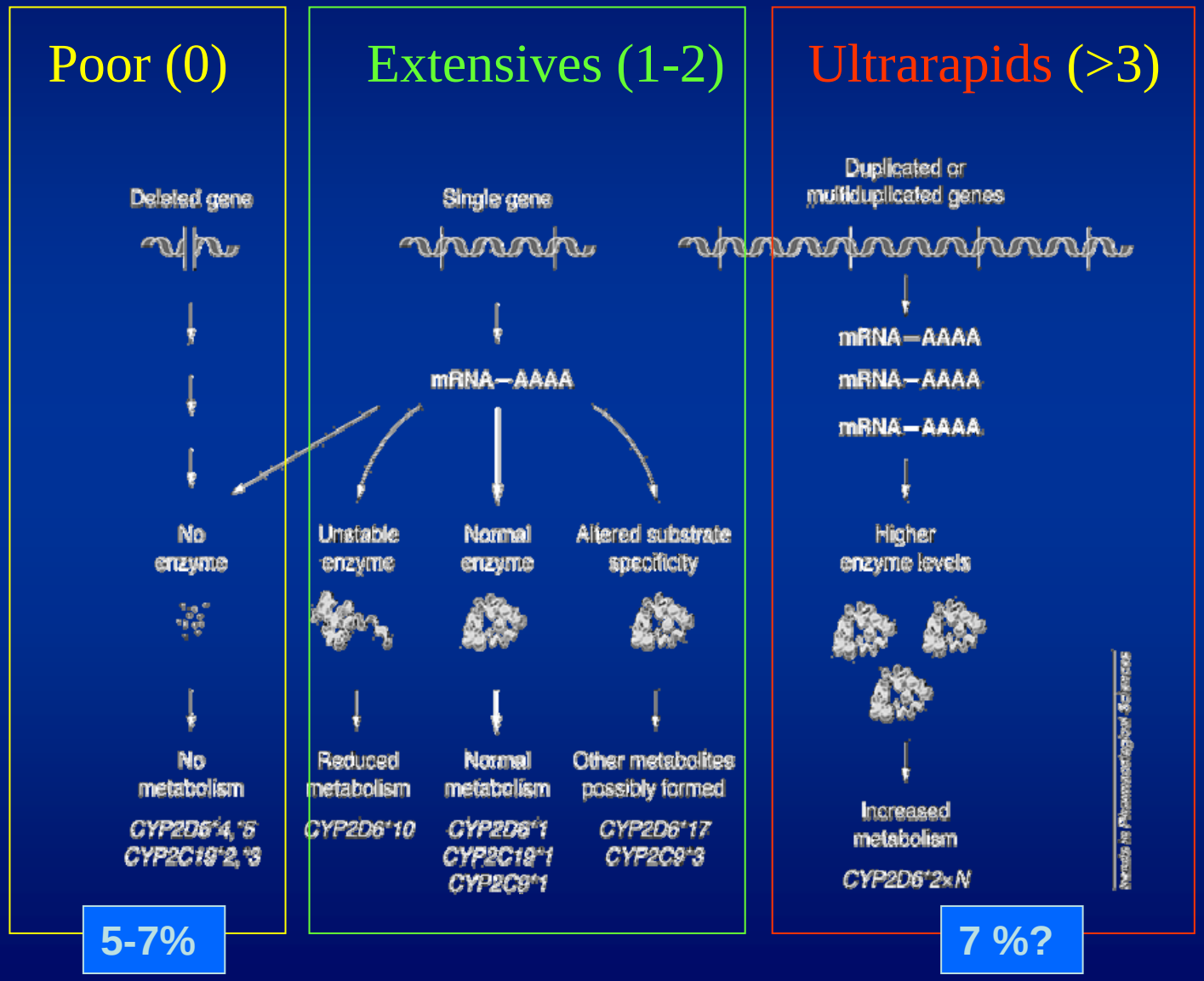


Fig. 2 : Distribution of the debrisoquine metabolic ratio (MR) in a population of 925 Spanish volunteers. Subjects with log (MR) > 1.1 were considered as poor metabolizers.

CYP2D6 Genotypes

(Dorado et al, 2005)




Poor (0)
Extensives (1-2)
Ultrarapids (>3)
Deleted gene
Single gene
Duplicated or multiduplicated genes
mRNA–AAAA
mRNA–AAAA
mRNA–AAAA
mRNA–AAAA
No enzyme
Unstable enzyme
Normal enzyme
Altered substrate specificity
Higher enzyme levels
No metabolism
CYP2D6*4, *5
CYP2C19*2, *3
Reduced metabolism
CYP2D6*10
Normal metabolism
CYP2D6*1
CYP2C19*1
CYP2C9*1
Other metabolites possibly formed
CYP2D6*17
CYP2C9*3
Increased metabolism
CYP2D6*2×N
5-7%
7 %?

IMPLICACIONES CLINICAS

Variabilidad interétnica

- Metabolizadores Lentos:

-Aumento de las concentraciones plasmáticas del fármaco: > Efectos adversos
-Disminución del metabolito (si es activo): < Eficacia terapeutica

-Metabolizadores Ultrarápidos

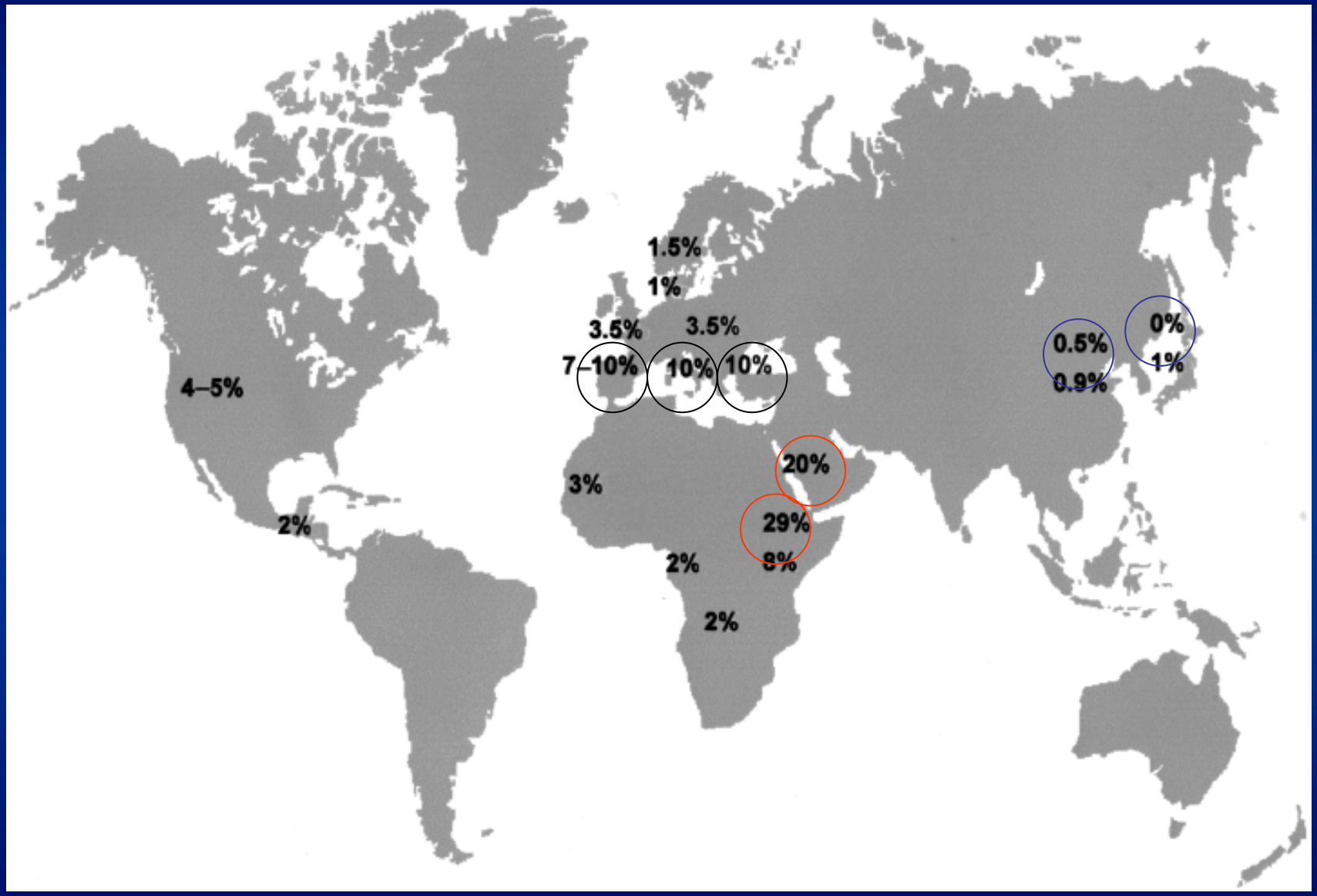
-Disminución del fármaco y metabolito: disminución de los efectos terapéuticos

-INTERACCIONES FARMACOLÓGICAS

Mas frecuentes dependiendo de la afinidad del fármaco por la enzima,
de su capacidad inhibitoria

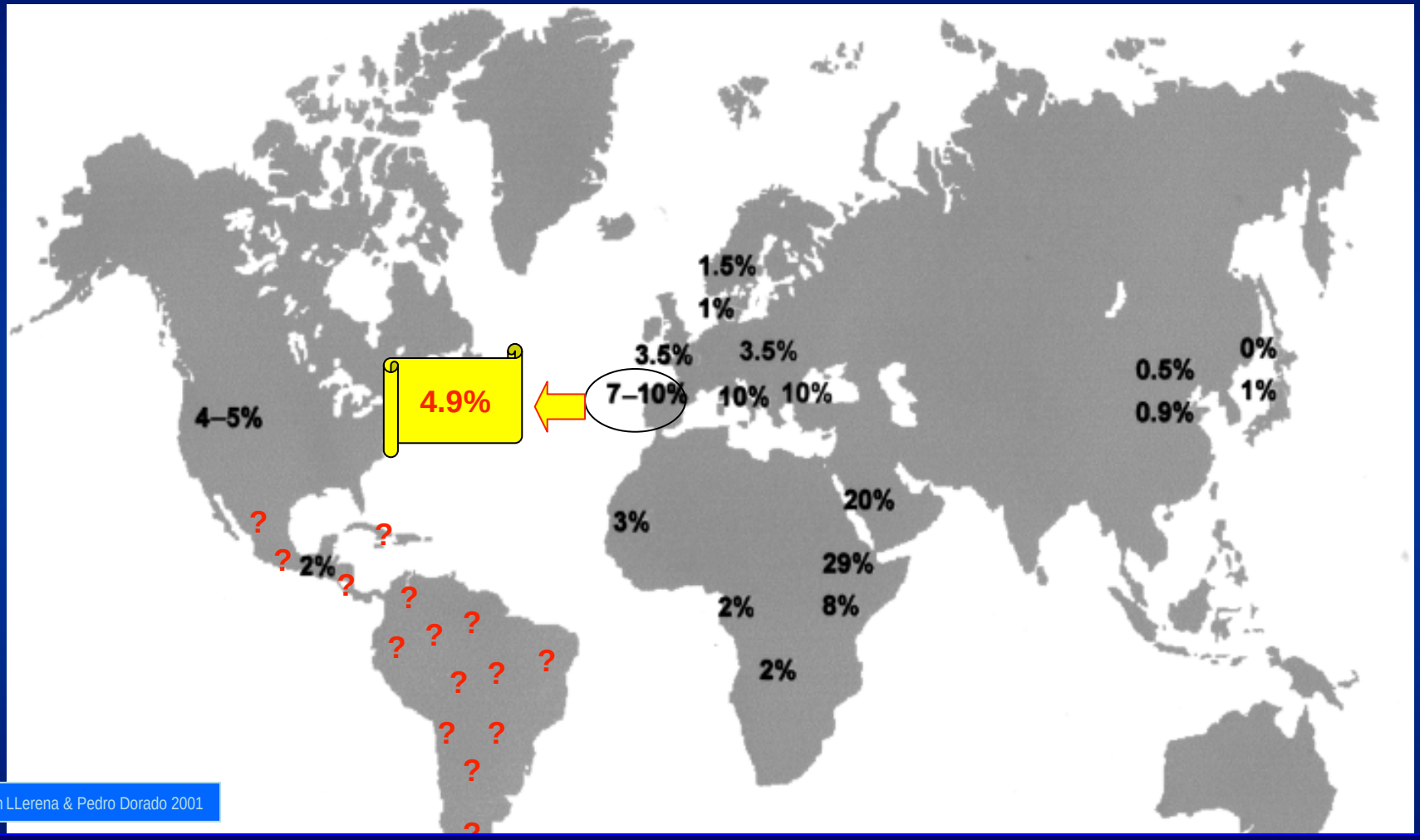
1. Genetic polymorphism of CYP2D6 (Pheno/genotyping)
2. Interthnic variability
3. Endogeous metabolism: Psychological functions in healthy volunteeers
4. Vulnerability to psychiatric disorders: Depression / Schizophrenia
5. Pheno and genotypes in psychiatric patients
6. Clinical implications : Plasma concentration and QTc interval lenghtening

Interethnical variability: CYP2D6 gene multiplication (Ultrarapids?)



Interethnic distribution of individuals with *CYP*2D6 gene duplicated

Interethnical variability: CYP2D6 gene multiplication
(Reviewed by Dorado et al, 2006)



Encontramos una alta frecuencia de multiplicación de alelos CYP2D6, sin embargo el porcentaje de individuos **Ultrarápidos** fenotípicamente en la población española es inferior al 7-10% publicado previamente.

Development of a PCR-based strategy for *CYP2D6* genotyping including gene multiplication of worldwide potential use

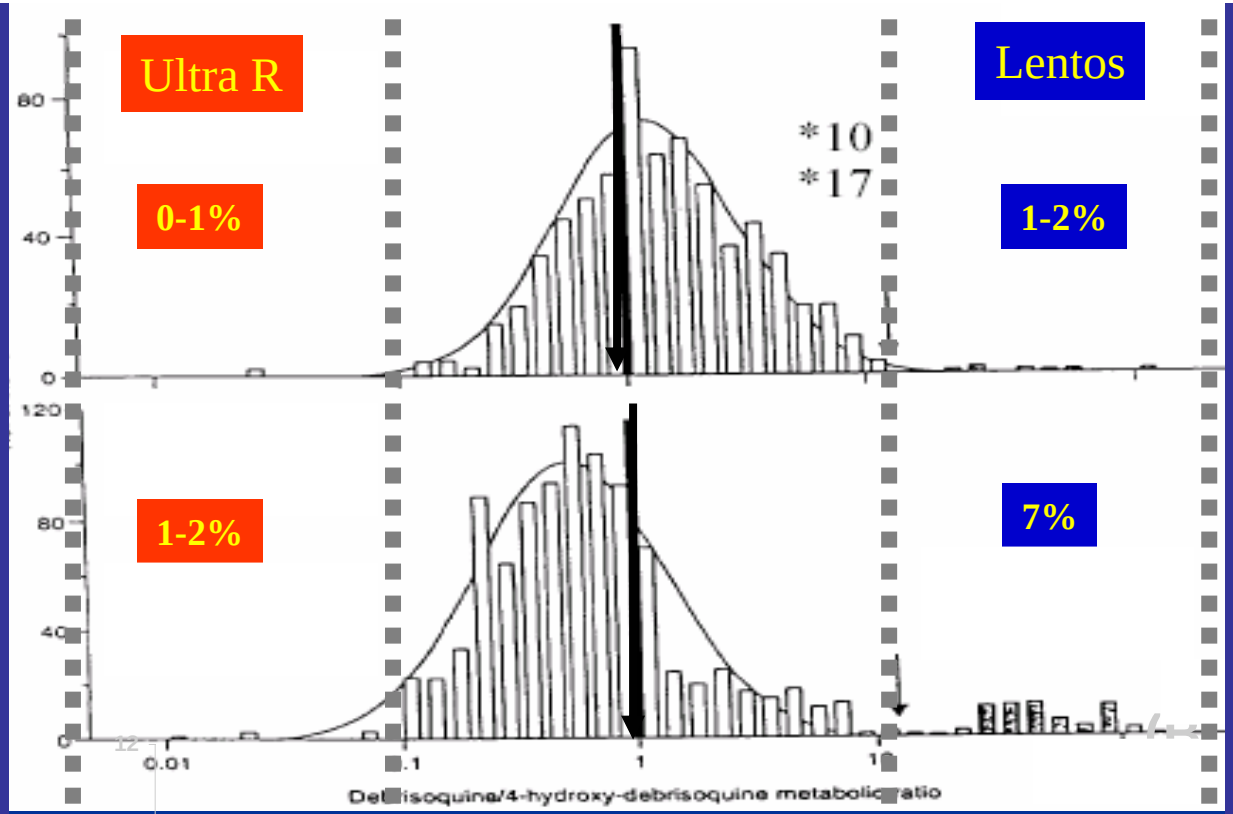
Pedro Dorado[1], Macarena C. Cáceres[2], Eulalia Pozo-Guisado[2], Ma-Li Wong[3], Julio Licinio[3], and Adrián LLerena[1–3]
[1]University of Beira Interior, Covilhã, Portugal, [2]University of Extremadura, Badajoz, Spain, and [3]University of California, Los Angeles, CA, USA

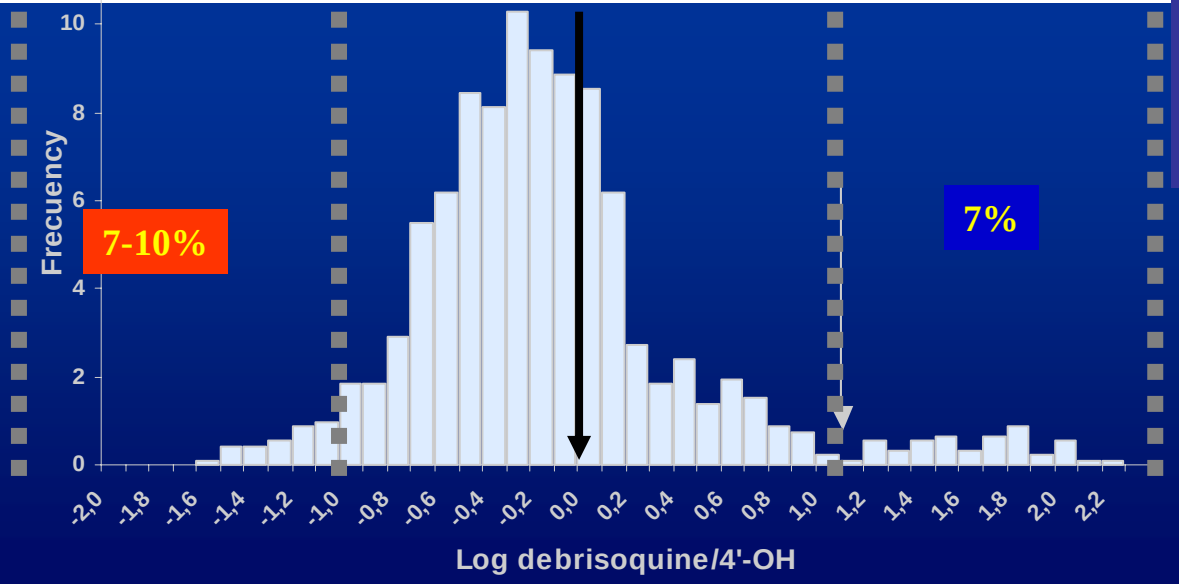
BioTechniques 39:571–574 (October 2005)
doi 10.2144/000112044

Chinos 695

Suecos 1011

Españoles 925





RIFF - Adrián Llerena, Pedro Dorado 2004

CHAPTER 5

Pharmacogenetics of Cytochrome P450 in Hispanic Populations

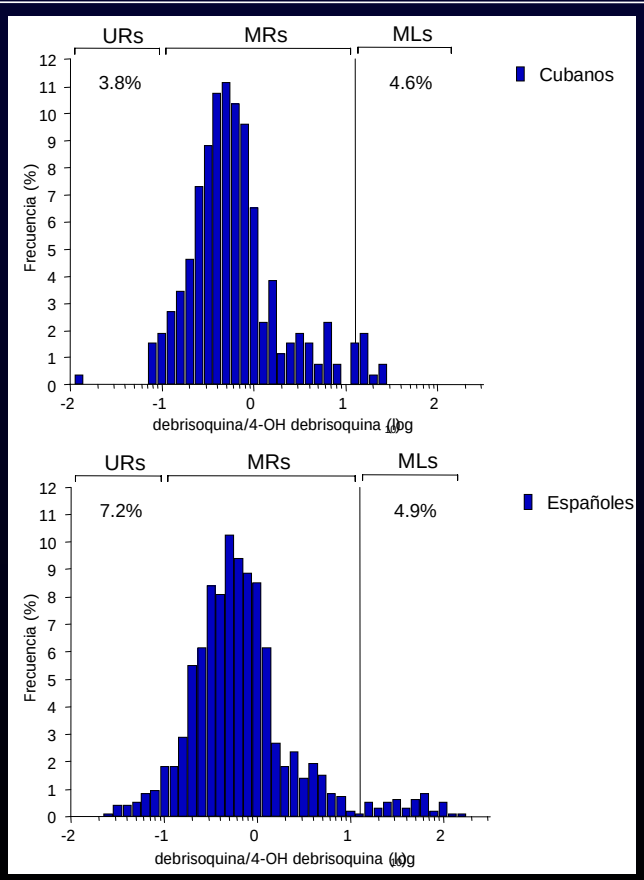
Pedro Dorado, Guilherme Suarez Kurtz and Adrián LLerena*

Abstract

The present review focuses on the pharmacogenetics of the cytochrome P450 (CYP) enzymes in Hispanic populations, comprising the people living in Spanish speaking countries of the Americas as well as those categorized as Hispanics in the United States. We acknowledge the diversity of these people by their country of origin or residence, culture, as well as genetic composition, the latter resulting from centuries of inter-ethnic crosses between Amerindians, Europeans and Africans. This diversity is reflected in the frequency distribution of polymorphisms of the CYP genes that encode the main CYP enzymes involved in the biotransformation of xenobiotics, namely CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5. Our review of the literature disclosed data for all these CYPs only in Mexican or Mexican Americans. For other populations, including recent Amerindian groups, scattered information was recovered on individual CYPs. For several Latin American countries, no information could be retrieved on any of these enzymes or indeed other pharmacogenetic targets. With the purpose of fulfilling this information gap and to promote collaborative pharmacogenetic/genomic research in Spanish- and Portuguese-speaking peoples in the Americas and the Iberian peninsula, a network—the Iberian American Network of Pharmacogenetics and Pharmacogenomics—was recently created. This initiative represents a promising step towards the inclusion of Latin American populations among those who will benefit from the implementation of pharmacogenetic principles and tools in drug therapy.

CYP2C9 genetic polymorphism: Interethnical variability

Fenotipo metabólico oxidativo de debrisoquina



ORIGINALES BREVES

Estudio farmacogenético del polimorfismo metabólico de la debrisoquina (CYP2D6) en la población cubana en relación con la española

Idilio González, Bárbaro Pérez, Mayra Alvarez, Pedro Dorado y Adrian Llerena

*Idilio González, Med Clin 2007

1. Genetic polymorphism of CYP2D6 (Pheno/genotyping)

2. Interthnic variability

3. Endogeous metabolism: Psychological functions in healthy volunteeers

4. Vulnerability to psychiatric disorders: Depression / Schizophrenia

5. Pheno and genotypes in psychiatric patients

6. Clinical implications : Plasma concentration and QTc interval lenghtening

CYP2D6 AND PERSONALITY

4. Relationship between CYP2D6 activity and personality in a Spanish population (LLerena *et al.*, 1993):

HIPOTHESIS

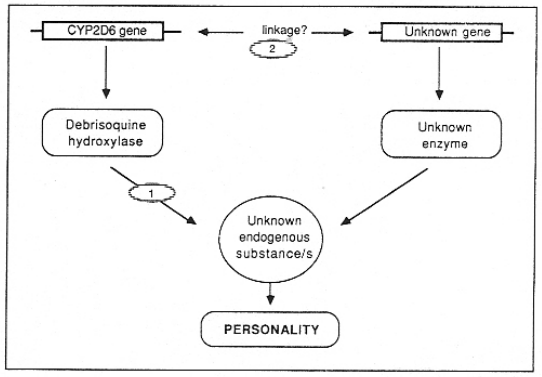


Fig. 1. Illustration of two possible connections between debrisoquine hydroxylation phenotype and personality. Hypothesis 1: the liver or brain debrisoquine hydroxylase metabolizes an unknown endogenous substance of importance for central nervous system activity and personality. Hypothesis 2: there might be a linkage between the debrisoquine hydroxylase gene (CYP2D6) on chromosome 22 and a gene regulating an unknown enzyme (or receptor etc.) of importance for personality.

METHDOS

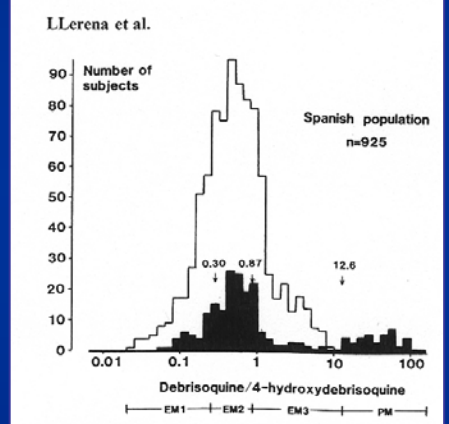


Fig. 2. Distribution of the urinary metabolic ratio (MR) of debrisoquine/4-hydroxydebrisoquine in 925 healthy Spanish subjects. The KSP inventory was distributed to all 45 poor metabolizers (PM) (MR> 12.6) and to 180 age- and sex-matched extensive metabolizers (EM) of debrisoquine. The 225 subjects participating in the study are indicated as dark bars. The EM subjects were divided into: EM1 (very rapid EMs); EM2 (intermediate EMs) and EM3 (slow EMs).

Relationship between personality and debrisoquine hydroxylation capacity

Suggestion of an endogenous neuroactive substrate or product of the cytochrome P4502D6

LLerena A, Edman G, Cobaleda J, Benítez J, Schalling D, Bertilsson L. Relationship between personality and debrisoquine hydroxylation capacity. Suggestion of an endogenous neuroactive substrate or product of the cytochrome P4502D6.
Acta Psychiatr Scand 1993: 87: 23–28. © Munksgaard 1993.

We administered the Karolinska Scales of Personality to 225 healthy subjects in Spain selected from a group of 925 individuals previously phenotyped with regard to their capacity to hydroxylate debrisoquine. A significant relationship was found between the scores in as many as 4 of the 15 subscales (psychic anxiety, psychasthenia, inhibition of aggression and socialization) and the debrisoquine hydroxylation capacity. Poor metabolizers were more anxiety-prone and less successfully socialized than extensive metabolizers of debrisoquine. This and a previous study among subjects in Sweden suggest that there may be a relationship between personality and the activity of the enzyme hydroxylating debrisoquine (cytochrome P4502D6). This polymorphic enzyme may have an endogenous neuroactive substrate or product, such as a biogenic neurotransmitter amine.

A. LLerena [1,3], G. Edman [2], J. Cobaleda [3], J. Benítez [3], D. Schalling [2], L. Bertilsson [1]

[1] Department of Clinical Pharmacology, Karolinska Institute, Huddinge Hospital, [2] Department of Psychiatry and Psychology, Karolinska Institute, Karolinska Hospital, Stockholm, Sweden, [3] Department of Pharmacology and Psychiatry, University of Extremadura, Badajoz, Spain

Key words: pharmacogenetics; debrisoquine; personality

Leif Bertilsson, Department of Clinical Pharmacology, Karolinska Institute, Huddinge Hospital, S-14186 Huddinge, Sweden

Accepted for publication August 27, 1992

Poor metabolizers were more **anxiety-prone** and less successfully socialized than extensive metabolizers of debrisoquine

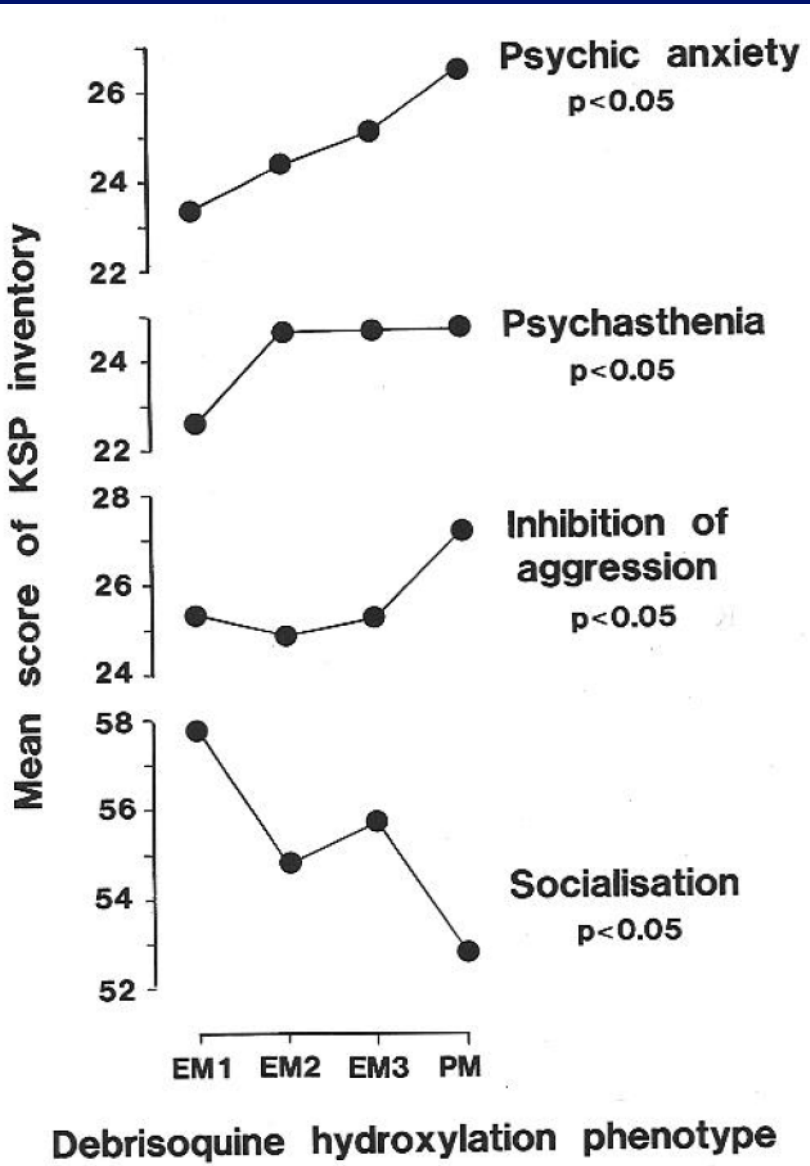
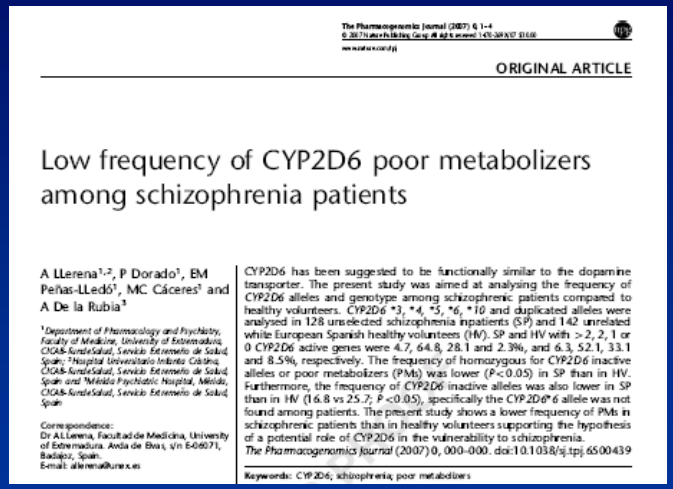


Fig. 3. Mean scores of KSP in the 4 subscales where a significant relationship was found with the debrisoquine hydroxylation groups EM1, 2 and 3 and PM

Psychiatric Patients: *CYP2D6* PMs & Schizophrenia



The Pharmacogenomics Journal (2007) 0, 1–4

ORIGINAL ARTICLE

Low frequency of CYP2D6 poor metabolizers among schizophrenia patients

A LLerena[1,2], P Dorado[1], EM Peñas-LLedó[1], MC Cáceres[3] and A De la Rubia[3]

[1]Department of Pharmacology and Psychiatry, Faculty of Medicine, University of Extremadura, CIGAS-SaludExtremeño de Salud, Spain; [2]Hospital Universitario Infanta Cristina, CIGAS-SaludExtremeño de Salud, Spain and [3]Mérida Psychiatric Hospital, Mérida, CIGAS-SaludExtremeño de Salud, Spain

Correspondence: Dr A LLerena, Facultad de Medicina, University of Extremadura. Avda de Elvas, s/n E-06071, Badajoz, Spain. E-mail: allerena@unex.es

CYP2D6 has been suggested to be functionally similar to the dopamine transporter. The present study was aimed at analysing the frequency of *CYP2D6* alleles and genotype among schizophrenic patients compared to healthy volunteers. *CYP2D6* *3, *4, *5, *6, *10 and duplicated alleles were analysed in 128 unselected schizophrenia inpatients (SP) and 142 unrelated white European Spanish healthy volunteers (HV). SP and HV with >2, 2, 1 or 0 *CYP2D6* active genes were 4.7, 64.8, 28.1 and 2.3%, and 6.3, 52.1, 33.1 and 8.5%, respectively. The frequency of homozygous for *CYP2D6* inactive alleles or poor metabolizers (PMs) was lower ($P<0.05$) in SP than in HV. Furthermore, the frequency of *CYP2D6* inactive alleles was also lower in SP than in HV (16.8 vs 25.7; $P<0.05$), specifically the *CYP2D6*6* allele was not found among patients. The present study shows a lower frequency of PMs in schizophrenic patients than in healthy volunteers supporting the hypothesis of a potential role of CYP2D6 in the vulnerability to schizophrenia.

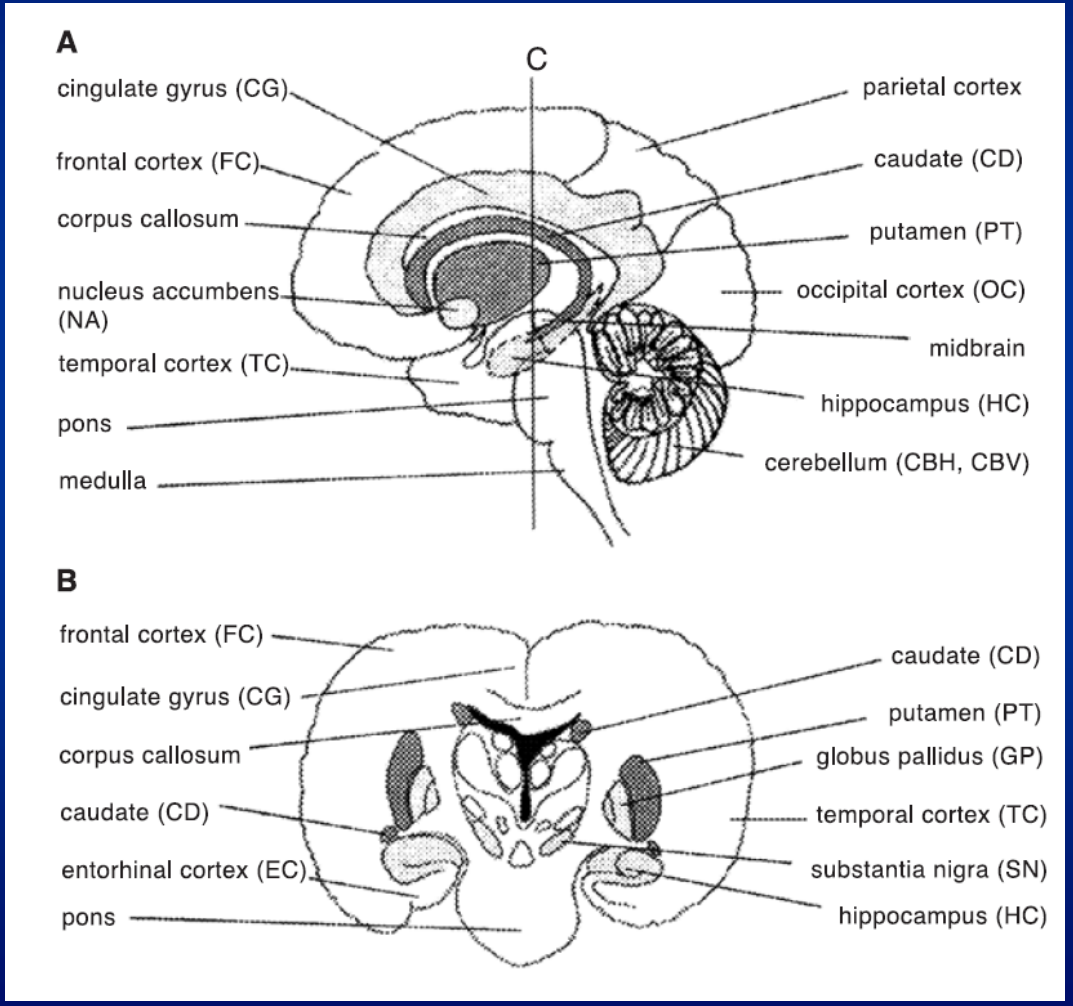
The Pharmacogenomics Journal (2007) 0, 000–000. doi:10.1038/sj.tpj.6500439

Keywords: CYP2D6; schizophrenia; poor metabolizers

CYP2D6 Genotype (no. active genes)	*CYP2D6 genotypes*	*Schizophrenic patients (n=101)*	*Healthy Volunteers (n=142)*
UM (>2)	***wt/wtxN***	**5 (5%)**	**7 (4,9%)**
EM (2)	***wt/wt; wtxN/*4; wt/*10; wtxN/*10***	**69 (68,3%)**	**76 (53,5%)**
IM (1)	***wt/*4; wt/*4xN; wt/*6;wt/*5; *5/*10***	**24 (23,7%)**	**47 (33%)**
PM (0)	****4/*4; *4/*6; *5/*6; *6/*6***	**3 (3%)**	**12 (8,5%)**

(LLerena A *et al.*, The Pharmacogenomics Journal 2007).

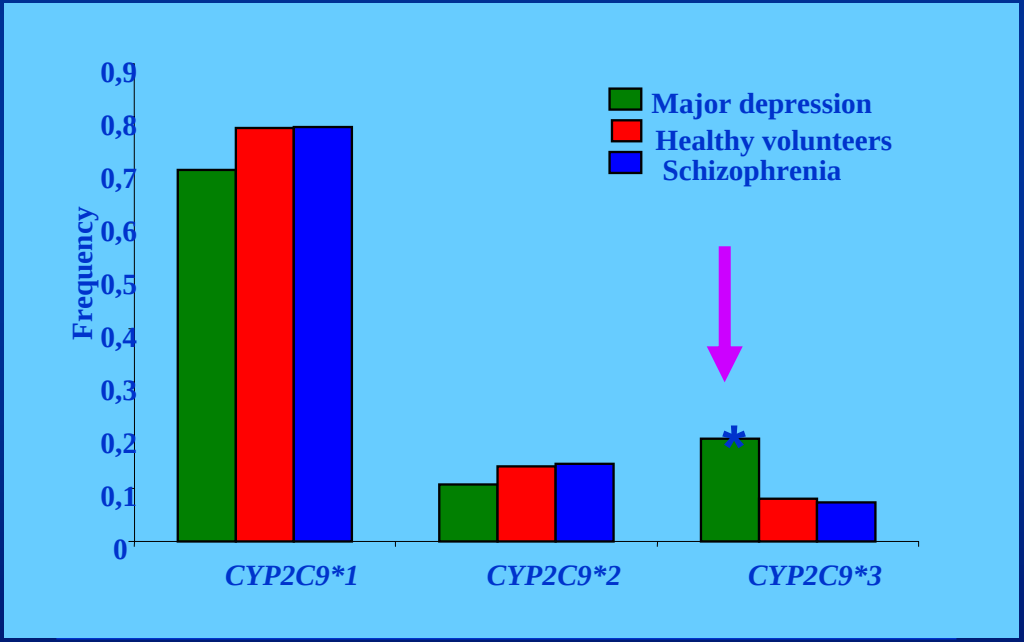
CYP2D EXPRESSION IN THE HUMAN BRAIN

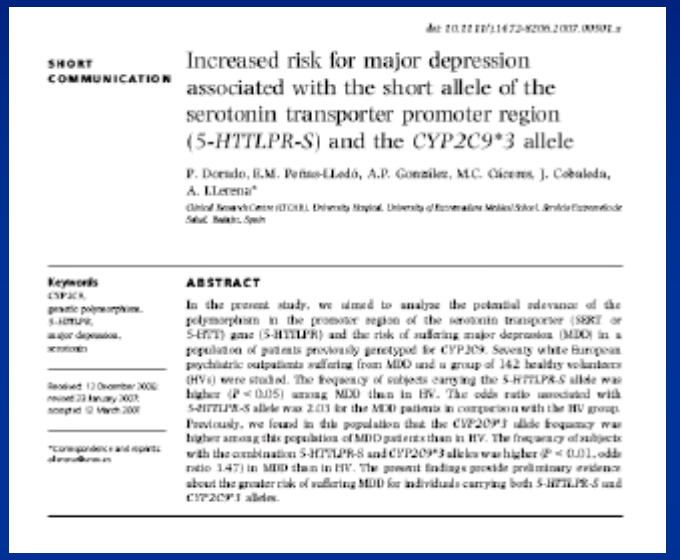


(Miksys and Tyndale, 2004)

Psychiatric Patients: *CYP2C9*3* & Depression

CYP2C9*3 as a risk factor for **major depression**. (LLerena A *et al*., The Pharmacogenomics Journal 2004).





SHORT COMMUNICATION

Increased risk for major depression associated with the short allele of the serotonin transporter promoter region (*5-HTTLPR-S*) and the *CYP2C9*3* allele

P. Dorado, B.M. Peñas-LLedó, A.P. González, M.C. Cáceres, J. Cobaleda, A. LLerena*

ABSTRACT

In the present study, we aimed to analyze the potential relevance of the polymorphism in the promoter region of the serotonin transporter (SERT or 5-HTT) gene (5-HTTLPR) and the risk of suffering major depression (MDD) in a population of patients previously genotyped for CYP2C9. Seventy white European psychiatric outpatients suffering from MDD and a group of 142 healthy volunteers (HVs) were studied. The frequency of subjects carrying the *5-HTTLPR-S* allele was higher ($P < 0.05$) among MDD than in HV. The odds ratio associated with *5-HTTLPR-S* allele was 2.03 for the MDD patients in comparison with the HV group. Previously, we found in this population that the *CYP2C9*3* allele frequency was higher among this population of MDD patients than in HV. The frequency of subjects with the combination 5-HTTLPR-S and *CYP2C9*3* alleles was higher ($P < 0.01$, odds ratio 3.47) in MDD than in HV. The present findings provide preliminary evidence about the greater risk of suffering MDD for individuals carrying both *5-HTTLPR-S* and *CYP2C9*3* alleles.

The *CYP2C9*3* allele frequency was higher (p<0.01) among the depressive patients than in the population of schizophrenic patients (odds ratio=3.3) and healthy volunteers (odds ratio=2.8).

CYP2D6 Phenotyping in psychiatric patients: Clinical Implications

(LLerena et al., 2005)

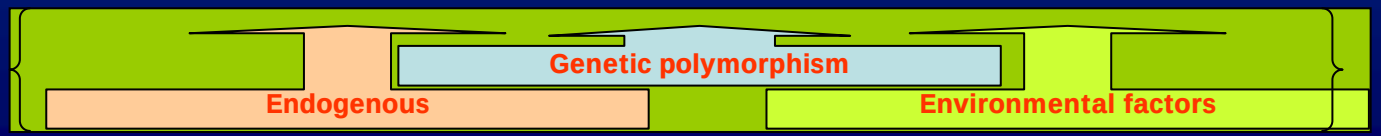
I

II

Dose → Plasma concentration → Effects:

Plasma concentration ↕ Metabolism: CPYs

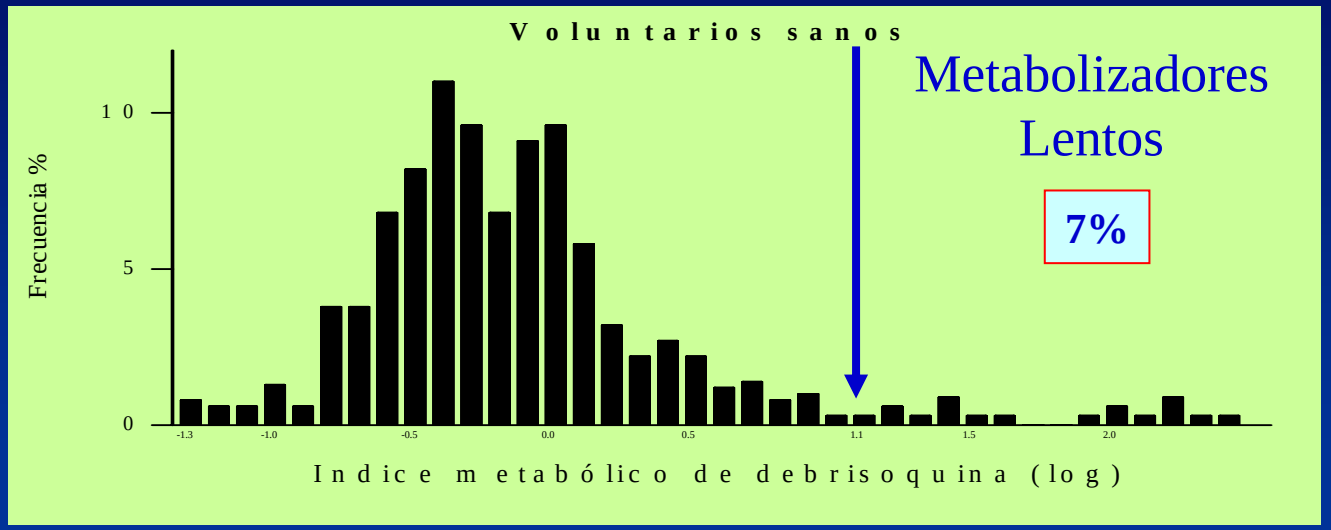
Effects: ↕ Transporters, Receptors



1. Genetic polymorphism of CYP2D6 (Pheno/genotyping)
2. Interthnic variability
3. Endogeous metabolism: Psychological functions in healthy volunteeers
4. Vulnerability to psychiatric disorders: Depression / Schizophrenia
5. Pheno and genotypes in psychiatric patients
6. Clinical implications : Plasma concentration and QTc interval lenghtening

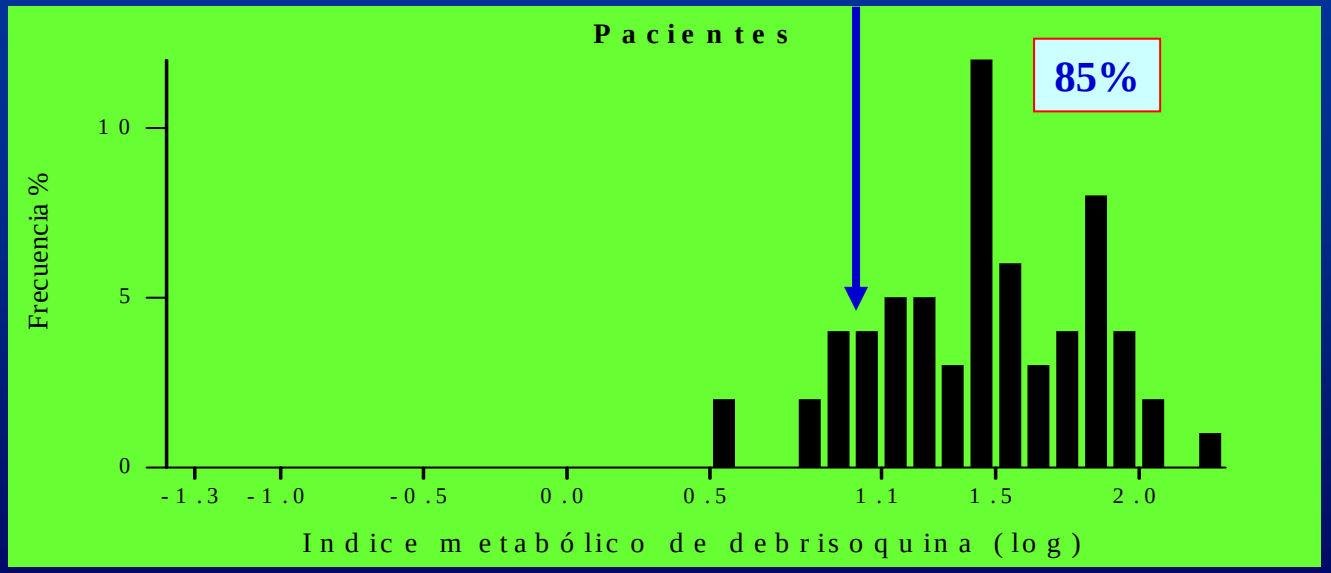
1. Genetic polymorphism of CYP2D6 (Pheno/genotyping)
2. Interthnic variability
3. Endogeous metabolism: Psychological functions in healthy volunteeers
4. Vulnerability to psychiatric disorders: Depression / Schizophrenia
5. Pheno and genotypes in psychiatric patients
6. Clinical implications : Plasma concentration and QTc interval lenghtening

V. Sanos



LLerena, 1988

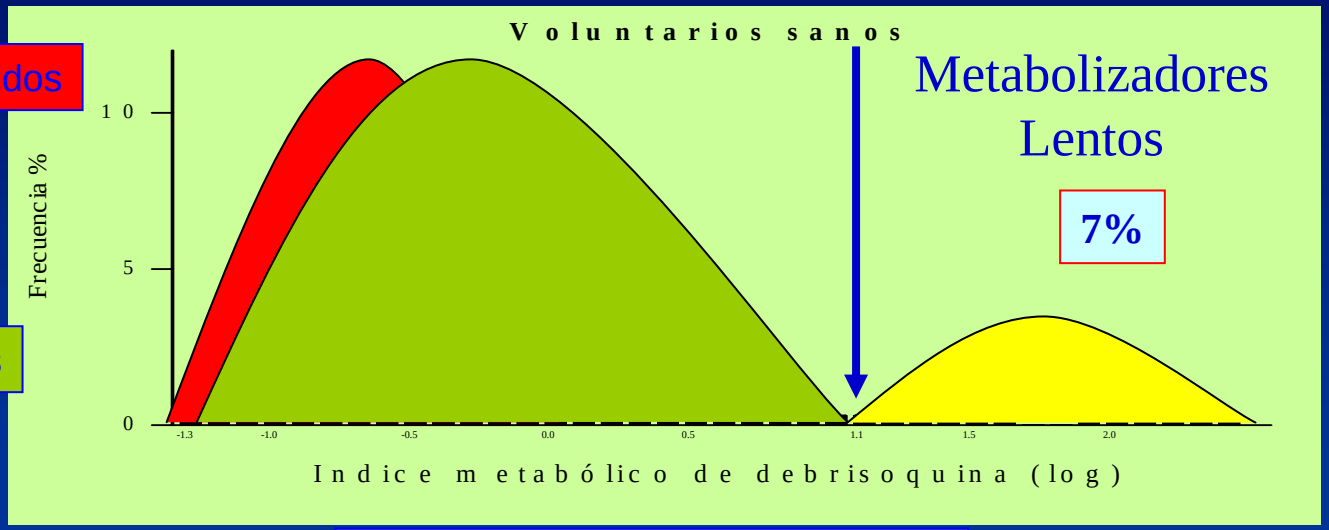
Pacientes psiquiátricos en tratamiento



Debrisoquine and mephenytoin hydroxylation phenotypes in healt. volunt.and patients treated with neuroleptic drugs

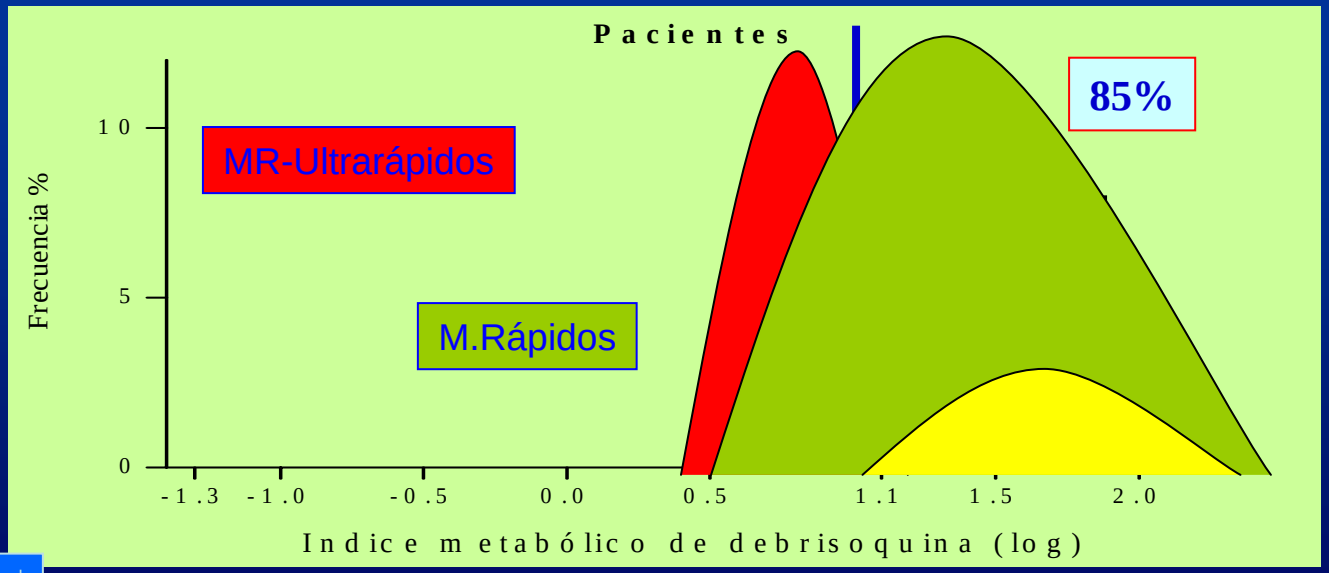
MR-Ultrarrápidos

M.Rápidos



M.Lentos

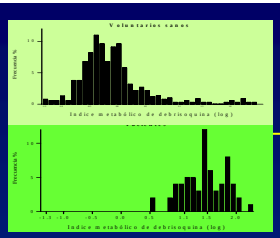
Voluntarios Sanos Españoles



M.Lentos

De la Rubia1998,Tesis Doctoral
Berecz 2001, Tesis Doctoral
Dorado et al 2006.

Pacientes psiquiátricos en tratamiento con politerapia



PATIENT STUDIES DURING STEADY STEATE

CLINICAL IMPLICATIONS

During treatment with:

Clozapine

Risperidone

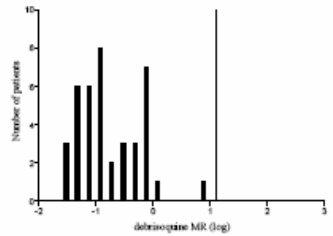
Haloperidol

Thioridacine

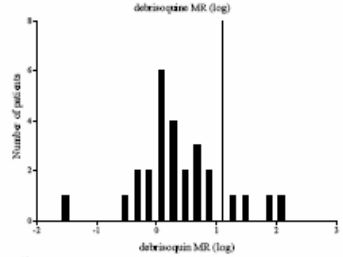
1. Genetic polymorphism of CYP2D6 (Pheno/genotyping)
2. Interthnic variability
3. Endogeous metabolism: Psychological functions in healthy volunteeers
4. Vulnerability to psychiatric disorders: Depression / Schizophrenia
5. Pheno and genotypes in psychiatric patients: drug interactions
6. Clinical implications: Plasma concentration and QTc interval lenghtening

CYP2D6 phenotyping during treatment with antipsychotic drugs

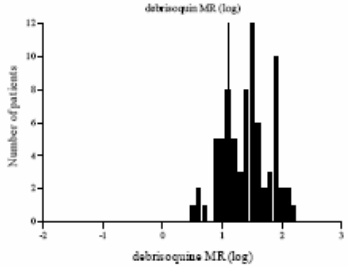
Risperidone



Haloperidol



Thioridazine



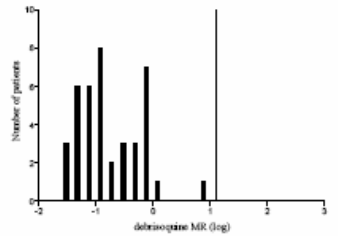
Dorado et al, 2006

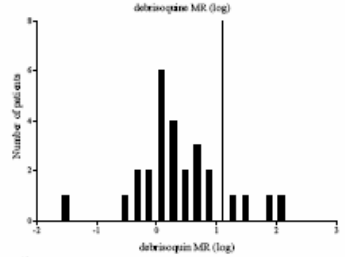
De la Rubia, 1998
Berecz, 2001
Dorado, 2003

CYP2D6 phenotyping during treatment with antipsychotic drugs

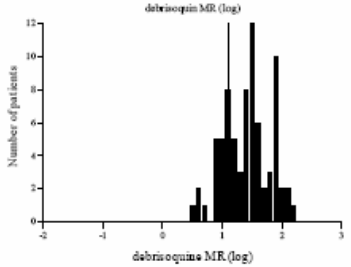
Haloperidol

Risperidone





Thioridazine



De la Rubia, 1998
Berecz, 2001
Dorado, 2003

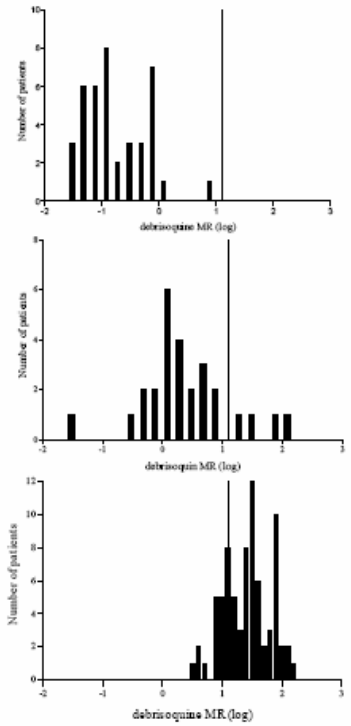
Dorado et al, 2006

CYP2D6 phenotyping during treatment with antipsychotic drugs

Risperidone

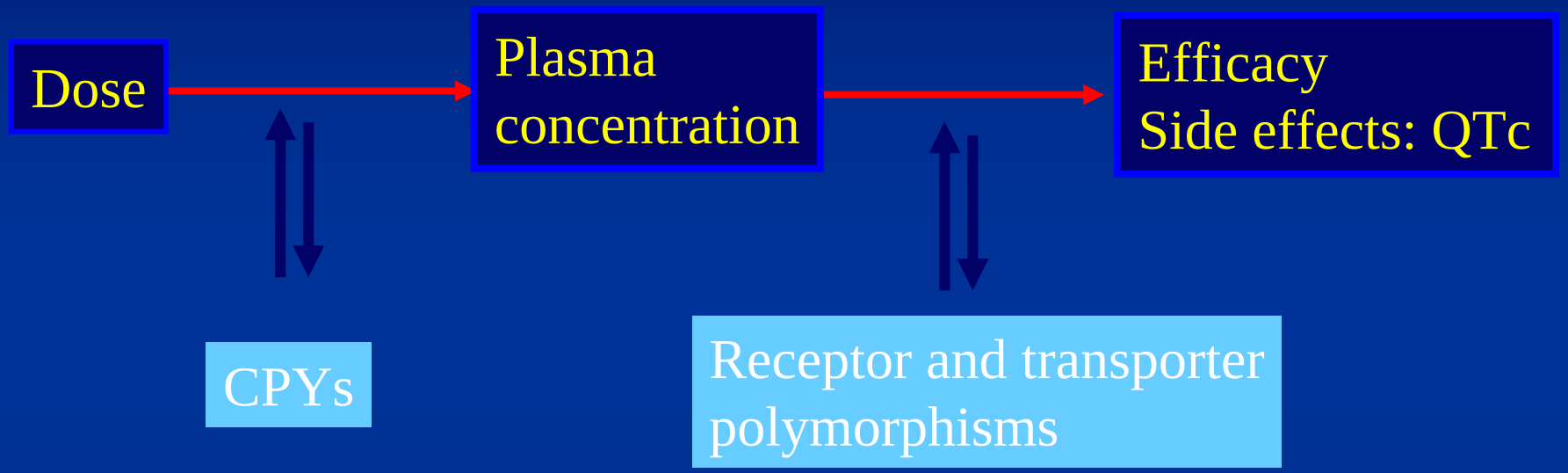
Haloperidol

Thioridazine



De la Rubia, 1998
Berecz, 2001
Dorado, 2003

Dorado et al, 2006



Fluoxetine/norfluoxetine ratio among 64 patients with different number of *CYP2D6* active gene (LLerena et al., 2003)

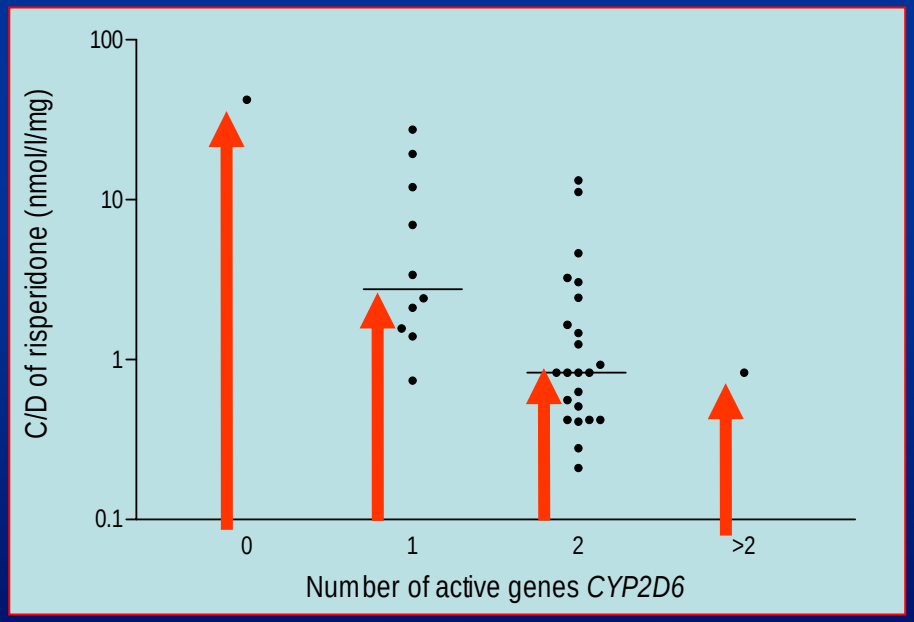
CYP2D6 Psychiatric patients: Clinical Implications **Risperidone**

Phenotype: DBQ

Genotype: *CYP2D6*

Plasma concentration

QTc



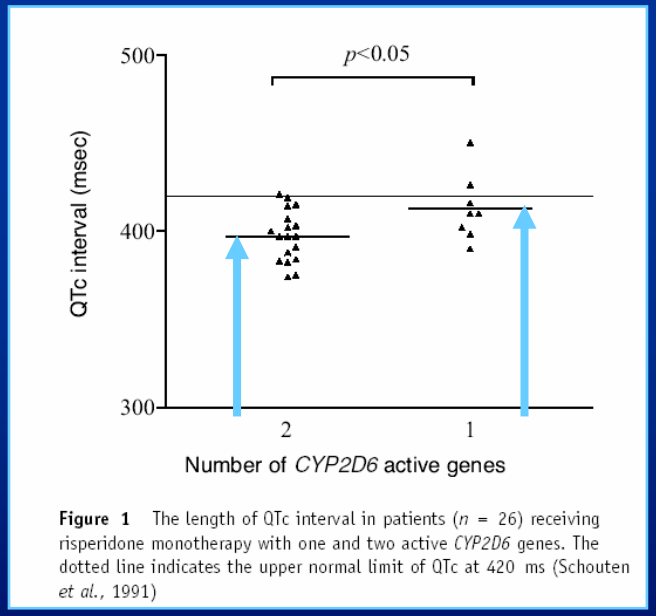
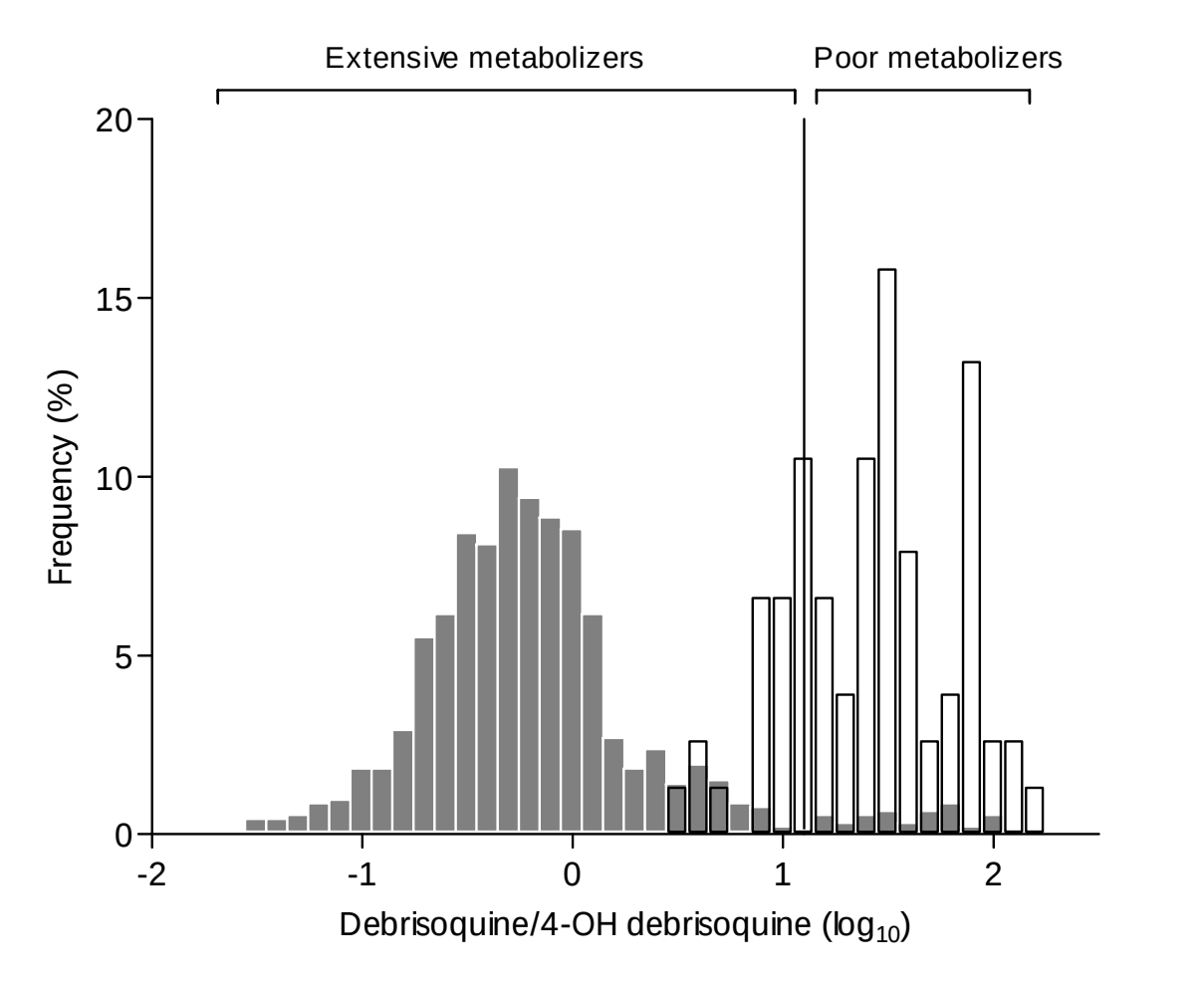


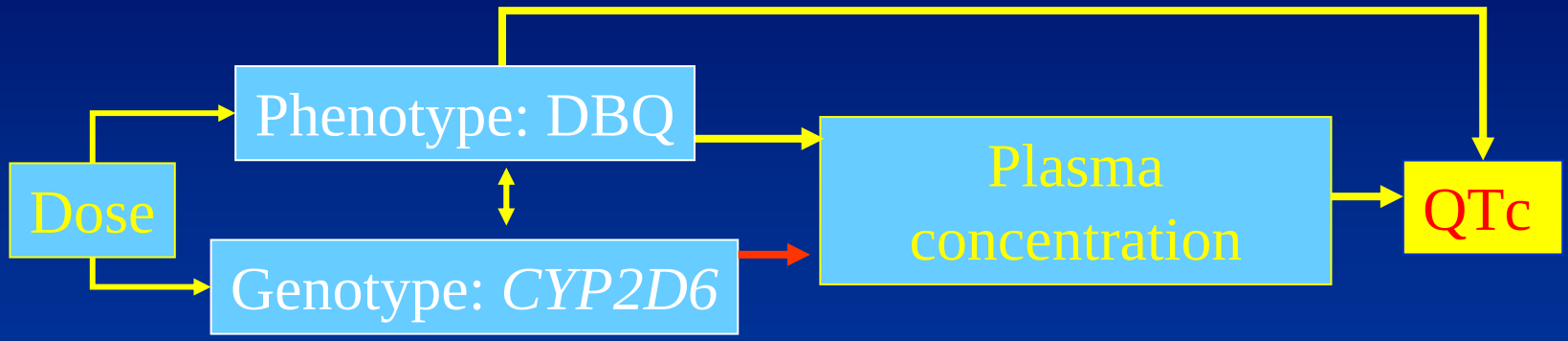
Figure 1 The length of QTc interval in patients (n = 26) receiving risperidone monotherapy with one and two active *CYP2D6* genes. The dotted line indicates the upper normal limit of QTc at 420 ms (Schouten *et al.*, 1991)

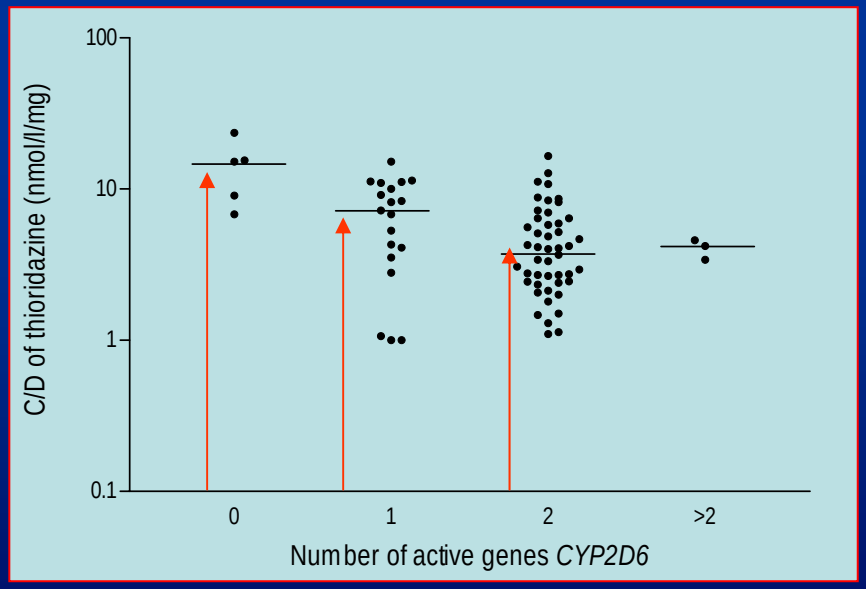
CYP2D6 number of functional genes and dose-corrected (C/D) plasma levels (log_{10}) of **risperidone** (n=34) and QTc. The median in each group is indicated with a solid line.

Histograms of debrisoquine/4-OH debrisoquine metabolic ratio (log10) in psychiatric 76 patients treated at therapeutic doses of thioridazine (clear; *Berecz et al., 2003*) and Spanish healthy population of 925 volunteers (grey; *LLerena et al., 1993*).



CYP2D6 Psychiatric patients: Clinical Implications **Thioridazine**





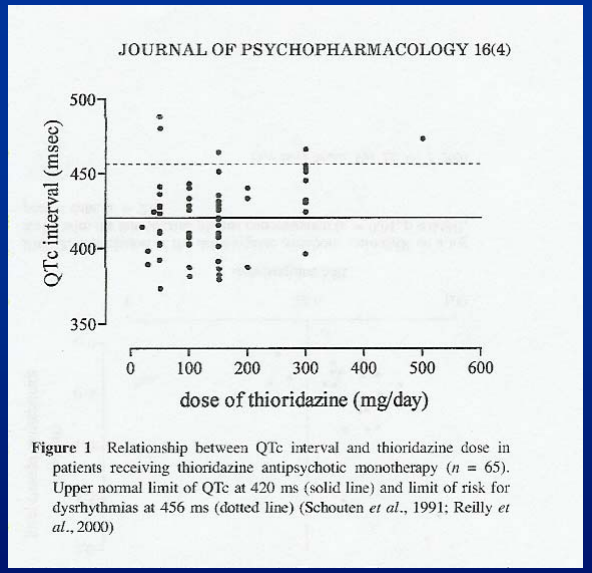
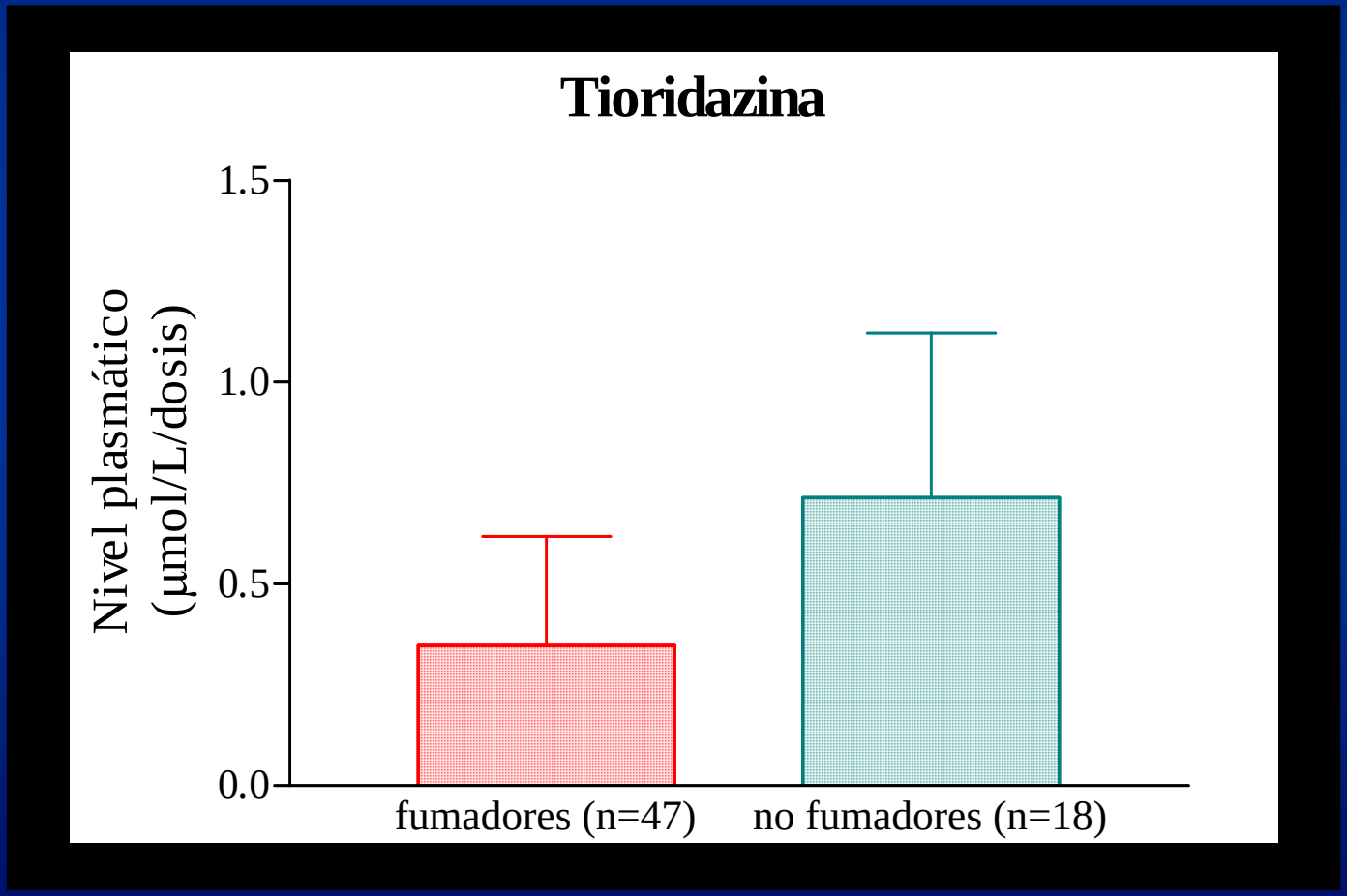

JOURNAL OF PSYCHOPHARMACOLOGY 16(4)

Figure 1 Relationship between QTc interval and thioridazine dose in patients receiving thioridazine antipsychotic monotherapy (n = 65). Upper normal limit of QTc at 420 ms (solid line) and limit of risk for dysrhythmias at 456 ms (dotted line) (Schouten *et al.*, 1991; Reilly *et al.*, 2000)

Dose-corrected (C/D) plasma levels (log_{10}) of **thioridazine** (n=74) different *CYP2D6* number of functional genes (zero, one, two and more than two). The median in each group is indicated with a solid line.

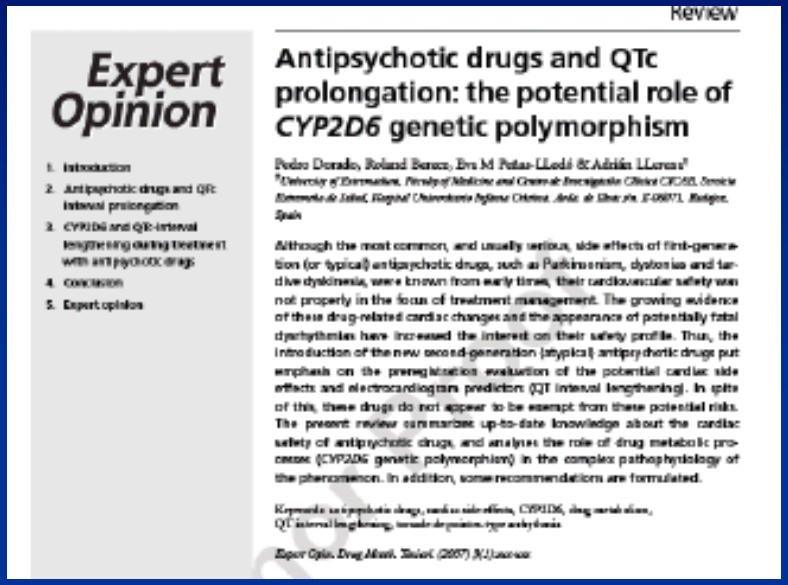
Pacientes en tratamiento con tioridacina

Cosumo de tabaco y nivel plasmático /dosis (mg/kg/día)



LLerena et al 2002

RED IBEROAMERICANA DE FARMACOGENETICA Y FARMACOGENOMICA
(CYTED.206RT0290) (Coordinador: Dr. Adrián LLerena) www.ribef.org



Review

Expert Opinion

1. Introduction
2. Antipsychotic drugs and QTc interval prolongation
3. CYP2D6 and QTc-interval lengthening during treatment with antipsychotic drugs
4. Conclusion
5. Expert opinion

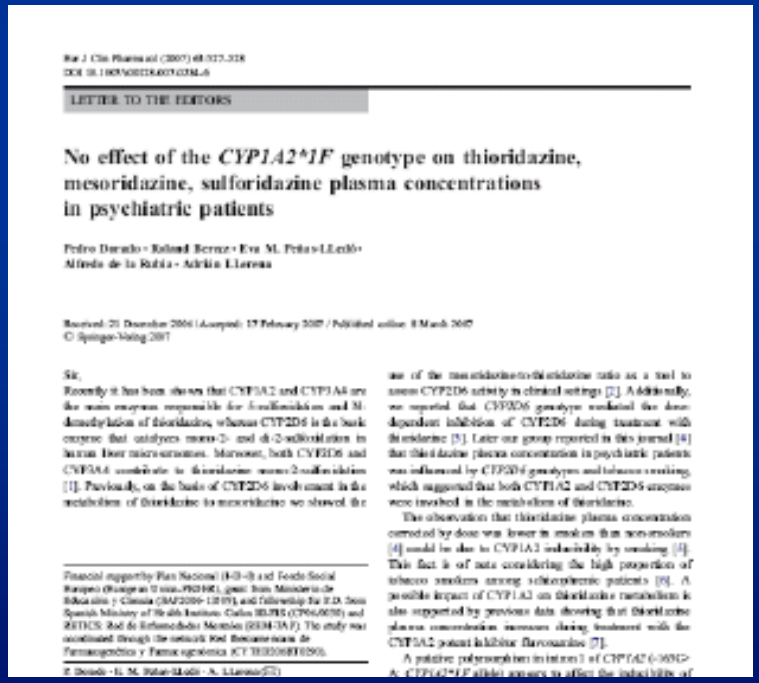
Antipsychotic drugs and QTc prolongation: the potential role of *CYP2D6* genetic polymorphism

Pedro Dorado, Roland Berecz, Eva M Peñas-LLedó & Adrián LLerena†
†University of Extremadura, Faculty of Medicine and Centro de Investigación Clínica CICAB, Servicio Extremeño de Salud, Hospital Universitario Infanta Cristina, Avda. de Elvas s/n, E-06071, Badajoz, Spain

Although the most common, and usually serious, side effects of first-generation (or typical) antipsychotic drugs, such as Parkinsonism, dystonias and tardive dyskinesia, were known from early times, their cardiovascular safety was not properly in the focus of treatment management. The growing evidence of these drug-related cardiac changes and the appearance of potentially fatal dysrhythmias have increased the interest on their safety profile. Thus, the introduction of the new second-generation (atypical) antipsychotic drugs put emphasis on the preregistration evaluation of the potential cardiac side effects and electrocardiogram prediction (QT interval lengthening). In spite of this, these drugs do not appear to be exempt from these potential risks. The present review summarizes up-to-date knowledge about the cardiac safety of antipsychotic drugs, and analyzes the role of drug metabolic processes (*CYP2D6* genetic polymorphism) in the complex pathophysiology of the phenomenon. In addition, some recommendations are formulated.

Keywords: antipsychotic drugs, cardiac side effects, CYP2D6, drug metabolism, QT interval lengthening, torsade de pointes-type arrhythmia

Expert Opin. Drug Metab. Toxicol. (2007) 3(1):xxx-xxx



Eur J Clin Pharmacol (2007) 63:317–318
DOI 10.1007/s00228-007-0258-6

LETTER TO THE EDITORS

No effect of the *CYP1A2*1F* genotype on thioridazine, mesoridazine, sulforidazine plasma concentrations in psychiatric patients

Pedro Dorado · Roland Berecz · Eva M. Peñas-LLedó · Alfredo de la Rubia · Adrián LLerena

Received: 21 December 2006 / Accepted: 17 February 2007 / Published online: 8 March 2007

Sir,

Recently it has been shown that CYP1A2 and CYP3A4 are the main enzymes responsible for S-oxidation and N-demethylation of thioridazine, whereas CYP2D6 is the basic enzyme that catalyzes mono-2- and di-2-sulfoxidation in human liver microsomes. Moreover, both CYP2D6 and CYP3A4 contribute to thioridazine mono-2-sulfoxidation [1]. Previously, on the basis of CYP2D6 involvement in the metabolism of thioridazine to mesoridazine we showed the use of the mesoridazine-to-thioridazine ratio as a tool to assess CYP2D6 activity in clinical settings [2]. Additionally, we reported that *CYP2D6* genotype mediated the dose-dependent inhibition of CYP2D6 during treatment with thioridazine [3]. Later our group reported in this journal [4] that thioridazine plasma concentration in psychiatric patients was influenced by *CYP2D6* genotypes and tobacco smoking, which suggested that both CYP1A2 and CYP2D6 enzymes were involved in the metabolism of thioridazine.

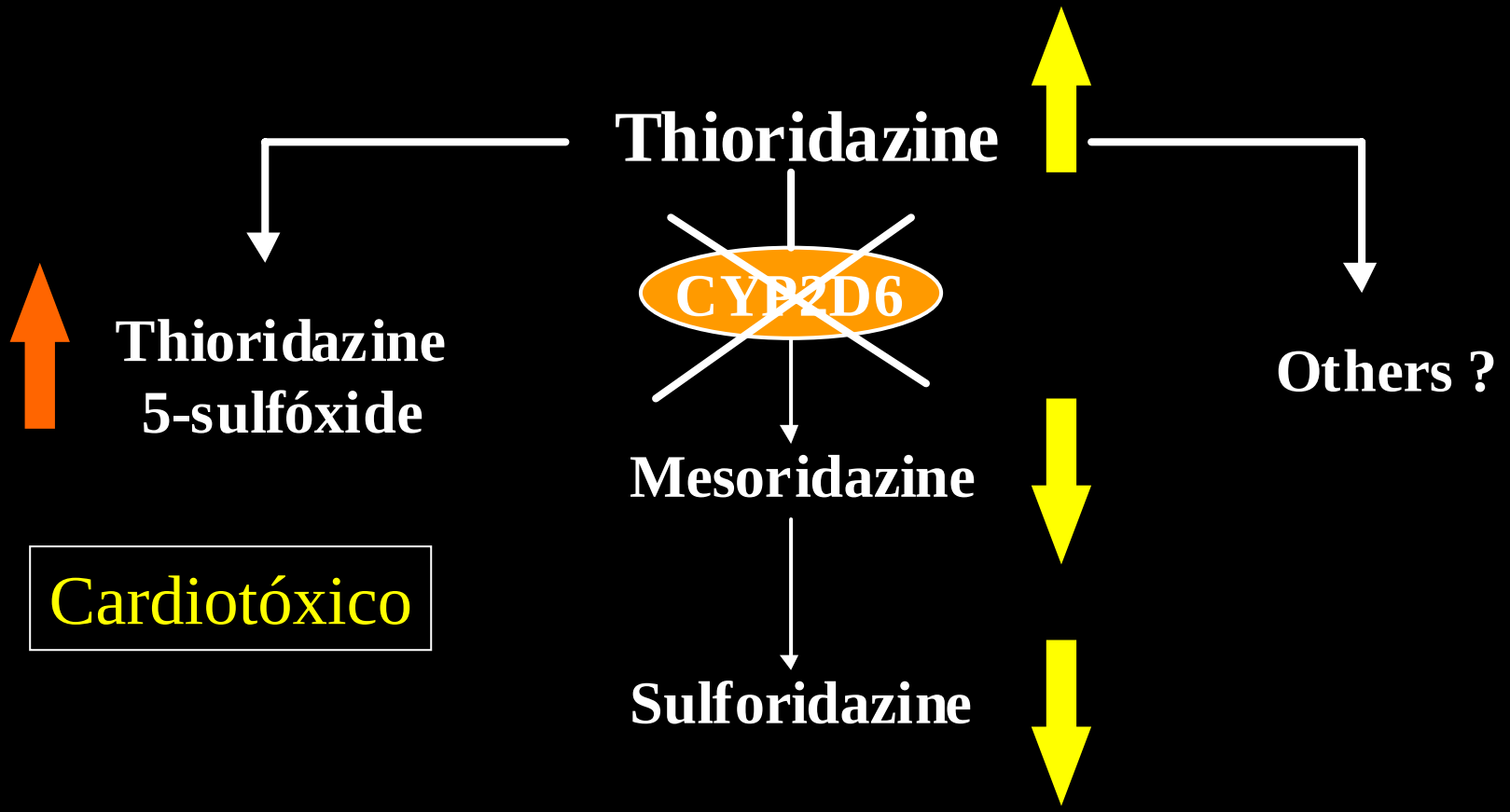
The observation that thioridazine plasma concentration corrected by dose was lower in smokers than non-smokers [4] could be due to CYP1A2 inducibility by smoking [5]. This fact is of note considering the high proportion of tobacco smokers among schizophrenic patients [6]. A possible impact of CYP1A2 on thioridazine metabolism is also supported by previous data showing that thioridazine plasma concentration increases during treatment with the CYP1A2 potent inhibitor fluvoxamine [7].

A putative polymorphism in intron 1 of CYP1A2 (-163C>A, *CYP1A2*1F* allele) appears to affect the inducibility of

Financial support by Plan Nacional I+D+i and Fondo Social Europeo (European Union, FEDER), grant from Ministerio de Educación y Ciencia (SAF2006-12019), and fellowship for P.D. from Spanish Ministry of Health Instituto Carlos III, FIS (CP06/00158) and RETICS Red de Enfermedades Mentales (RD06/0011). The study was coordinated through the network Red Iberoamericana de Farmacogenética y Farmacogenómica (CYTED BIO0501).

P. Dorado · E. M. Peñas-LLedó · A. LLerena (✉)

Effects on drug response ?



Current Drug Targets, 2006, 7, 000-000 1

Clinical Implications of *CYP2D6* Genetic Polymorphism During Treatment with Antipsychotic Drugs

P. Dorado[1,2], R. Berecz[3], E.M. Peñas-LLedó[1], M.C. Cáceres[1], A. LLerena[1,2,4,*]

[1]*University of Extremadura, Faculty of Medicine, Department of Pharmacology and Psychiatry;* [2]*CICS-Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal;* [3]*University of Debrecen, Medical and Health Science Center, Department of Psychiatry, Debrecen, Hungary and* [4]*Clinical Research Center, FUNDESALUD, Extremadura University Hospital*

Abstract: CYP2D6 is described as the most relevant enzyme in the metabolism of many antipsychotic drugs. Its contribution to the inter-individual differences in drug response is reviewed here highlighting its role in the kinetics of antipsychotic drugs and the occurrence of drug interactions.

The activity of CYP2D6 is inherited as a monogenetic trait and the *CYP2D6* gene appears highly polymorphic in humans. The polymorphic alleles may lead to altered activity of the CYP enzymes causing absent, decreased (poor), or increased (ultrarapid) metabolism that in turn influence the disposition of the antipsychotic drugs. Antipsychotic drug biotransformation is mainly determined by genetic factors mediating *CYP2D6* gene polymorphism, however the importance of environmental factors (dietary, smoking, diseases, etc.) is also recognized. Additionally, the potential interaction between *CYP2D6* and the endogenous metabolism must be taken into consideration.

The present review summarizes the relevance of physiological and environmental factors in CYP2D6 hydroxylation capacity, the inhibition of CYP2D6 activity during treatment, the use of drug/metabolite ratio as a tool to evaluate CYP2D6 hydroxylation capacity in a patient, and the relevance of CYP2D6 for drug plasma concentration and for QTc interval lengthening during treatment with antipsychotic drugs.

Key Words: pharmacogenetics, antipsychotic drugs, CYP2D6, pharmacogenomics.

Table 2. Major Human Drug-Metabolizing Enzymes and their Antipsychotic Drug Substrates

	Drug	*In vitro*	Healthy volunteers	In patients
CYP1A2	chlorpromazine	+	**NA**	**NA**
	clozapine	+	+	+
	haloperidol	-	+	+/-
	olanzapine	+	+	+/-
	perhenazine	+	**NA**	**NA**
	thioridazine	+	**NA**	+
CYP2C9	perazine	+	**NA**	**NA**
CYP2C19	clozapine	+/-	**NA**	-
	perhenazine	+	**NA**	**NA**
	thioridazine	NA	**NA**	+
CYP2D6	chlorpromazine	+	+	+
	haloperidol	+	+	+/-
	perphenazine	+	+	+
	thioridazine	+	+	+
	zuclopenthixol	NA	+	+
	aripiprazol	+	+	**NA**
	clozapine	+/-	+/-	+/-
	olanzapine	+	-	+
	quetiapine	+/-	**NA**	-
	risperidone	+	+	+
CYP3A4	aripiprazol	+	+	**NA**
	clozapine	+	**NA**	+/-
	haloperidol	+	**NA**	+
	perazine	+	**NA**	**NA**
	perhenazine	+	**NA**	**NA**
	quetiapine	+	+	+
	risperidone	+	**NA**	+
	ziprasidone	+	+	**NA**

+ = positive results, - = negative results, NA = no information available.

1. Genetic polymorphism of CYP2D6 (Pheno/genotyping)
2. Interthnic variability
3. Endogeous metabolism: Psychological functions in healthy volunteeers
4. Vulnerability to psychiatric disorders: Depression / Schizophrenia
5. Pheno and genotypes in psychiatric patients
6. Clinical Implications: Plasma concentration and QTc interval lenghtening
7. Interacciones

Beta Blockers:
carvedilol
S-metoprolol
propafenone
timolol

Antidepressants:
amitriptyline
clomipramine
desipramine
imipramine
paroxetine

Antipsychotics:
haloperidol
perphenazine
risperidone
thioridazine

Others:
amphetamine
atomoxetine
chlorpromazine
codeine
debrisoquine
dextromethorphan
fluoxetine
fluvoxamine
lidocaine
metoclopramide
nortriptyline
propranolol
sparteine
tamoxifen
venlafaxine

DRUGS & CYP2D6

DRUGS & CYP2C9

NSAIDs:
diclofenac
ibuprofen
meloxicam
S-naproxen
piroxicam
suprofen

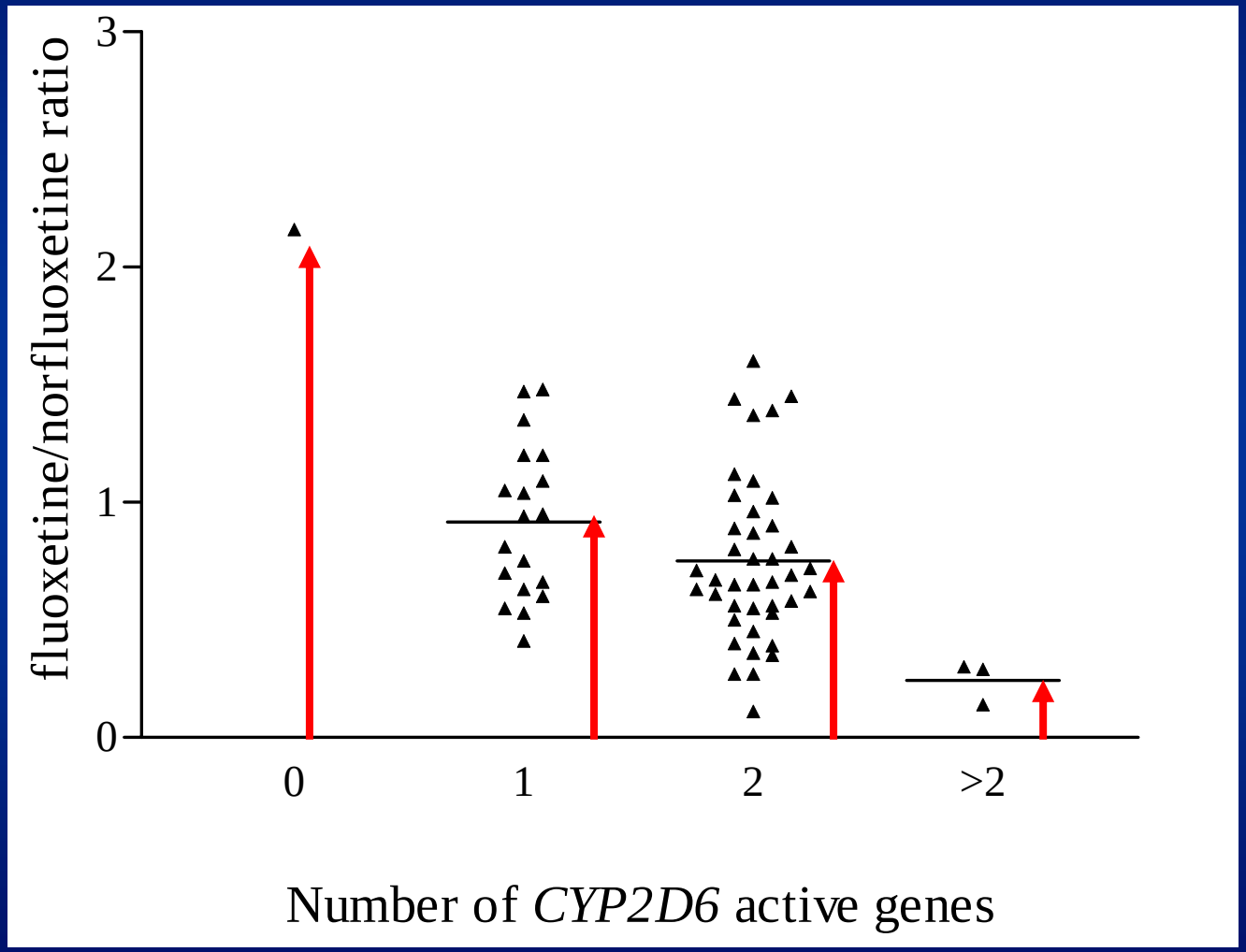
Oral Hypoglycemic Agents:
tolbutamide
glipizide

Angiotensin II Blockers:
losartan
irbesartan

Sulfonylureas:
glyburide
glibenclamide
glipizide
glimepiride
tolbutamide

Others:
amitriptyline
celecoxib
fluoxetine
fluvastatin
nateglinide
phenytoin
rosiglitazone
tamoxifen
torsemide
S-warfarin

CYP2C9 and Fluoxetine plasma concentrations



Fluoxetine/norfluoxetine ratio among 64 patients with different number of *CYP2D6* active gene (LLerena et al., 2003)

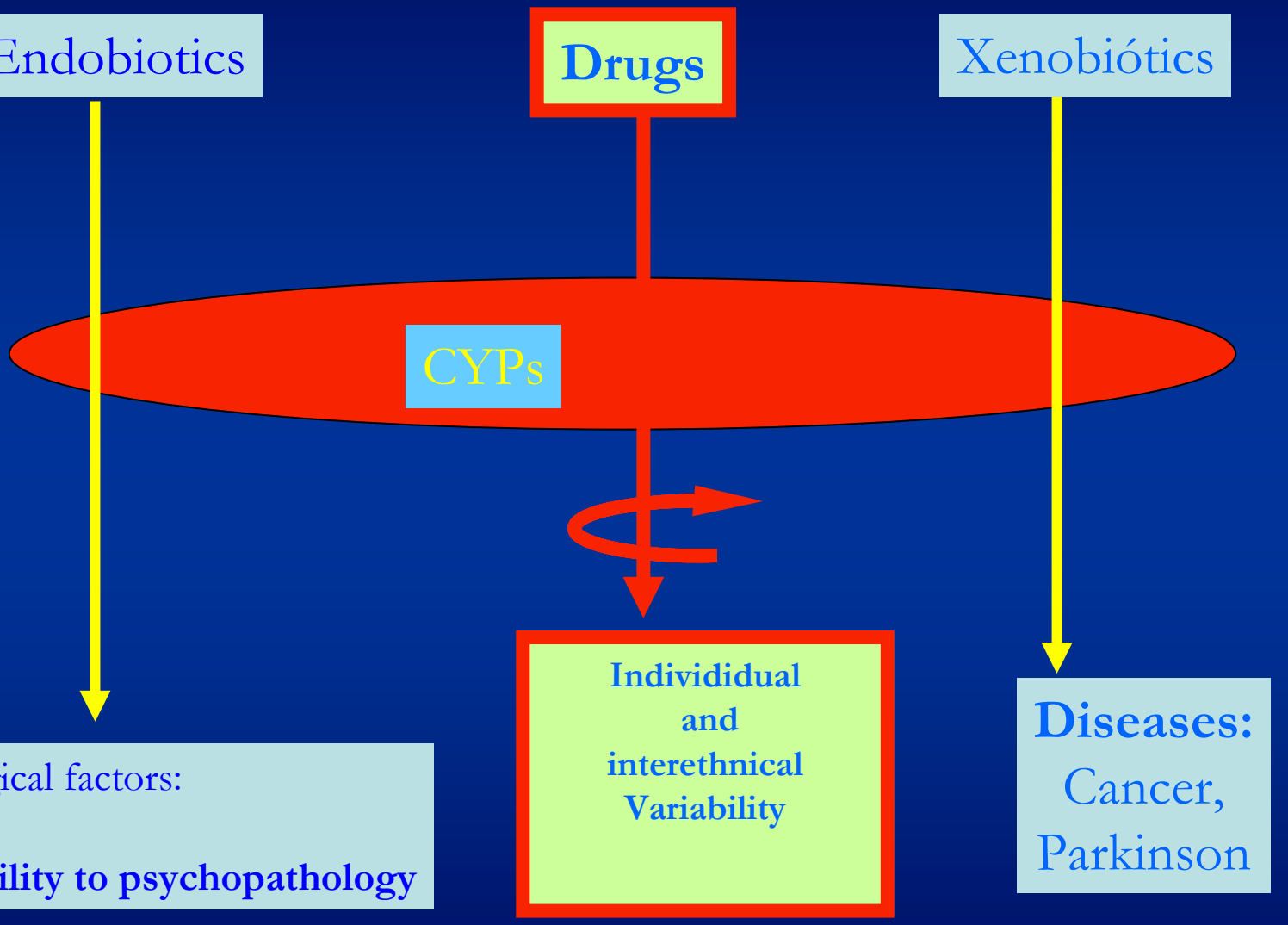
CYP2C9 substrates

Metabolism of Psychoactive substances

Tetrahydrocannabinol

Amitryptyline

	Drugs
Antidiabetic	Tolbutamide
Anticoagulants	Warfarine
Antidepressants	Amitryptiline Fluoxetine
Antihypertensives	Losartan Tienilic acid
Antiepileptics	Phenyton
NSAIDs	Diclofenac Ibuprofen Flurbiprofen Mephenamic Piroxicam Tenoxicam Indometacina Meloxicam Acetil salicílic acid


Endobiotics
Drugs
Xenobiótics
CYPs
Psychological factors:
Vulnerability to psychopathology
Individidual
and
interethnical
Variability
Diseases:
Cancer,
Parkinson

1. Existe variabilidad individual y regional en la respuesta a los fármacos:
cada paciente necesita un regimen terapéutico individual
cada región necesita unas recomendaciones terapéuticas

2. Esta variabilidad depende de la interacción dinámica del estado de los sistemas fisiológicos/patológicos, de la herencia genética y de la interacción ambiental

3. Los polimorfismos genéticos de enzimas metabolizadoras de fármacos participan en el metabolismo endógeno y por tanto en la vulnerabilidad a la enfermedad

4. Existe una relación entre la vulnerabilidad a la enfermedad y la idiosincrasia en la respuesta a los fármacos.

1. Existe variabilidad individual y regional en la respuesta a los fármacos:
cada paciente necesita un regimen terapéutico individual
cada región necesita unas recomendaciones terapéuticas

2. Esta variabilidad depende de la interacción dinámica del estado de los sistemas fisiológicos/patológicos, de la herencia genética y de la interacción ambiental

3. Los polimorfismos genéticos de enzimas metabolizadoras de fármacos participan en el metabolismo endógeno y por tanto en la vulnerabilidad a la enfermedad

4. Existe una relación entre la vulnerabilidad a la enfermedad y la idiosincrasia en la respuesta a los fármacos.

1. Existe variabilidad individual y regional en la respuesta a los fármacos:
cada paciente necesita un regimen terapéutico individual
cada región necesita unas recomendaciones terapéuticas

2. Esta variabilidad depende de la interacción dinámica del estado de los sistemas fisiológicos/patológicos, de la herencia genética y de la interacción ambiental

3. Los polimorfismos genéticos de enzimas metabolizadoras de fármacos participan en el metabolismo endógeno y por tanto en la vulnerabilidad a la enfermedad

4. Existe una relación entre la vulnerabilidad a la enfermedad y la idiosincrasia en la respuesta a los fármacos.

1. Existe variabilidad individual y regional en la respuesta a los fármacos:
cada paciente necesita un regimen terapéutico individual
cada región necesita unas recomendaciones terapéuticas

2. Esta variabilidad depende de la interacción dinámica del estado de los sistemas fisiológicos/patológicos, de la herencia genética y de la interacción ambiental

3. Los polimorfismos genéticos de enzimas metabolizadoras de fármacos participan en el metabolismo endógeno y por tanto en la vulnerabilidad a la enfermedad

4. Existe una relación entre la vulnerabilidad a la enfermedad y la idiosincrasia en la respuesta a los fármacos.

Clinical implications of CYP2D6 polymorphism and its relevance for the world global health.

- Pharmacogenetics might contribute to narrowing the "biotechnological gap" between the developed and undeveloped world.
- This together with information from independent clinical studies may help to the individualization of drug therapy in every place of the world.

we truly believe that newly developed drugs must be available for every patient according exclusively to his or her clinical needs

www.RIBEF.ORG (CYTED.206RT0290)

RED IBEROAMERICANA DE FARMACOGENETICA Y FARMACOGENOMICA

• Fac. de CC MM G.C. Garcia y Hosp. Psiquiátrico. Inst. Superior de CCMM	**La Habana,**	CUBA.
• Instituto de Errores Innatos del Metablismo. Universidad Javeriana,	**Bogotá,**	COLOMBIA.
• Facultad de Medicina. Universidad de Extremadura,	**Badajoz,**	ESPAÑA.
• Instituto Politécnico Nacional,	**Durango,**	MÉXICO.
• Universidad Nacional Mayor de San Marcos,	**Lima,**	PERÚ.
• Universidade da Beira Interior,	**Covilha,**	PORTUGAL.
• Unidad de Genética, ICB. Facultad de Medicina. Universidad del Rosario,	**Bogotá,**	COLOMBIA.
• Division of Pharmacology, Instituto Nacional de Cancer,	**Rio Janeiro,**	BRASIL
• Universidad Austral de Chile,	**Puerto Montt,**	CHILE.
• Facultad de Medicina.Universidad Nacional Autónoma de Nicaragua,	**León,**	NICARAGUA
• Universidade do Algarve,	**Faro,**	PORTUGAL.
• GENELAB. Universidad Nacional de La Plata.	**Buenos Aires,**	ARGENTINA.
• Universidad Nacional Autonoma de México UNAM.	**México DF,**	MÉXICO

GRUPOS: 12.
PAISES: 10. Brasil, Chile, Colombia, Cuba, España, México, Nicaragua, Perú, Portugal.

allerena@unex.es

www. RIBEF.ORG

RED IBEROAMERICANA DE

FARMACOGENETICA Y FARMACOGENOMICA

Implicaciones clínicas

- VARIABILIDAD EN POBLACIONES

- SALUD MENTAL
- DOLOR
- CANCER
- MEDICINA TROPICAL

CYTED

CIENCIA Y TECNOLOGÍA PARA EL DESARROLLO

RED CYTED 206RT0290

Coordinador:

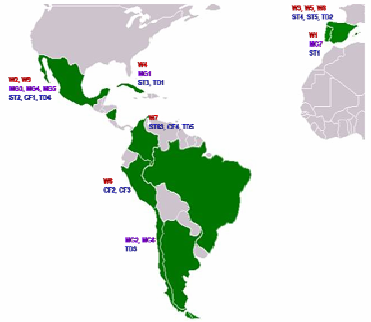
Adrián LLerena Ruiz

RED IBEROAMERICANA DE FARMACOGENETICA: IMPACTO EN SALUD PUBLICA

GRUPOS PARTICIPANTES

Cubre una amplia representación de la comunidad iberoamericana, 12 grupos de 10 países, que van de norte a sur (desde la Patagonia chilena hasta Durango en México) y de este a oeste (desde Lima en Perú hasta Río de Janeiro en Brasil), incluyendo León (Nicaragua), Bogotá (Colombia) y la Habana (Cuba), además de la Península Ibérica (Portugal y España).

Genetab, Universidad Nacional de La Plata (IBIMOLAL)	Buenos Aires, ARGENTINA
Hospital Psiquiátrico y Centro de Salud Mental de la Habana Vieja (HPH)	La Habana, CUBA
Instituto Nacional de Cancer (INCA)	Río de Janeiro, BRASIL
Instituto Politecnico Nacional (IPN/CI)	Durango, MEXICO
Pontificia Universidad Javeriana (PUJ)	Bogotá, COLOMBIA
Universidad Austral de Chile (UACH)	Puerto Montt, CHILE
Universidad de Extremadura (UEX)	Badajoz, ESPAÑA
Universidad del Rosario (UR)	Bogotá, COLOMBIA
Universidad Nacional Autónoma de Nicaragua (UNAN-LEON)	León, NICARAGUA
Universidad Nacional Mayor de San Marcos (UNMSM)	Lima, PERU
Universidade do Algarve (UALG)	Faro, PORTUGAL
Universidade do Algarve (UALG)	Lagos, PORTUGAL



www.ribef.org

FARMACOGENÉTICA DE POBLACIONES IBEROAMERICANAS

ACTAS DEL I SIMPOSIUM IBEROAMERICANO EN FARMACOGENÉTICA DE POBLACIONES

Badajoz (España), 17 de noviembre de 2006

Editado por:

Adrián LLerena Ruiz y Pedro Dorado Hernández

Organizado por:

- Red Iberoamericana de Farmacogenética y Farmacogenómica (CYTED 206RT0290)
- Sociedad Iberoamericana de Farmacogenética y Farmacogenómica (SIFF)
- Centro de Investigación Clínica del Área de Badajoz (CICAB)

Financiado por:

RED IBEROAMERICANA DE FARMACOGENÉTICA Y FARMACOGENOMICA (206RT0290)

JUNTA DE EXTREMADURA
Consejería de Infraestructuras Desarrollo Tecnológico e Innovación
D.G de Investigación Desarrollo Tecnológico e Innovación

Universidade do Algarve Faro Portugal

Universidad de La Plata Buenos Aires Argentina

Universidade del Rosario Bogotá Colombia

www.ribef.org

UNAM IIB México DF México

INCA Rio de Janeiro Brasil

ESPAÑA

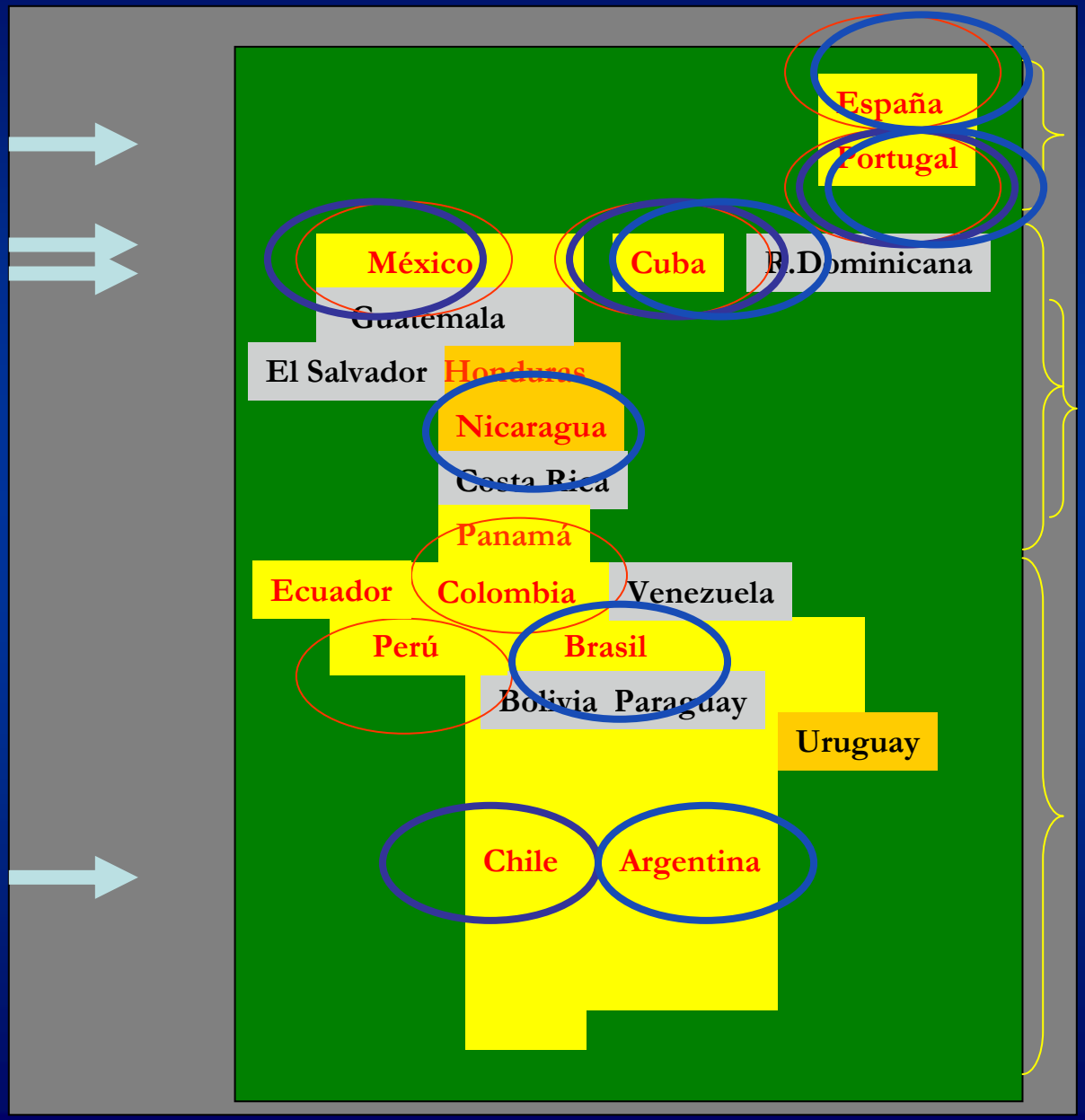
Pontificia Universidad JAVERIANA Bogotá COLOMBIA

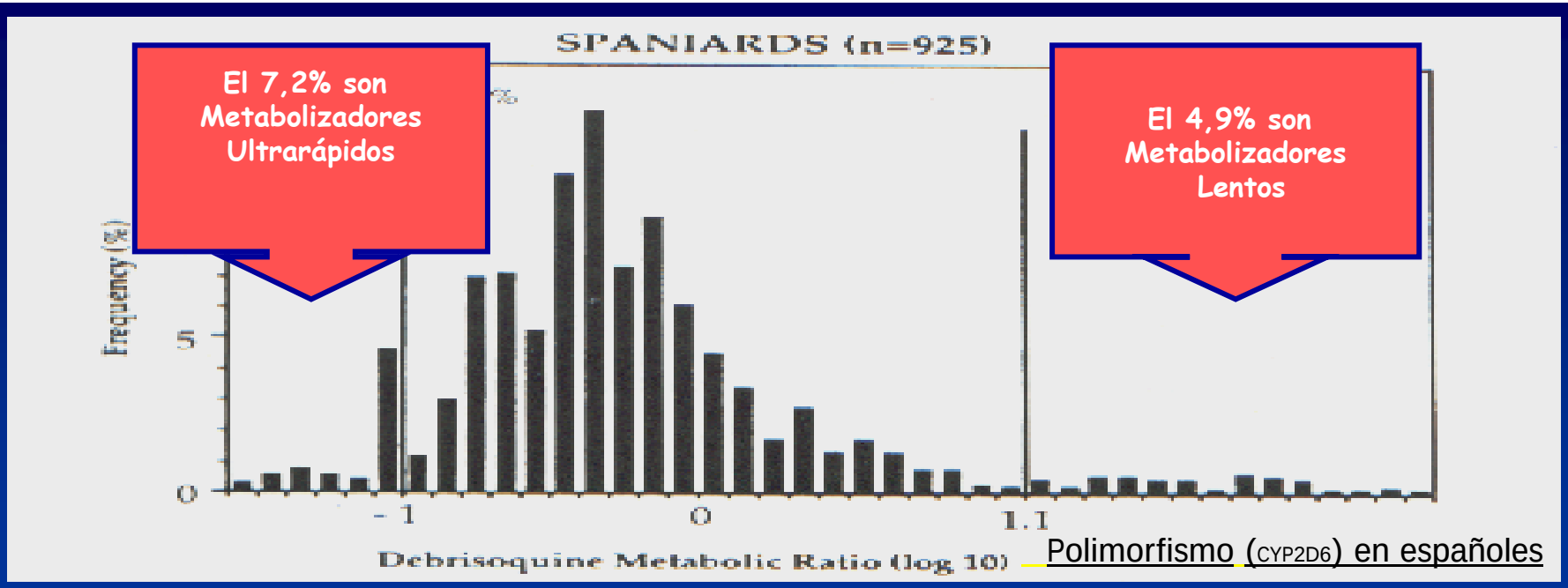
CIDIR I. Politécnico N Durango México

Universidad Nacional Autónoma León Nicaragua

Universidad Austral de Chile Puerto Montt Chile

Área geográfica de la Red (2006-2009)





Polimorfismo (CYP2D6) en españoles

UTILIDAD CLINICA de Estudios en Farmacogenética:

- Conocimiento de las enfermedades
- Mejora del uso del medicamentos:
  - a) prevención de reacciones adversas
  - b) optimización de la eficacia

- Obtención de resultados válidos para mas personas del planeta

Valencia 26 Enero 2008

Writing prescription is easy,
Undertanding people is hard

Franz Kafka

www.ribef.org

www.cicab.es

allerena@unex.es