EMA Workshop on Pharmacogenomics: from science to clinical care

October 8-9, 2012

"Genomics in Patients with Hispanic ancestry"

- Pharmacogenetics in Hispanics and Its clinical implications -

Adrián LLerena MD PhD

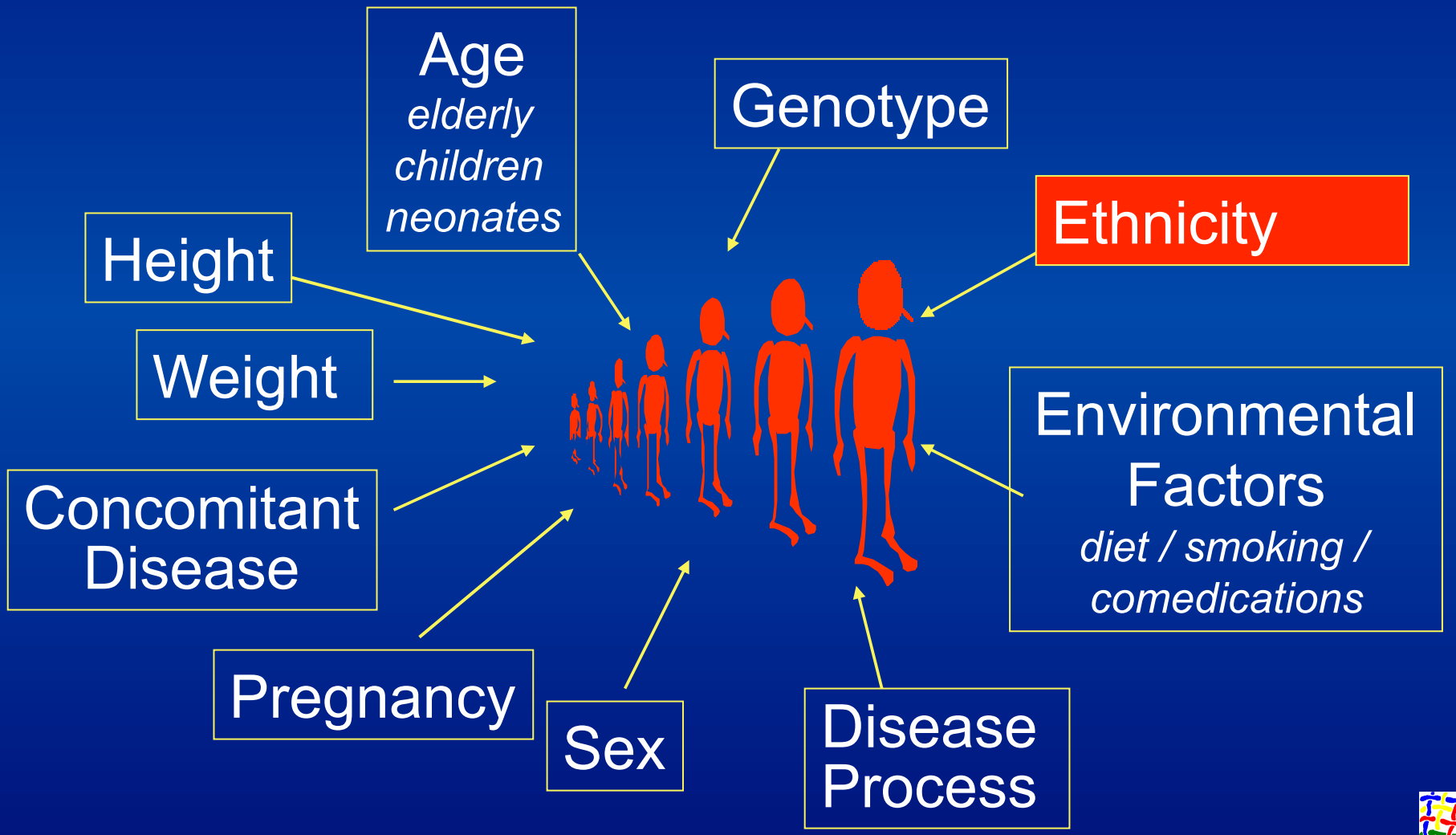
Clinical Research Centre
University Hospital. Faculty of Medicine. University of Extremadura, Badajoz, Spain

allerena@unex.es

08.10.2012

Ibero-America is a term used since the second half of the 19th century to refer collectively to the countries in the Americas which were formerly colonies of Spain or Portugal.

Interindividual Variability on Drug Response



Major drug metabolizing enzymes

CYP2D6

CYP2C9

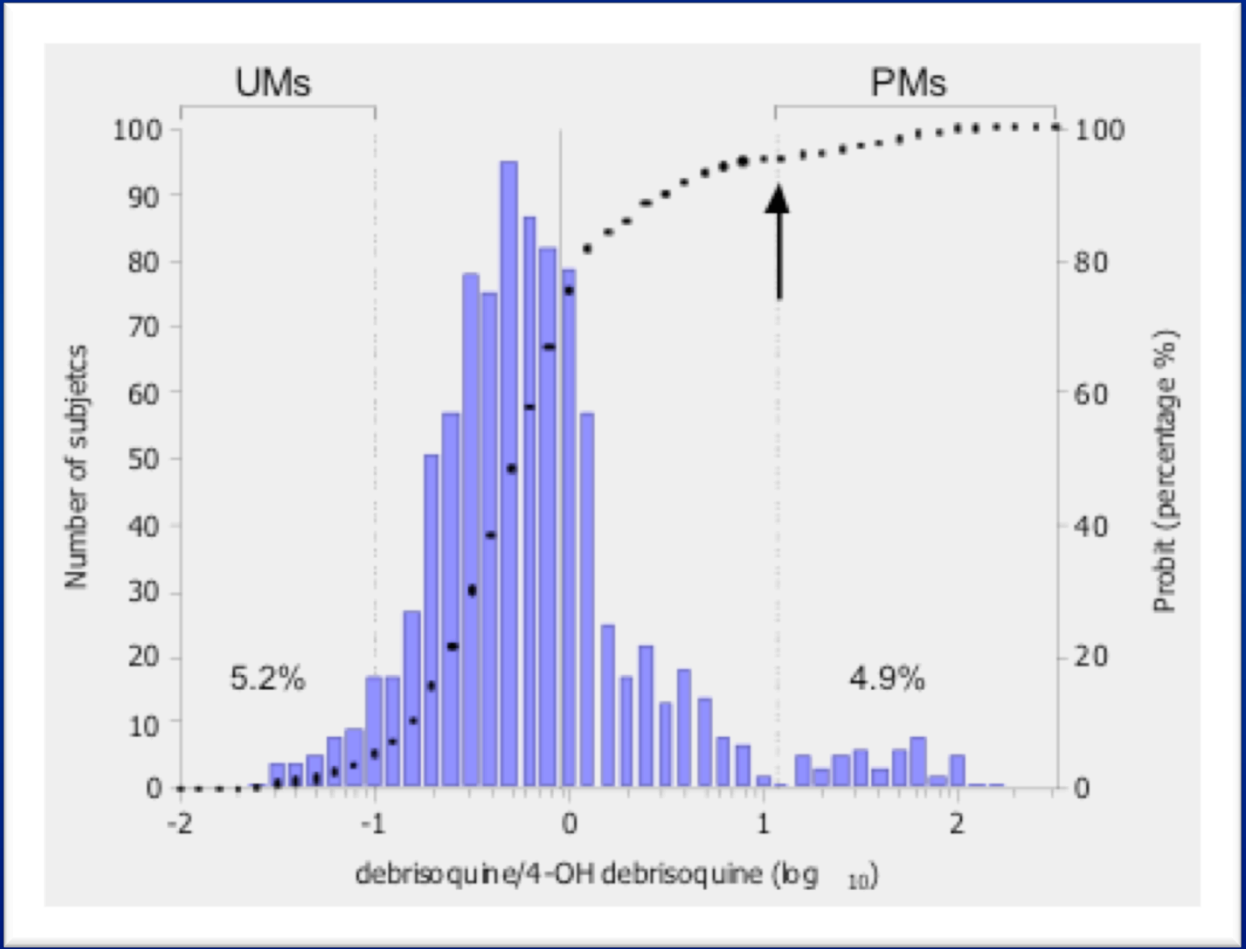
CYP2C19

CYP1A2

Adrián LLerena 2012
allerena@unex.es

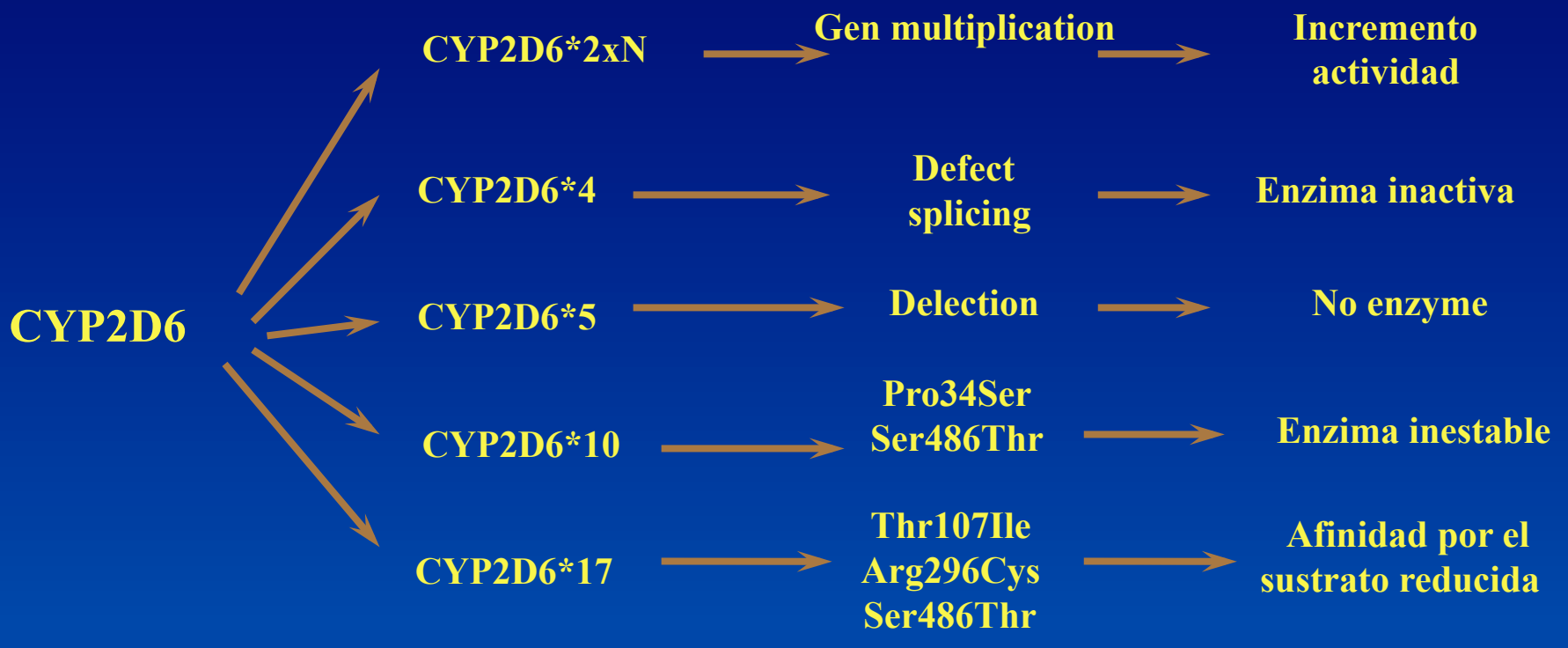
CYP2D6

CYP2D6 polymorphism in Spaniards (LLerena et al 1993)



Debrisoquine hydroxylation phenotype (CYP2D6) in the Spanish Population (n=923) (LLerena et al 1993)

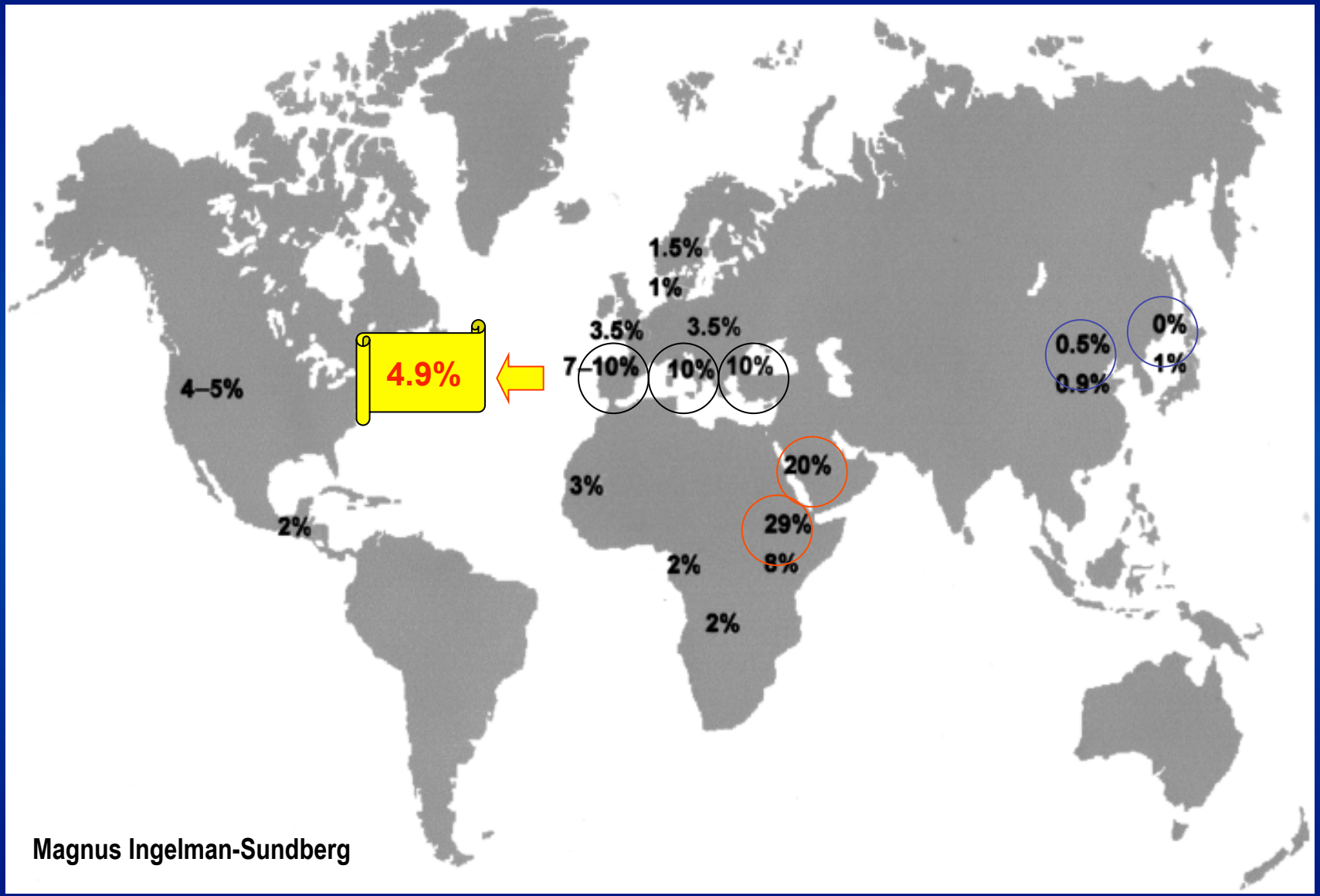
Adrián LLerena 2012
allerena@unex.es



PMs

	Caucasians	Asians	Black African	Ethiopians and Arabs
CYP2D6*2xN	1-5	0-2	2	10-16
CYP2D6*4	12-21	1	2	1-4
CYP2D6*5	2-7	6	4	1-3
CYP2D6*10	1-2	51	6	3-9
CYP2D6*17	0	ND	34	3-9

Interethnical variability: CYP2D6 gene multiplication (Ultrarapids?)



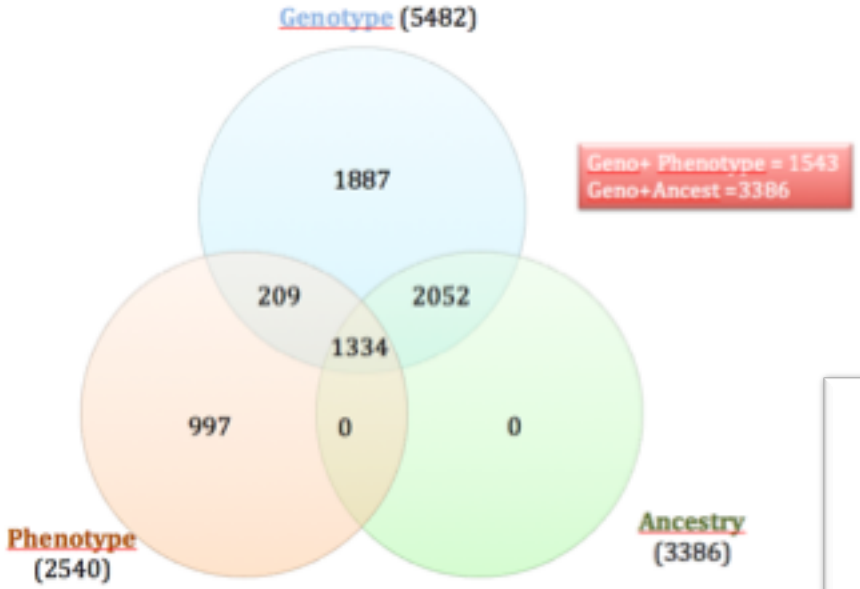
Interethnic distribution of individuals with *CYP*2D6 gene duplicated

Ibero American Network of Pharmacogenetics

RIBEF - SIFF

CEIBA Consorcio Europeo Ibero Americano Farmacogenética

Populations included in the CEIBA consortium for Pharmacogenetics of IberoAmerican Populations



Population Pharmacogenetics among LA populations

N= 6479

R BEF

Iberoamerican Consortium (CEIBA) Population Pharmacogenetics

1. Monterrey MEXICO
2. Durango MEXICO
3. México DF MEXICO
4. Chiapas MEXICO

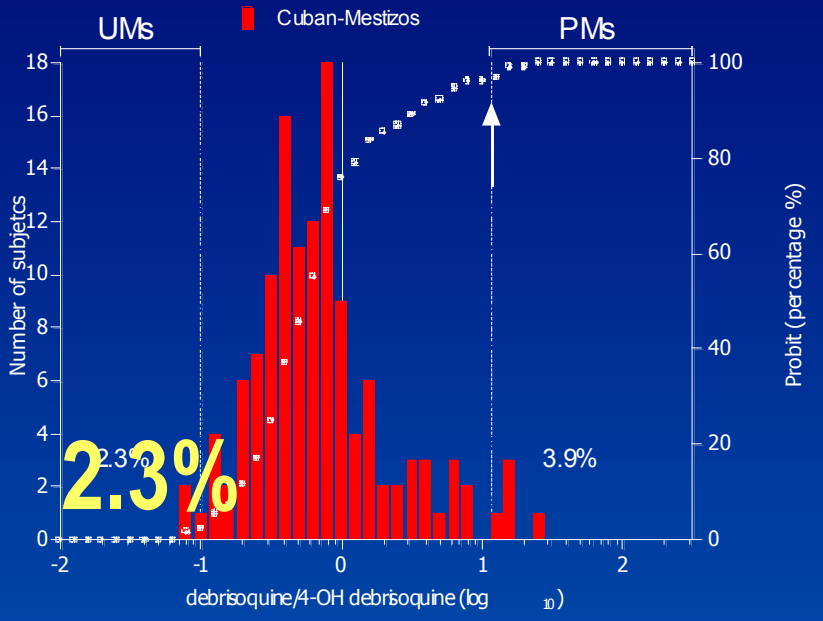
5. La Habana CUBA
6. León NICARAGUA
7. San José COSTA RICA

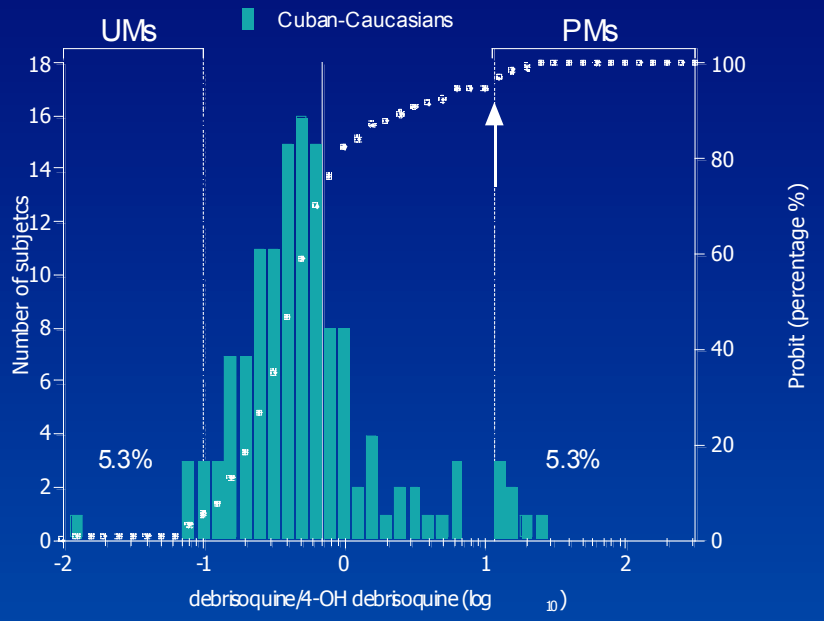
8. Bogotá COLOMBIA
9. Quito ECUADOR
10. Lima PERÚ
11. Belo Horizonte BRAZIL
12. B. Aires ARGENTINA
13. Montevideo URUGUAY
14. Santiago CHILE
15. Coimbra PORTUGAL
16. Extremadura, ESPAÑA

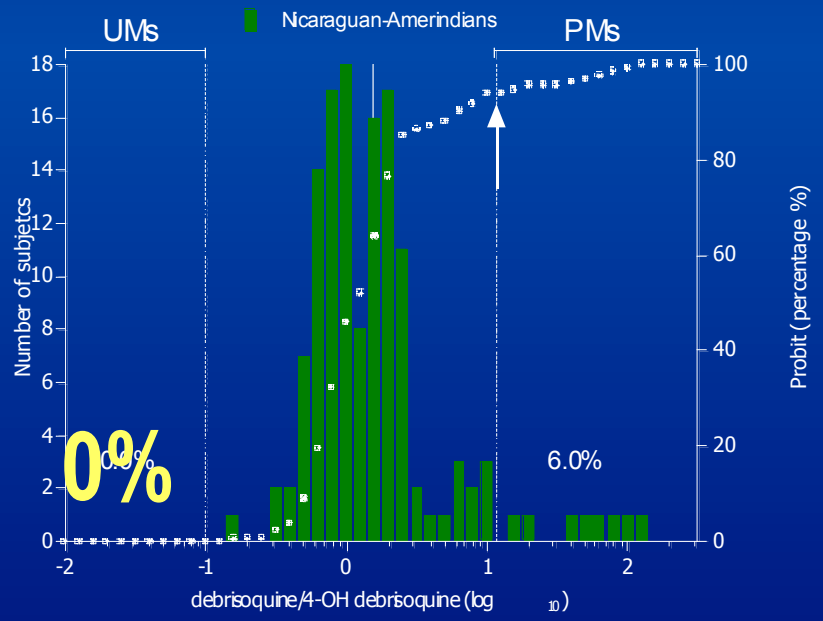
Achivements:

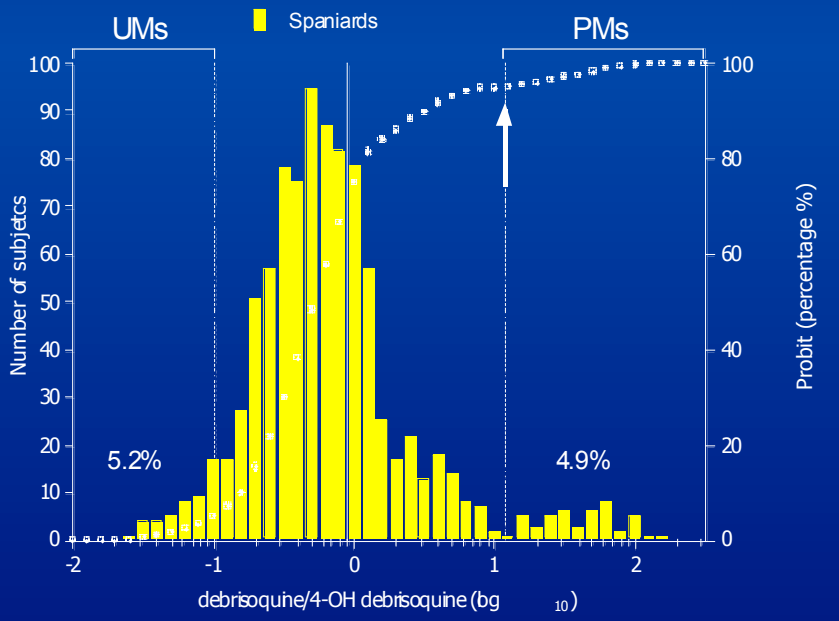
6 479 healthy volunteers studied

Pheno and Genotype



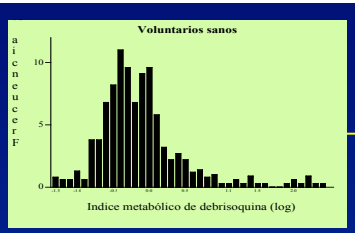






LLerena et al; Pharmacogenomics 2011

Adrián LLerena 2012
allerena@unex.es



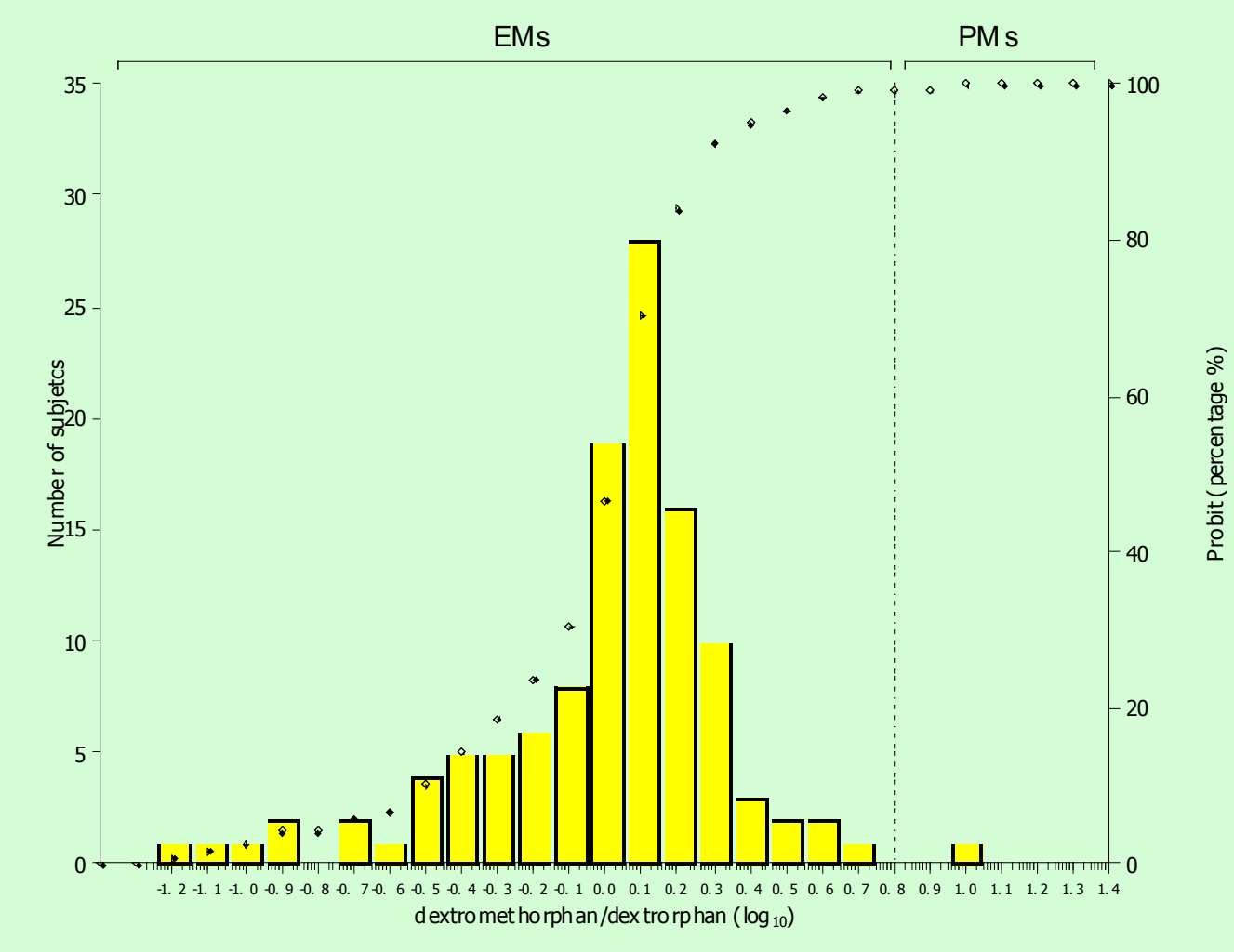
CYP2D6 among Hispanics: Spaniards, Cubans, Nicaraguans

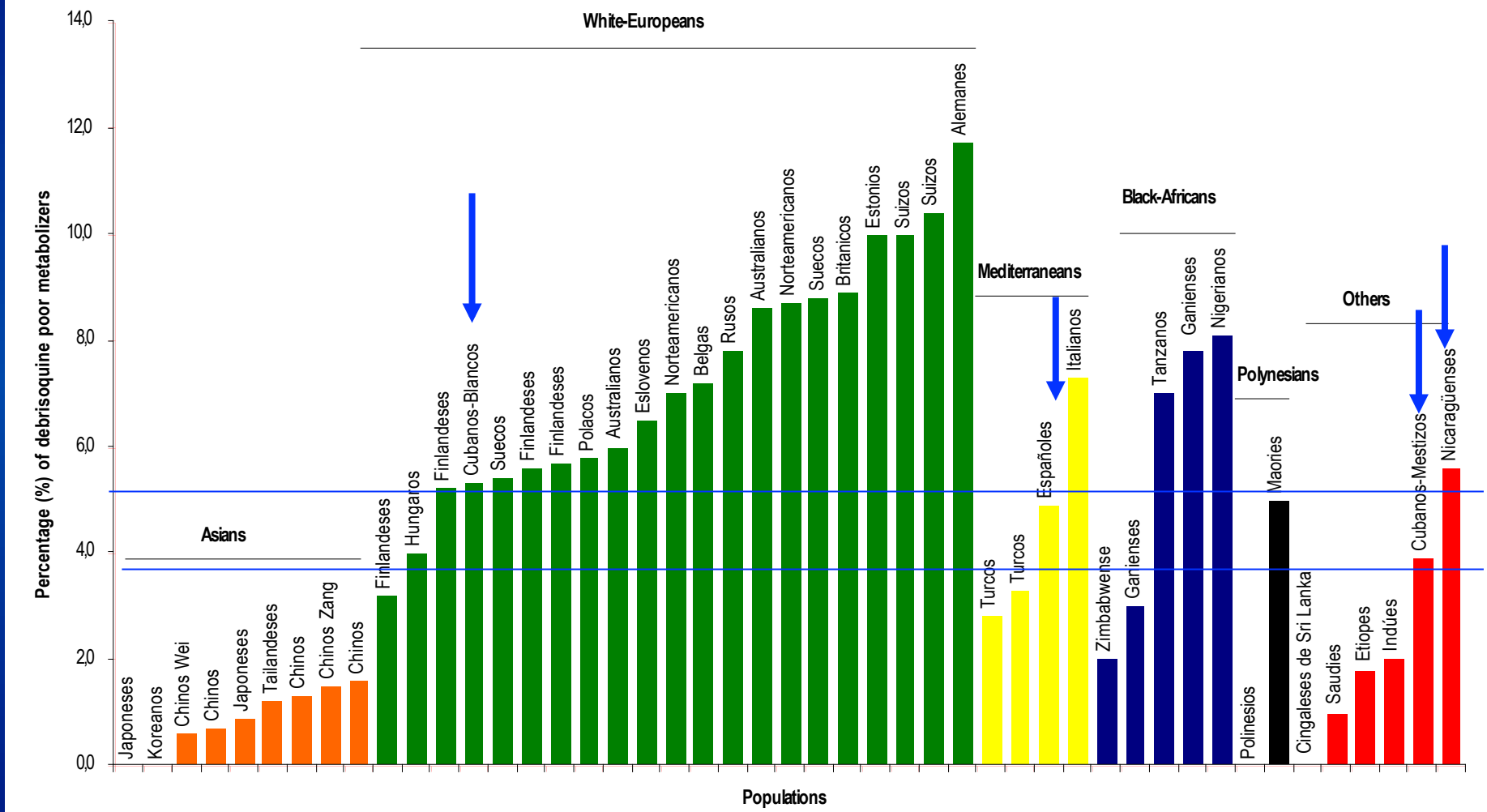
CYP2D6 alleles	Cuban -Caucasians (n=260)	Cuban -Mestizos (n=252)	Nicaraguan -Amerindian (n=196)
*wt (*1 or *2)*	0.754	0.663	0.761
**3*	0	0	0
**4*	0.146	0.143	0.142
**5*	0.019	0.016	0.046
**6*	0.008	0.012	0
**10*	0.004	0.008	0.031
**17*	0.027	0.102	0.
Duplications			
*wt (*1 or *2) xN*	0.038	0.047	0.020
**4xN*	0.004	0	0

Frequencies of *CYP2D6* variant alleles among Cuban-Caucasian, Cuban-Mestizo, and Nicaraguan-Amerindian populations (n= number of alleles.) Unpublished data from (LLerena, P. Dorado, B. Pérez, I. González, La Habana, R. Ramírez, León, Nicaragua).

ECUADORIANS

+Eur J Clin Pharmacol 2012)




INTERETHNIC DIFFERENCES ON DEBRISOQUINE HYDROXYLAXE POLYMORPHISMS
Percentage (%) of debrisoquine poor metabolizers
14,0
12,0
10,0
8,0
6,0
4,0
2,0
0,0
White-Europeans
Asians
Mediterraneans
Black-Africans
Polynesians
Others
Japoneses
Koreanos
Chinos Wei
Chinos
Japoneses
Tailandeses
Chinos
Chinos Zang
Chinos
Finlandeses
Hungaros
Finlandeses
Cubanos-Blancos
Suecos
Finlandeses
Finlandeses
Polacos
Australianos
Eslovenos
Norteamericanos
Belgas
Rusos
Australianos
Norteamericanos
Suecos
Britanicos
Estonios
Suizos
Suizos
Alemanes
Turcos
Turcos
Españoles
Italianos
Zimbabwense
Ganienses
Tanzanos
Ganienses
Nigerianos
Polinesios
Maories
Cingaleses de Sri Lanka
Saudies
Etiopes
Indúes
Cubanos-Mestizos
Nicaragüenses
Populations

CEIBA Consorcio Europeo Ibero Americano Farmacogenética n=6479

GENOTYPING n= 5482 Phenotyping=2540 Ancestry= 3386

North America

México North Durango

México North Monterrey

México DF Center

México South Chiapas

Central America

Nicaragua

Costa Rica

Caribe

Cuba

Iberians

España, Extremadura

Portugal, Coimbra

South America Pacific

Colombia, Bogotá

Ecuador, Quito

Perú, Lima

Perú, Puno

South America Atlantic

Brasil

Chile

Uruguay, Montevideo

Argentina, B Aires

Argentina, Ashkenazy

RIBEF

CYP2C9

CYP2C9 genetic polymorphism: Interethnical variability

Population	n	*CYP2C9 *1*	*CYP2C9 *2*	*CYP2C9 *3*
Spanish	**276**	**0.78**	**0.14**	**0.08**
White-Americans	280	0.83	0.13	0.04
White-Americans	200	0.86	0.08	0.06
Swedish	860	0.82	0.11	0.07
British	200	0.79	0.13	0.09
Italians	314	0.80	0.11	0.09
Total caucasians	2444	0.80	0.12	0.08
Indo-europeans	1812	0.80	0.11	0.08
Africans	740	0.96	0.03	0.01
Asians	2494	0.97	---	0.03
***Mexican-Americans**	98	0.86	**0.08**	0.06

*LLerena et al, 2005. The Pharmacogenomic Journal

Center for Pharmacogenomics and Clinical Pharmacology. UCLA, USA.

The Pharmacogenomics Journal (2010), 1–5

www.nature.com/tpj

ORIGINAL ARTICLE

CYP2C9 allele frequency differences between populations of Mexican-Mestizo, Mexican-Tepehuano, and Spaniards

P Dorado[1,4], M Sosa[2,4], EM Peñas-LLedó[1], RE Alanis-Bañuelos[1], M-L Wong[3], J Licinio[3], I Lares-Asseff[2] and A LLerena[1]

Earlier we had found that the *CYP2C9*2* allelic frequency was lower in Mexican-Americans living in California than in Spaniards (SP). This was assumed to be related to the low *CYP2C9*2* and **3* allele frequencies in Orientals. This study was therefore aimed at analyzing whether there were also differences in *CYP2C9* allele frequencies between Mexican-Tepehuanos (MT) and Mexican-Mestizos (MM) living in northwestern Mexico and SP. The *CYP2C9*2* frequency was expected to be lower in the indigenous MT than in

Table 1 *CYP2C9* genotypes among Mexican-Mestizos ($n = 102$), Mexican-Tepehuanos ($n = 99$), and Spaniards ($n = 327$)

CYP2C9 genotype	*Mexican-Mestizos*			*Mexican-Tepehuanos*			*Spaniards*		
	N	%	95% CI	N	%	95% CI	N	%	95% CI
*CYP2C9*1/*1*	84	82.4	73.7–88.6	94	94.9	88.4–98.1	195	59.6	54.2–64.8
*CYP2C9*1/*2*	14	13.7	8.23–21.9	2	2.02	0.11–7.51	78	23.9	19.5–28.8
*CYP2C9*1/*3*	3	2.9	0.64–8.66	3	3.03	0.66–8.91	30	9.2	6.47–12.8
*CYP2C9*2/*2*	0	—	—	0	—	—	8	2.45	1.16–4.84
*CYP2C9*2/*3*	0	—	—	0	—	—	13	3.97	2.27–6.75
*CYP2C9*3/*3*	0	—	—	0	—	—	3	0.92	0.18–2.79
*CYP2C9*1/*6*	1	0.98	0.01–5.88	0	—	—	0	—	—

CYP2D6 Drugs and vulnerability to Psychopatology

Antidepressants

- SSRI Fluoxetine
- TCA Clomipramine

Antipsychotics

-Haloperidol

- Risperidone

Catecholamines

- Serotonine
- Dopamine?

Variability in therapeutic response and adverse effects

PERSONALITY

NEUROCOGNITION

PSYCHOPATHOLOGY

DIFFERENCES IN DRUG RESPONSE — VARIABILITY IN PSYCHOPATHOLOGY

CYP2D6 and endogenous monoamines metabolism

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.

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

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.

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

5-methoxytryptamine

CYP2D6

serotonin

Yu *et al.*, 2003

CYP2D6 and endogenous monoamines metabolism: serotonine

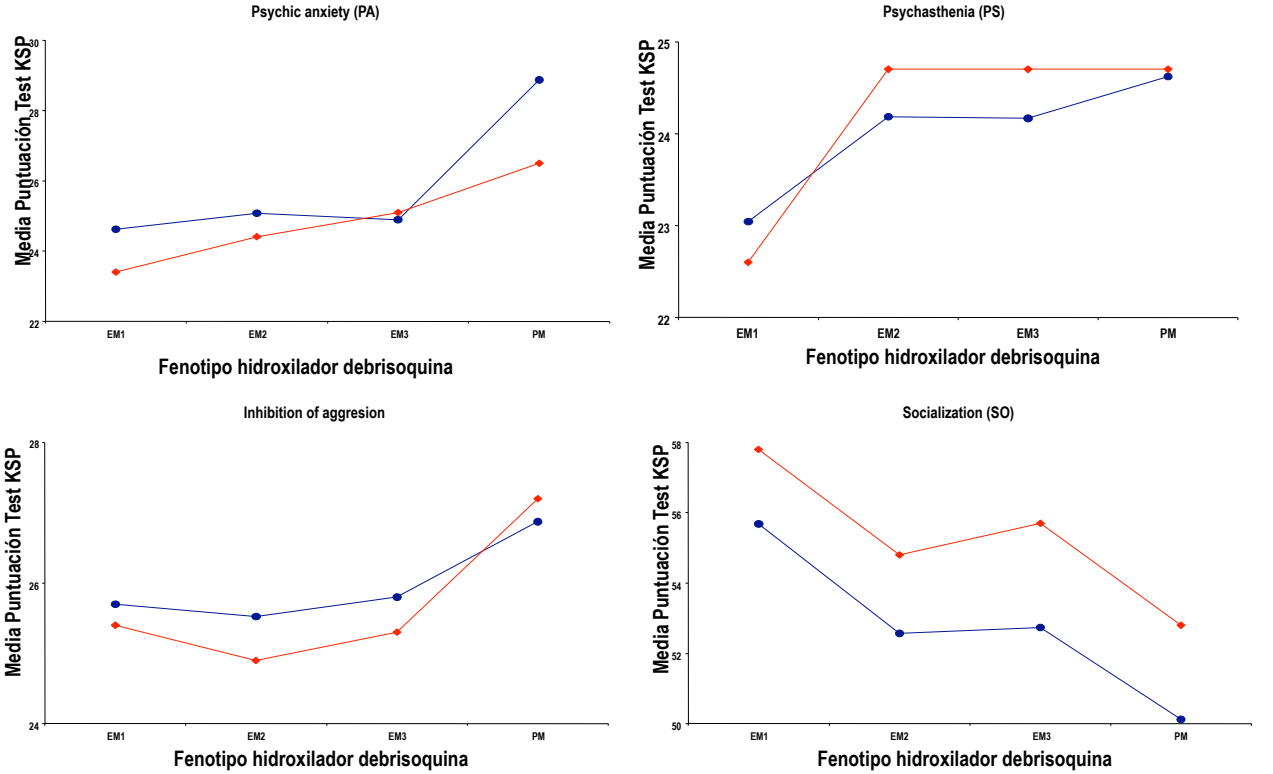
CYP2D6 and personality: replication in Cubans

Relation between CYP2D6 phenotype and genotype and personality in healthy volunteers

Idilio González[1,2], Eva M Peñas-Lledó[2], Bárbaro Pérez[3], Pedro Dorado[3], Mayra Álvarez[2] & Adrián LLerena[2†]

[†]Author for correspondence
[1]Hospital Psiquiátrico de La Habana, Cuba
[2]Faculty of Medicine, University of Extremadura & Clinical Research Centre (CICAB), Hospital Infanta Cristina, Servicio Extremeño de Salud. Avda. de Elvas, s/n. E-06080, Badajoz, Spain
Tel.: +34 924 218 040; Fax: +34 924 218 040;
E-mail: allerena@unex.es
[3]Facultad de Ciencias Médicas Calixto García, Instituto Superior de Ciencias Médicas de La Habana, Cuba

Spaniards | Cubans



CYP2D6 activity and personality in a Cuban population is replicated (Gonzalez et al., 2008):

Same results!

KSP Personality PM Cuba = Spain

Suicide

Sixth cause of death

First Non-natural cause of death
(higher than trafic accidents)

University of Extremadura, Spain
Adrián Llerena allerena@unex.es

CYP2D6 and Eating Disorders

(Peñas-Lledó et al., 2010)

CYP2D6 polymorphism in patients with eating disorders

EM Peñas-LLedó[1], P Dorado[1], Z Agüera[2], M Gratacós[3], X Estivill[3], F Fernández-Aranda[2,4] and A LLerena[1]

The Pharmacogenomics Journal (2010), 1–3

www.nature.com/tpj

ORIGINAL ARTICLE

Table 1 *CYP2D6* active alleles among patients with eating disorders and controls

Diagnostic subtype	PMs (CYP2D6 = 0)			EMs (CYP2D6 = 1)			EMs (CYP2D6 = 2)			UMs (CYP2D6 > 2)		
	n	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
ANR (*n* = 42)	3	7.1	1.8–19.7	7	16.7	8.0–30.9	29	69.0	53.9–81.0	3	7.1	1.8–19.7
ANP (*n* = 39)	1	2.6	0.0–14.4	11	28.2	16.4–43.9	25	64.1	48.4–77.3	2	5.1	0.5–17.8
BNP (*n* = 120)	6	5.0	2.1–10.7	31	25.8	18.8–34.4	74	61.7	52.7–69.9	9	7.5	3.8–13.8
BNNP (*n* = 14)	1	7.1	0.0–33.5	3	21.4	6.8–48.3	9	64.3	38.6–83.8	1	7.1	0.0–33.5
EDNOS (*n* = 51)	2	3.9	0.3–14.0	3	5.9	1.41–16.5	41	80.4	67.4–89.2	5	9.8	3.8–21.4
BED (*n* = 1)	—	—	—	—	—	—	1	100	—	—	—	—
Total patients (*N* = 267)	13	4.9	2.8–8.2	55	20.6	16.2–25.9	179	67.0	61.2–72.4	20	7.5	4.9–11.3
Controls (*N* = 285)	18	6.3	4.0–9.8	86	30.2	25.1–35.8	168	58.9	53.2–64.5	13	4.6	2.6–7.7

Abbreviations: ANP, anorexia nervosa-purging ubtype; ANR, anorexia nervosa-restrictive subtype; BED, binge eating disorder; BNNP, bulimia nervosa-non purging subtype; BNP, bulimia nervosa-purging subtype; EDNOS, eating disorder not otherwise specified; EMs, extensive metabolizers; PMs, poor metabolizers; UMs, ultrarapid metabolizers; 95% CI, 95%, confidence interval.

> Active genes in Eating Disorders

CYP2D6 URs and Eating Disorders Symptoms

(Peñas-Lledó et al. 2012 in press)

Manuscript for CPPM 10.05.2012

Title: Eating disorder symptoms and CYP2D6 in Cuban healthy females.

Running Title: Eating Symptoms and CYP2D6 in Cubans

5

Authors: [1]Eva M. Peñas-LLedó PhD, [2*]Idilio González MD PhD, [1]Pedro Dorado PhD, [3]Bárbaro Pérez MD PhD, [2**]Luis R. Calzadilla MD, [3]Mayra Alvárez BSPharm, [1] M Eugenia G. Naranjo [1]Adrián LLerena MD, PhD.

	CYP2D6 PMs N (%; CI95%)	CYP2D6 EMs N (%; CI95%)	CYP2D6 UMs N (%; CI95%)
EDI-Bulimia (<5; n=82)*	6 (7.3; 3.1-15.3)	75 (91.5; 83.1-96.1)	1 (1.2; 0.0-7.2)
EDI-Bulimia (≥5; n=77)	1 (1.3; 0.0-7.7)	68 (88.3; 79.0-93.9)	8 (10.4; 5.1-19.4)

CYP2D6 and Suicidal Behaviour among Eating Disorders (Peñas-Lledó et al., 2011)

Molecular Psychiatry (2011) 1–2

www.nature.com/mp

LETTER TO THE EDITOR

High risk of lifetime history of suicide attempts among *CYP2D6* ultrarapid metabolizers with eating disorders

> Active genes among ED with history of Suicidal Behaviour

Table 1 Prevalence of lifetime suicide attempts and number of *CYP2D6* active alleles (0, 1, 2 or >2) among patients with eating disorders ($N=203$)

Eating disorder patients	*CYP2D6 (0),* N *(%; 95% CI)*	*CYP2D6 (1),* N *(%; 95% CI)*	*CYP2D6 (2),* N *(%; 95% CI)*	*CYP2D6 (>2),* N *(%; 95% CI)*
Suicidal behavior ($n=38$)	2 (5.3%; 0.5–18.2)	7 (18.4%; 8.9–33.7)	22 (57.9%; 42.2–72.2)	7 (18.4%; 8.9–33.7)*
No suicidal behavior ($n=165$)	8 (4.8%; 2.3–9.4)	40 (24.2%; 18.3–31.3)	107 (64.8%; 57.3–71.7)	10 (6.1%; 3.2–10.9)*

Relationship of CYP2D6 and suicide

HYPOTHESIS

1. Implication of CYP2D6 in **endogenous metabolism**

2. Treatment failure with drugs metabolized by CYP2D6

Molecular Psychiatry (2012) 1 – 2

www.nature.com/mp

LETTER TO THE EDITOR

CYP2D6 ultrarapid metabolism and early dropout from fluoxetine or amitryptiline monotherapy treatment in major depressive patients

EM Peñas-LLedó[1], HD Trejo[2], P Dorado[1], A Ortega[2], H Jung[3], E Alonso[2], MEG Naranjo[1], M López-López[4] and A LLerena[1]

[1]CICAB Clinical Research Center. Extremadura University Hospital Medical School and CIBERSAM, Badajoz, Spain; [2]Neurogenetics Department, National Institute of Neurology and Neurosurgery 'Manuel Velasco Suárez', Mexico City, Mexico; [3]Neuropsychopharmacology Department, National Institute of Neurology and Neurosurgery 'Manuel Velasco Suárez', Mexico City, Mexico and

Table 1. Discontinuation rates of the antidepressant drugs fluoxetine or amitriptyline under monotherapy with regard to *CYP2D6* number of active genes

	PMs CYP2D6 = 0+0.5,	*IMs CYP2D6 = 1,*	*EMs CYP2D6 = 1.5+2,*	*UMs CYP2D6 = > 2,*
Discontinuation (at week 4 /day 28)	*n = 4 (%)*	*n = 18 (%)*	*n = 74 (%)*	*n = 4 (%)*
Yes (*n* = 26)	0 (0%)	2 (11.1%)	20 (27%)	4 (100%)
Number (*n* = 74)	4 (100%)	16 (88.9%)	54 (73%)	0 (0%)

Abbreviations: Ems, extensive metabolizers; Ims, intermediate metabolizers; MDD, major depressive disorder; PMs, poor metabolizers; Ums, ultrarapids metabolizers.

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.