BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12227

CYP2D6 variation, behaviour and psychopathology: implications for pharmacogenomics-guided clinical trials

Eva M. Peñas-LLedó[1] & Adrián LLerena[1,2]

[1]CICAB Clinical Research Centre, Extremadura University Hospital and Medical School, Badajoz and [2]CIBERSAM, ISCIII, Madrid, Spain

Correspondence
Dr Adrián LLerena MD, CICAB, Centro de Investigación Clínica, Hospital Universitario Infanta Cristina. Avda. de Elvas s/n. 06080 Badajoz, Spain.
Tel.: +34 924 218040
Fax: +34 924 219881
E-mail: allerena@unex.es

Keywords
clinical trials, CYP2D6, endogenous compound metabolism, personality traits, pharmacogenetics, psychopathology

Received
12 May 2013
Accepted
11 August 2013
Accepted Article Published Online
22 August 2013

Individual and population differences in polymorphic cytochrome P450 enzyme function have been known for decades. The biological significance of these differences has now been deciphered with regard to drug metabolism, action and toxicity as well as disposition of endogenous substrates, including neuroactive compounds. While the cytochrome P450 enzymes occur abundantly in the liver, they are expressed in most tissues of the body, albeit in varying amounts, including the brain. The latter location of cytochrome P450s is highly pertinent for susceptibility to neuropsychiatric diseases, not to mention local drug metabolism at the site of psychotropic drug action in the brain. In the current era of personality medicine with companion theranostics (i.e. the fusion of therapeutics with diagnostics), this article underscores that such versatile biological roles of cytochrome P450s offer multiple points of entry for personalized medicine and rational therapeutics. We focus our discussion on CYP2D6, one of the most intensively researched drug and endogenous compound metabolism pathways, with a view to relevance for, and optimization of, pharmacogenomic-guided clinical trials. Working on the premise that CYP2D6 is related to human behaviour and certain personality traits such as serotonin and dopamine system function, we further suggest that the motivation of healthy volunteers to participate in clinical trials may in part be influenced by an under- or over-representation of certain CYP2D6 metabolic groups.

CYP2D6 genetic polymorphisms and neuroactive endogenous compound metabolism

Among cytochrome P450s, CYP2D6 is one of the most intensively researched and clinically important enzymes involved in the metabolism of a large number of widely used central nervous system (CNS) drugs. CYP2D6 is highly polymorphic. Multiple allelic variants of the *CYP2D6* gene have been identified, which are associated with an absent or increased enzyme activity in individuals who are respectively so called poor (PMs) and extensive metabolizers (EMs), including in the latter group a subgroup of ultrarapid metabolizers (UMs). This polymorphic enzyme is involved in the metabolism of many drugs of relevance to psychiatry, neurology and addiction medicine such as antidepressants, antipsychotics and opioids [1, 2]. Moreover, CYP2D6 has also been shown to contribute to endogenous metabolism of neuroactive substrates, which can explain the associations hitherto observed with human behaviour and disease susceptibility (e.g., personality, neurocognition and neuropsychiatric disorders) [3, 4]

CYP2D6 was identified in both animal and human brain tissues in the late 1980s [5]. More than a decade later, dextromethorphan to dextrorphan metabolism was demonstrated in human brain microsomes [6]. CYPD6 has been described in neurons in the human cerebral cortex, hippocampus and cerebellum [7], basal ganglia and midbrain [8, 9]. Other studies have provided additional evidence of CYP2D6 expression in these brain regions and the thalamus [10] as well as in glial cells in those brain areas [11].

In addition to the mapping of CYP2D6 in the brain, this enzyme has also been involved in the metabolism of tyramine to dopamine (DA) *in vitro* [12, 13] and in the regeneration of serotonin (5-HT) from 5-methoxytryptamine [14,

15]. Interestingly, *in vivo* studies have shown that UMs display higher serotonin concentrations in platelets than EMs and PMs [16]. A potential influence of CYP2D6 polymorphism in the balanced functioning and physiological cross-talk of the DA and 5-HT endogenous systems has been proposed [17, 18]. This hypothesis was based on the results from another *in vivo* study suggesting that PMs might have a higher DA tone in the pituitary [19], which might be in combination with lower serotonin tone since the serotonin systems exerts a tonic inhibitory control on the dopaminergic circuits. Recently, it has been proposed that a potential mechanism for the interaction of the serotonin and DA system would be the synthesis of 5-HT in DA neurones [20].

Additionally, CYP2D6 has been implicated in the endogenous metabolism of the ligand for the cannabinoid receptor CB1, anandamide [21]. The possibility that CYP2D6 may be involved in the regulation of endogenous neuroactive steroids, such as progesterone and its derivatives in brain tissues has been suggested [22, 23]. The trace amines betacarbolines, pinolines, harmaline and harmine have been also related [24].

Taken together, the relationships observed between CYP2D6 variation and personality that are to be detailed in the next section could be mediated by the influence of this enzyme activity in the serotonergic/dopaminergic tone plus other neurotransmitters or neuromodulators.

Relationship between CYP2D6 genetic variation and personality

With the aim to clarify existing data, the key studies on the relationship between CYP2D6 and personality are summarized in Tables 1 and 2, and discussed subsequently in the same order. For further clarity, we separated those studies conducted in healthy volunteers from those in patients.

Studies about CYP2D6 and personality in healthy volunteers

The first hypothesis anticipating that CYP2D6 could have an endogenous neuroactive substrate or product such as a biogenic amine was put forward as early as 1993 [25]. However, a subtle but significant hint about the putative influence of CYP2D6 on personality traits came even earlier from a study in healthy volunteers in Sweden where the participants were phenotyped with debrisoquine and evaluated with Karolinska Scales of Personality (KSP). Curiously, the PMs were found to report lower levels of psychastenia than the rest of the healthy volunteers or EMs [26].

Later in Spain [25] a larger and independent population of healthy volunteers were phenotyped with debrisoquine and evaluated with KSP that had just been translated into Spanish [27]. The difference from the previous study was that instead of comparing just the two broad groups of PMs and EMs, four groups were identified: PMs and other three relatively homogeneous groups of EMs separated on the basis of their CYP2D6 debrisoquine hydroxylation capacity. Yet, significant differences were again noted/replicated between PMs and the EM groups in this independent study sample of Spanish subjects, admittedly from a social and environmental context different from that of Sweden, thereby lending further support for linkages between CYP2D6 variation and personality or behavioural traits. PMs were shown to report greater levels of psychic anxiety and lower socialization than EMs. These two seminal observations and studies using KSP personality traits and CYP2D6 phenotype, as well as subsequent research trying to replicate this relationship about personality and CYP2D6 are summarized in Table 1.

Personality differences between CYP2D6 PMs and EMs were later compared in several healthy volunteer populations. Three of the studies, the two previous one in Swedish and Spanish, and a third one in Cuban healthy volunteers used the same phenotyping procedure (debrisoquine test) and the same personality measure (KSP) [25, 26, 28]. These studies were similar with regard to establishing differences in psychastenia between PMs and EMs [25, 26, 28]. Above all, Spaniards and Cubans showed almost identical results for some personality traits [25, 28]. PMs presented higher psychic anxiety and lower socialization than the three groups of EMs. It is of note that these two studies (in Spain and Cuba) shared also the same recruiting procedure and type of volunteers (mostly university students) as well as cultural background. On the contrary, the Swedish population was older, with different education, and recruitment procedures since they were participants in clinical trials. Differences across studies may have highly influenced the different pattern of associations observed between Swedes and Latinos.

Posterior studies in German [29], Japanese [30, 31] as well as in another group of Spanish volunteers [32] used different methods for determining CYP2D6 activity, which was assumed by genotypes (Table 1). They also used different personality measures, mostly the Temperament and Character Inventory (TCI), making it almost impossible to establish comparisons. Additional differences were related to recruitment methods of the German volunteers since they were a heterogeneous population from the community that responded to a newspaper advertisement [29]. Furthermore, this study used a new measure, the NEO Five-Factor Inventory (NEO-FFI) [33], finding differences between PM and EM females. PMs reported higher 'conscientiousness' or responsibility, orderliness, and the pursuit for achievement through perseverance. This NEO-FFI trait has been consistently associated with hard working and reliable individuals, who demonstrate excellence in the workplace [34]. Thus, this result of high 'conscientiousness' can be interpreted in the light of previous ones signalling higher anxiety among healthy PMs, which may indicate that anxiety levels help them to increase performance

Table 1

YP2D6 and personality studies

Reference	Population	*n*	Nationality	CYP2D6 debrisoquine hydroxylation capacity (Phenotype)	CYP2D6 alleles (Genotype)	Personality measures	Main results
Bertilsson *et al.* 1989 [26]	Healthy volunteers	769	White Swedish	PMs (MR>12,6) and EMs (MR< 12,6)		KSP	PMs scored lower in psychastenia subscale and had a higher frequency of extreme responses than EMs.
LLerena *et al.* 1993 [25]	Healthy volunteers (students)	225	White Spanish	EM1 (MR≤0.30), EM2 (0.30 < MR≥0,87); EM3 (0,87 < MR≤12,6) and PM (MR>12,6)		KSP	PMs scored lower in socialization measures, and higher in psychic anxiety, somatic anxiety, psychastenia, and inhibition of aggression.
González *et al.* 2008 [28]	Healthy volunteers (students)	246	Mestizo Cuban	EM1 (MR≤0.28), EM2 (0.28 < MR≥0,77); EM3 (0,77 < MR≤12,6) and PM (MR>12,6)	*CYP2D6* allelic variants with abolished (**3*, **4*, **4xN*, **5* and **6*), decreased (**10* and **17*) and increased (**1xN* and **2xN*) activity.	KSP	PMs (phenotype) scored lower in socialization and higher in psychic anxiety, and irritability.
Peñas-LLedó *et al.*, 2009 [32]	Healthy volunteers (students)	144	White Spanish		*CYP2D6* allelic variants with abolished (**3*, **4*, **4xN*, **5* and **6*), decreased (**10* and **17*) and increased (**1xN* and **2xN*) activity.	KSP TCI-R	PMs (genotype) presented higher 'impulsivity' in both KSP and TCI-R scalesand lower distress (SCL-90-R).
Kirchheiner *et al.*, 2006 [29]	Healthy volunteers	222	White German		*CYP2D6* allelic variants with abolished (**3*, **4*, **5* and **6*) activity and the duplication allele	NEO-Five Factor Inventory	PM (genotype) females showed higher conscientiousness
Suzuki *et al.*, 2003 [30]	Healthy students	255†	Asian Japanese		*CYP2D6 *10* (**1/*1* and **1/*10 vs. *10/*10*)	TCI	No association with *CYP2D6*10* genotype frequencies in any of the personality traits. Absence of UMs (genotype) and PMs (genotype).
Iwashima *et al.*, 2007 [31]	Healthy volunteers (students)	342	Asian Japanese		*CYP2D6* allelic variants with abolished (**3*, **4*, **4xN*, **5*, **6*, **7*, **8*, **11*, **14*, **15*, **19*, **20* and **40*), decreased (**9*, **10*, **17*, **29*, **36* and **41*), normal (**2* and **35*) and increased (**1xN* and **2xN*) activity	TCI	No association with CYP2D6. Low frequency of UMs (genotype) and PMs (genotype).
Roberts *et al.*, 2004 [36]	Depressed patients	121	White (95% New Zealand)		*CYP2D6 *1*, **2*, **4*, **5*, **9*, **10*, **13*, **16*, and the duplication alleles.	TCI	PMs (genotype) scored lower in harm avoidance (fear of uncertainty, fatigability and shyness)
Gan *et al.*, 2004 [35]	Patients‡	48	Asian Malay (44), Chinese (3) and Indian (1)		EM1 (*CYP2D6*1/*1*), EM2 (*CYP2D6*1/*4,*1/*5*, **1/*9* and **1/*10*), EM3 (*CYP2D6*4/*10*, **5/*10*, **10/*10* and **10/*17*).	Type A and B personality questionnaire	EM2 and EM2 were found to be mainly of personality type B compared with EM1 (predominance of type A personality). Absence of UMs (genotype) and PMs (genotype).

EMs, extensive metabolizers; KSP, Karolinska Scales of Personality; *n*, number of subjects; PMs (genotype), individuals with two or more CYP2D6 allelic variants with abolished activity; TCI, temperament and Character Inventory; UMs (genotype), individuals with more than two active allelic variants; PMs, poor metabolizers; TCI-R, Temperament and Character Inventory-Revised. †255 students (222 = females); ‡Patients were individuals hospitalized for orthopaedic surgery, but otherwise healthy by medical history and physical examination.

Table 2

Studies about the relationship between CYP2D6 and neurocognition and psychopathology

Reference	Population	Nationality	CYP2D6 alleles (Genotype)	Measures	Main results
Peñas-LLedó *et al.*, 2009 [32]	144 healthy volunteers mostly students	White Spanish	*CYP2D6* allelic variants with abolished (**3*, **4*, **4xN*, **5* and **6*), decreased (**10* and **17*) and increased (**1xN* and **2xN*) activity.	CANTAB SCL-90-R GSI	PMs (genotype) presented better Rapid visual processing or sustained attention as well as lower distress/psychopathology.
Stingl *et al.*, 2011 [50]	113 healthy volunteers	White German	*CYP2D6* allelic variants with inactived (**3*, **4*, **5* and **6*), decreased (**9*, **10*, **17* and **41*), fully functional (**2* and **35*) activity, and the gene duplication.	Functional brain imaging: a n-back memory task and an implicit emotional face matching task	A significant effect of *CYP2D6* genotype was found in the precuneus and the cuneus. In both tasks activation increased with increasing CYP2D6 activity.
LLerena *et al.*, 2007 [40]	128 schizophrenia patients and 142 healthy volunteers	White Spanish	*CYP2D6* allelic variants with abolished *(*3*, **4*, **4xN*, **5* and **6*), decreased (**10* and **17*) and increased (**1xN* and **2xN*) activity.		Frequency of PMs (genotype) was lower in schizophrenic patients than in healthy volunteers.
Peñas-LLedó *et al.*, 2012 [55]	267 patients with ED and 285 healthy volunteers	White Spanish	*CYP2D6* allelic variants with abolished (**3*, **4*, **4xN*, **5* and **6*), decreased (**10* and **17*) and increased (**1xN* and **2xN*) activity.		Frequency of UMs (genotype) was higher in patients with ED than in healthy volunteers.
Peñas-LLedó *et al.*, 2012 [54]	Healthy Volunteers	White and Mestizo Cubans	*CYP2D6* and debrisoquine hydroxylation phenotype.	EDI	Higher frequency of UMs among bulimia scorers >5.
Zackrisson *et al.*, 2010 [57]	242 individuals who died of fatal intoxication, 262 of suicide and 212 of natural death	White Swedish	*CYP2D6* allelic variants with abolished (**3*, **4*, **4xN*, **5* and **6*) and normal (**2*) and increased (**1xN* and **2xN*) activity. *CYP2C19* allelic variants with abolished (**2*, **3* and **4*) activity.		A higher number of UMs (genotype) among individual who died of suicide than in the other groups.
Peñas-LLedó *et al.*, 2011 [56]	203 patients with ED (165 without suicidal behavior and 38 with suicidal behaviour†)	White Spanish	*CYP2D6* allelic variants with abolished (**3*, **4*, **4xN*, **5* and **6*)and increased (**1xN* and **2xN*) activity.		Frequency of UMs (genotype) was higher in patients with lifetime suicidal behaviour than in patients without suicidal behaviour.
Peñas-LLedó *et al.*, 2012 [58]	342 suicide attempters and 377 healthy controls.	White Spanish	*CYP2D6* allelic variants with abolished (**3*, **4*, **4xN*, **5* and **6*), decreased (**10* and **17*) and increased (**1xN* and **2xN*) activity.	Beck-SIS§	A higher number of 'severe' suicide attempters carrying two or more than two active *CYP2D6* genes as compared with the rest of the patient population or the healthy control group was found.
Blasco-Fontecilla *et al.*, 2013 [59]	342 suicide attempters	White Spanish	*CYP2D6* allelic variants with abolished (**3*, **4*, **4xN*, **5* and **6*), decreased (**10* and **17*) and increased (**1xN* and **2xN*) activity.	MINI IPDE-SQ	Suicide attempters with two or more *CYP2D6* active genes were more likely to be diagnosed with personality disorders.
Stingl & Viviani, 2011 [50]	285 depressed inpatients.	White German	*CYP2D6*3*, **4*, **5*, **6*, **9*, **10*, and **35* alleles, and the duplication of gene.	MINI‡ HAM-D	In UMs (genotype) the risk of a high suicidality score was elevated as compared to those with other genotypes. No association between UM status and basal HAM-D scores at study entry.
Höfer *et al.*, 2013 [74] discussed in Peñas-LLedó *et al.*, 2013 [75]	243 MDD patients	White European¶	Genotyping was performed for all relevant variations of the *CYP1A2* gene (**1A*, **1F*, **1C*, **1 J*, **1 K*), the *CYP2C9* gene (**2*, **3*), the *CYP2C19* gene (**2*, **17*) and the *CYP2D6* gene (**3*, **4*, **5*, **6*, **9*, **19*, **XN*).	MINI HAM-D††	No association between both suicide risk and personal history of suicide attempts, and the CYP1A2, CYP2C9, CYP2C19 and CYP2D6 metabolic profiles were found.‡‡

Beck-SIS, Beck Suicide Intent Scale; ED, eating disorders; IPDE-SQ, International Personality Disorder Examination Screening Questionnaire; KSP, Karolinska Scales of Personality; MDD, major depressive disorder.; MINI, Mini-International Neuropsychiatric Interview; PMs (genotype), individuals with two or more CYP2D6 allelic variant; s with abolished activity; TCI-R, Temperament and Character Inventory-Revised; UMs (genotype), individuals with more than two active allelic variants. †A suicide attempt was defined as a self-destructive act with some degree of intent to end one's life. Thus, to be considered an attempt, the attempt was required to have two components, an action that was self-destructive and an acknowledgement of intent to die. ‡MINI includes six specific items on suicidality. §Those individuals scoring above percentile 75 in the objectives circumstances section of the Beck-SIS were classified as 'severe' suicide attempters. ¶Individuals were recruited from Austria, Israel, Belgium, France and Italy. ††Suicidality was assessed using two items: Presence or absence of current suicidal risk in the MINI item on suicidality (A current suicidal risk was defined by the presence ofat least one of the following suicide-related items: having in the past month thought that it would be better being dead or wishing to die, wanting to harm oneself, thinking about suicide, having a suicide plan, attempting suicide and ever attempted suicide at least once in the lifetime) and the HAM-D item 3 on suicidality (score 0–4). ‡‡Some aspects of the methodology and results of this study have been discussed by Peñas-LLedó *et al.*, 2013) [75]. This paper had limitations related to the inaccuracy and imprecision of the main measures (misclassification of metabolizer status and definition of suicidal phenotypes).

instead of being related to anxiety disorders and the pursuit of unrealistic standards.

In Japan, two other studies [30, 31] also determined only the *CYP2D6* genotype, and personality was measured with the TCI. Both studies found no association between *CYP2D6* and personality traits, which is reasonable given the very low number of PMs and low CYP2D6 variability [30] included no PMs, only individuals homozygous or heterozygous for the *CYP2D6*10* variant (with decreased activity) that were compared with individuals with apparently functional or wild-type alleles. Consistently, no differences emerged between EMs (**1/*1*) and individuals with **10/*10* and **1/*10* genotypes. Nevertheless, those with reduced CYP2D6 activity presented a tendency to higher impulsivity (novelty seeking). Similarly, Iwashima *et al*. [31] only included one PMs carrying two alleles related to null enzyme activity (**5/*5*). This PM was compared with the remaining 341 participants separated into 'intermediate' metabolizers (IM) with either two reduced activity alleles or one reduced activity allele and one no activity allele (e.g. **4/*10*, **5/*10*, **10/*10*), EMs with one or more wild type alleles (e.g. **1/*1*, **1/*2*, **1/*5*, **1/*10*), and UMs considered those with more than two copies of wild type (e.g. **1/*1XN*, **1/*2XN*). As expected no differences were found. Just out of curiosity, the PM scored higher on impulsivity (novelty seeking) than the mean, minimum and maximum scores of EMs, IMs and UMs.

In summary, personality findings across heterogeneous populations appear difficult to replicate, since they rely on self-reports which may depend on cultural context, education, mood state, etc. Moreover, variability in recruitment may include, under the label of 'healthy volunteers', different types of participants (reviewed later).

Studies about CYP2D6 and personality in clinical settings

Two studies have explored the relationship between CYP2D6 and personality in clinical samples. The first of them was developed in Malaysian individuals, who were in hospital expecting to undergo orthopaedic surgery [35]. This study used a completely novel classification of individuals according to their genotype and a different measure of personality. As in the previous Asian studies there were no PMs, and individuals were divided into those carrying alleles related to null or reduced activity, who were categorized as 'slow' (**4/*10*; **5/*10*; **10/*10*; **10/*17*), those with at least one null or reduced activity allele or 'intermediate' (**1/*4*, **1/*5*; **1/*9*; **1/*10*), and those considered normal (**1/*1*). The evaluation of personality was done with a 'Type A personality' questionnaire, which measures a behavioural pattern characterized by tenseness, impatience, urgency and aggressiveness that often predicts stress-related disorders. The groups 'slow' and 'intermediate' were found to present lower scores on 'Type A personality', which suggests lower vulnerability to develop a stress related disorder in those carrying reduced or null function alleles [35].

Another study evaluated this relationship in patients with major depressive disorder in New Zealand [36]. PMs *vs*. EMs showed lower levels of anxiety. PMs scored lower than EMs on the TCI-R scale of 'harm avoidance', which has been related to the risk for depression and other illness and to their outcome [36].

Previous findings about CYP2D6 and personality traits in clinical samples suggest that PMs might have some protective personality features against disease severity. While it is difficult to draw conclusions from these data, other studies relying on more objective measures may help our understanding of the risks or benefits of the different CYP2D6 metabolic groups for the development of diseases that are mostly treated with CYP2D6 substrates.

Table 1 summarizes the main methodological aspects such as number of participants, nationality, CYP2D6 debrisoquine hydroxylation capacity (phenotype), *CYP2D6* alleles (genotype), the personality measures and most significant results. The sources of variability in the relationship between CYP2D6 activity and personality might be due to participants' differences in factors such as age, gender and ethnic background, culture, education, due to recruitment procedures and population characteristics. Differences may be also due to CYP2D6 and personality evaluation procedures. Furthermore, there might also be a population selection bias linked to personality across volunteers participating in biomedical studies involving an invasive procedure and/or psychological measures (reviewed later).

CYP2D6 and neurocognitive function in healthy volunteers

We decided to explore whether PMs and EMs presented differences in a more objective measure than personality such as cognitive functioning [32]. Participants were evaluated using computerized, non-linguistic and culturally blind cognitive tests (http://www.CANTAB.com). PMs showed a different performance in comparison with the rest in rapid visual information processing (RVP), a test of sustained attention. PMs appeared to have a better capacity than EMs to a task of vigilance or alertness for a period of time [32]. When controlling for distress by using a measure of overall psychopathology (SCL-90-R [37], PMs also showed better performance on spatial working memory [32]. Thus, PMs seem to perform more accurately in tasks that demand sustained attention or vigilance.

Moreover, CYP2D6 activity has been related to blood flow in brain regions underlying sustained attention or alertness such as the thalamus during resting [38] and the cuneus and precuneus during cognitive demands [39].

CYP2D6 and vulnerability to psychopathology: studies in patients

Table 2 summarizes studies about the relationship between CYP2D6 and neurocognition and psychopathology in patients.

Schizophrenia

A lower frequency of PMs than expected has been observed in schizophrenia inpatients [40], which is in agreement with previous studies [41, 42]. Other studies did not find these differences [43–47]. However, these studies should be interpreted with caution since they only analyzed two or three defective *CYP2D6* variant alleles (**3*, **4*, and/or **10*) as causing PM status, and/or used a diverse control group.

Anxiety and depression

A study testing whether *CYP2D6* homozygous carriers of the two null allele **4* were more predisposed to anxiety and depression disorders in the elderly found no associations [48], although an increased frequency of UMs has been reported among women with late pregnancy or post-partum depressive symptoms [49]. Among German UMs (genotype) depressive patients, the risk of a high suicidality was elevated as compared with those with other genotypes [50]. We recently demonstrated among UMs an earlier dropout from fluoxetine or amitriptyline treatment in major depressive patients, which might be related to suicide risk as discussed below [51]. Also, other clinically relevant CYPs have been related to depression, such as *CYP2C9*, [52] or depressive levels, such as *CYP2C19* [53].

Eating disorders

A higher frequency of CYP2D6 UMs (evaluated by debrisoquine test) was found among the group of the population with higher scores on a scale measuring symptoms of bulimia [54]. Similarly, *CYP2D6* allele distribution in patients with eating disorders was related to higher enzyme activity than in healthy controls [55]. However this latter finding may be biased by the number of UM patients with a lifetime history of suicidal behaviour [56] as described next.

UMs and suicide

The presence of a higher frequency of *CYP2D6* UMs among individuals who died by suicide than in those with a natural death has been reported [57] and also among patients with eating disorders with a history of suicidal attempts compared with those who had never attempted suicide [56]. In agreement with these findings, it was later reported that among suicide attempters, those with a higher number of *CYP2D6* active genes presented a greater severity of the suicide attempt [58] and greater personality psychopathology [59].

In summary, the involvement of CYP2D6 in endogenous metabolism could mediate both the pharmacological treatment and risk and evolution of the diseases that are being treated.

CYP2D6 and psychological functioning: Implications for clinical research

Besides the previously discussed potential double influence on the variability of both pharmacological treatment and vulnerability to certain diseases, CYP2D6 genetic polymorphism may be of relevance for clinical trials as discussed below. Our proposal is that clinical trial participants must be stratified according to pharmacogenomics in general, and to CYP2D6 in particular, since it could mediate a) a population selection bias and b) an inaccurate drug evaluation effect influencing both drug pharmacokinetics (PK) and pharmacodynamics (PD). Therefore, Drug Regulatory Agencies may consider using pharmacogenetics to stratify the subjects involved in human research protocols.

CYP2D6 and personality studies: relevance for population selection bias

Our original hypothesis for a role of CYP2D6 in the metabolism of endogenous biogenic neurotransmitter amines [25] was partially based on previous observations [60] of a greater frequency of CYP2D6 PMs among unrelated volunteers involved in a clinical trial. Therefore, the relationship between CYP2D6 and human behaviour may lead to a population selection bias of humans involved in clinical research.

Another factor to take into account would be the psychological status of homogeneous individuals enrolled in clinical trials. Self-proclaimed healthy volunteers, even if they report no history of psychopathology, might in fact include both healthy and subclinical individuals with vulnerability to distress. In support of this idea it has been shown that a proportion of healthy volunteer subjects participating in studies about personality present personality features related to mental disorders [61–67]. As an example in our last study about *CYP2D6* and personality [32], the subjects' psychological status was evaluated with Symptom Checklist-90-Revised (SCL-90-R) [37]. Interestingly, all PMs reported very low scores suggesting a bias. Indeed, the individuals with higher scores on the SCL-90-R (EMs) showed differences in most personality scales when compared with those with low scores. Thus, the psychological status of volunteers, despite being 'healthy' and passing the filter of a psychiatric interview, may influence the differences found in the relationship of personality and CYP2D6 across studies (Table 1). This bias might be

reduced if volunteers were screened for overall psychological status, otherwise it may have an effect.

Another potential bias in biomedical research is possibly an over-representation of certain personality features among participants. Because biomedical studies usually involve an invasive procedure (injections, the intake of drugs, etc.), volunteers tend to be altruistic and/or show higher than normative scores on personality traits such as impulsivity, novelty seeking or monotony avoidance [68, 69].

In summary, in light of the above findings there seems to exist a need for behavioural and pharmacogenetic stratification of humans involved in clinical research.

CYP2D6 and psychological functioning: implication for drug evaluation (PK/PD) in clinical trials

Certain CYP enzymes beyond their contribution to the metabolism of psychotropic drugs (i.e. antidepressants, antipsychotics) are involved in the biotransformation of neuroactive endobiotics, which may influence physiological processes. In the light of this, our hypothesis is that genetic polymorphisms of these CYPs could mediate therapeutic responses to a given drug by two different mechanisms: influencing pharmacological response (drug metabolism, PK) but also mediating the metabolism of endogenous products related to therapeutic response (placebo or nocebo effects) (PD). Thus, this could be relevant for clinical research, and the pharmacogenetic stratification of subjects for drug evaluation effects should be considered.

To finalize, it is highlighted that major Drug Regulatory Agencies (EMA, FDA and the Japanese Drug Regulatory Agency) support the use of pharmacogenetics in the drug development phase as recently published [70]. Therefore, pharmacogenetics should be taking into consideration for clinical trials as well as for drugs cost-effectiveness studies [71] and drug–drug interactions [72].

Conclusions and outlook

This review summarizes the findings on CYP2D6 polymorphisms and their role in endogenous substrate metabolism as well as the large body of association studies reporting the possible functional consequences of the polymorphism.

CYP2D6 metabolism of endobiotics and xenobiotics

CYP2D6 genetic polymorphism presents interindividual variation of the enzyme hydroxylation capacity. CYP2D6 may cause absent (PMs), decreased and normal enzyme activity (EMs). In addition, the latter group of EMs also includes individuals with increased enzyme hydroxylation capacity or UMs [1]. CYP2D6 is involved in the metabolism of many CNS drugs such as antidepressants, antipsychotics and opioids, as well as in the metabolism of endogenous neuroactive substrates (i.e. neuroactive monoamines, endocannabinoids and endomorphines). Moreover, CYP2D6 is located in several brain regions (i.e. cortex, hippocampus and cerebellum), which seem of relevance for human behaviour and psychopathology. Therefore, interindividual variability in CYP2D6 hydroxylation capacity may have implications not only for the metabolism of several psychotropic drugs but also for explaining differences in human behaviour and psychopathology. However, considering that most CYP2D6 endogenous neuroactive substrates show low affinity, new studies are necessary to identify the definitive role of CYP2D6 in different human brain tissues. Furthermore, CYP2D6 expression patterns in different brain regions and their functional implications in brain metabolism might be considered.

There are reports of associations between psychological factors and CYP2D6 variation. Most of them are pure association studies. Thus, the mechanistic link between the functional role of CYP2D6 in neurons and behaviour needs to be clarified.

CYP2D6, personality, neurocognition and psychopathology

In healthy volunteers, PMs have been associated with a personality profile characterized by higher impulsivity and anxiety than EMs [25, 28, 32, 73]. Nevertheless, the PM personality profile does not appear related to an increased vulnerability to psychopathology since PMs seem to have a better capacity than EMs to the cognitive function of sustaining attention, which is deficient in individuals with anxious and impulsive related disorders [32]. Moreover, CYP2D6 activity has been related to blood flow in brain regions underlying sustained attention or alertness [38, 39].

In support of this hypothesis, a lower frequency of PMs than expected has been observed in schizophrenia patients [40]. Moreover, a higher frequency of CYP2D6 UMs has been found among subjects who died by suicide [57], and among patients with eating disorders with a history of suicidal attempts [56]. In agreement with these findings, a higher number of *CYP2D6* active genes was related to a greater severity of the suicide attempt [58], and greater personality psychopathology [59]. In conclusion, there is evidence supporting the relationship between CYP2D6 variability and psychological and neurocognitive functioning as well as to psychopathology.

Nevertheless, new studies are necessary to support a direct involvement of CYP2D6 in psychiatric disorders since there are only small studies reporting associations, which increase the risk for false-positive findings.

CYP2D6 and clinical trials

Subjects with a different response to CNS drugs that are CYP2D6 substrates may also be those with a different

sensitivity to mental disorders. In other words, CYP2D6 might be of relevance for theranostics. Consequently, the current model of drug clinical research can be put into question. Since *CYP2D6* genetic polymorphism might be related to behaviour, this could influence a population selection bias when enrolling healthy volunteers, which will be particularly relevant for the study of CYP2D6 substrates as we found [60]. Furthermore, with regard to the evaluation of drug therapeutic effects, the effects of endogenous substrates could be also influencing the variability in the therapeutic response (placebo or nocebo effect) since the therapeutic response goes beyond the pharmacological effect.

Besides, the evaluation of CYP2D6 in clinical trials may be of importance for CYP2D6 substrates given its involvement in drug metabolism, in particular for active drugs in the CNS, because local brain metabolism may be important for the interaction with neuroactive substances and their biotransformation.

Overall, CYPs enzymes such as CYP2D6, which have been linked to behaviour, may lead to a population selection bias in clinical trials and to an over-representation of certain metabolic groups affecting the drug effect evaluation itself. Therefore, pharmacogenetic evaluation must be included in clinical research.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

The study has been partly supported by European Union (FEDER), Institute of Health Carlos III-FIS and the (PI10/02010) and Gobierno de Extremadura (BS10023). The contributionof M.E.G. Naranjo (supported by Gobierno de Extremadura, Consejería de Empleo, Empresa e Innovación and Fondo Social Europeo EU, Grant PD10199) is gratefully acknowledged.

REFERENCES

1 LLerena A, Dorado P, Peñas-LLedó EM. Pharmacogenetics of debrisoquine and its use as a marker for CYP2D6 hydroxylation capacity. Pharmacogenomics 2009; 10: 17–28.

2 LLerena A, Berecz R, de la Rubia A, Fernández-Salguero P, Dorado P. Effect of thioridazine dosage on the debrisoquine hydroxylation phenotype in psychiatric patients with different CYP2D6 genotypes. Ther Drug Monit 2001; 23: 616–20.

3 Dorado P, Berecz R, Penas-LLedo EM, Caceres MC, LLerena A. Clinical implications of CYP2D6 genetic polymorphism during treatment with antipsychotic drugs. Curr Drug Targets 2006; 7: 671–80.

4 Dorado P, Peñas-LLedó EM, LLerena A. CYP2D6 polymorphism: implications for antipsychotic drug response, schizophrenia and personality traits. Pharmacogenomics 2007; 8: 1597–608.

5 Fonne-Pfister R, Bargetzi MJ, Meyer UA. MPTP, the neurotoxin inducing Parkinson's disease, is a potent competitive inhibitor of human and rat cytochrome P450 isozymes (P450bufI, P450db1) catalyzing debrisoquine 4-hydroxylation. Biochem Biophys Res Commun 1987; 148: 1144–50.

6 Gilham DE, Cairns W, Paine MJ, Modi S, Poulsom R, Roberts GC, Wolf CR. Metabolism of MPTP by cytochrome P4502D6 and the demonstration of 2D6 mRNA in human foetal and adult brain by in situ hybridization. Xenobiotica 1997; 27: 111–25.

7 Miksys SL, Tyndale RF. Drug-metabolizing cytochrome P450s in the brain. J Psychiatry Neurosci 2002; 27: 406–15.

8 McFadyen MC, Melvin WT, Murray GI. Cytochrome P450 in normal human brain and brain tumours. Biochem Soc Trans 1997; 25: S577.

9 Mann A, Miksys S, Lee A, Mash DC, Tyndale RF. Induction of the drug metabolizing enzyme CYP2D in monkey brain by chronic nicotine treatment. Neuropharmacology 2008; 55: 1147–55.

10 Siegle I, Fritz P, Eckhardt K, Zanger UM, Eichelbaum M. Cellular localization and regional distribution of CYP2D6 mRNA and protein expression in human brain. Pharmacogenetics 2001; 11: 237–45.

11 Dutheil F, Dauchy S, Diry M, Sazdovitch V, Cloarec O, Mellottee L Bièche I, Ingelman-Sundberg M, Flinois JP, de Waziers I, Beaune P, Declèves X, Duyckaerts C, Loriot MA. Xenobiotic metabolizing enzymes and transporters in the normal human brain: regional and cellular mapping as a basis for putative roles in cerebral function. Drug Metab Dispos 2009; 37: 1528–38.

12 Hiroi T, Imaoka S, Funae Y. Dopamine formation from tyramine by CYP2D6. Biochem Biophys Res Commun 1998; 249: 838–43.

13 Bromek E, Haduch A, Daniel WA. The ability of cytochrome P450 2D isoforms to synthesize dopamine in the brain: an in vitro study. Eur J Pharmacol 2010; 626: 171–8.

14 Yu AM, Idle JR, Byrd LG, Krausz KW, Küpfer A, Gonzalez FJ. Regeneration of serotonin from 5-methoxytryptamine by polymorphic human CYP2D6. Pharmacogenetics 2003; 13: 173–81.

15 Yu AM, Idle JR, Gonzalez FJ. Polymorphic cytochrome P450 2D6: humanized mouse model and endogenous substrates. Drug Metab Rev 2004; 36: 243–77.

16 Kirchheiner J, Henckel HB, Franke L, Meineke I, Tzvetkov M, Uebelhack R, Roots I, Brockmöller J. Impact of the CYP2D6 ultra-rapid metabolizer genotype on doxepin

pharmacokinetics and serotonin in platelets. Pharmacogenet Genomics 2005; 15: 579–87.

17 Ozdemir V, Bertilsson L, Miura J, Carpenter E, Reist C, Harper P, Widén J, Svensson JO, Albers LJ, Kennedy JL, Endrenyi L, Kalow W. CYP2D6 genotype in relation to perphenazine concentration and pituitary pharmacodynamic tissue sensitivity in Asians: CYP2D6-serotonin-dopamine crosstalk revisited. Pharmacogenet Genomics 2007; 17: 339–47.

18 Ozdemir V, Gunes A, Dahl ML, Scordo MG, Williams-Jones B, Someya T. Could endogenous substrates of drug-metabolizing enzymes influence constitutive physiology and drug target responsiveness? Pharmacogenomics 2006; 7: 1199–210.

19 Aklillu E, Kalow W, Endrenyi L, Harper P, Miura J, Ozdemir V. CYP2D6 and DRD2 genes differentially impact pharmacodynamic sensitivity and time course of prolactin response to perphenazine. Pharmacogenet Genomics 2007; 17: 989–93.

20 Bertilsson L. CYP2D6, serotonin, and suicide – a relationship? Clin Pharmacol Ther 2010; 88: 304–5.

21 Snider NT, Sikora MJ, Sridar C, Feuerstein TJ, Rae JM, Hollenberg PF. The endocannabinoid anandamide is a substrate for the human polymorphic cytochrome P450 2D6. J Pharmacol Exp Ther 2008; 327: 38–545.

22 Hiroi T, Kishimoto W, Chow T, Imaoka S, Igarashi T, Funae Y. Progesterone oxidation by cytochrome P450 2D isoforms in the brain. Endocrinology 2001; 142: 3901–8.

23 Kishimoto W, Hiroi T, Shiraishi M, Osada M, Imaoka S, Kominami S, Igarashi T, Funae Y. Cytochrome P450 2D catalyze steroid 21-hydroxylation in the brain. Endocrinology 2004; 145: 699–705.

24 Yu AM, Idle JR, Krausz KW, Küpfer A, Gonzalez FJ. Contribution of individual cytochrome P450 isozymes to the O-demethylation of the psychotropic beta-carboline alkaloids harmaline and harmine. J Pharmacol Exp Ther 2003; 305: 315–22.

25 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 P-4502D6. Acta Psychiatr Scand 1993; 87: 23–8.

26 Bertilsson L, Alm C, De Las Carreras C, Widen J, Edman G, Schalling D. Debrisoquine hydroxylation polymorphism and personality. Lancet 1989; 1: 555.

27 Ortet G, Ibáñez M, LLerena A, Torrubia R. The underlying traits of the Karolinska Scales of Personality (KSP). Eur J Psychol Assess 2002; 18: 139–48.

28 González I, Peñas-LLedó EM, Pérez B, Dorado P, Alvarez M, LLerena A. Relation between CYP2D6 phenotype and genotype and personality in healthy volunteers. Pharmacogenomics 2008; 9: 833–40.

29 Kirchheiner J, Lang U, Stamm T, Sander T, Gallinat J. Association of CYP2D6 genotypes and personality traits in healthy individuals. J Clin Psychopharmacol 2006; 26: 440–2.

30 Suzuki E, Kitao Y, Ono Y, Iijima Y, Inada T. Cytochrome P450 2D6 polymorphism and character traits. Psychiatr Genet 2003; 13: 1–113.

31 Iwashima K, Yasui-Furukori N, Kaneda A, Saito M, Nakagami T, Sato Y, Kaneko S. No association between CYP2D6 polymorphisms and personality trait in Japanese. Br J Clin Pharmacol 2007; 64: 96–9.

32 Peñas-LLedó EM, Dorado P, Pacheco R, González I, LLerena A. Relation between CYP2D6 genotype, personality, neurocognition and overall psychopathology in healthy volunteers. Pharmacogenomics 2009; 10: 1111–20.

33 Costa PT, McCrae RR. NEO Personality Inventory Professional Manual. Odessa, FL: Psychological Assessment Resources, 1992.

34 Salgado JF. The five factor model of personality and job performance in the European community. J Appl Psychol 1997; 82: 30–43.

35 Gan SH, Ismail R, Wan Adnan WA, Zulmi W, Kumaraswamy N, Larmie ET. Relationship between type A and B personality and debrisoquine hydroxylation capacity. Br J Clin Pharmacol 2004; 57: 785–9.

36 Roberts RL, Luty SE, Mulder RT, Joyce PR, Kennedy MA. Association between cytochrome P450 2D6 genotype and harm avoidance. Am J Med Genet B Neuropsychiatr Genet 2004; 127: 90–3.

37 Derogatis LR. Misuse of the symptom checklist 90. Arch Gen Psychiatry 1983; 40: 1152–3.

38 Kirchheiner J, Seeringer A, Godoy AL, Ohmle B, Maier C, Beschoner P, Sim EJ, Viviani R. CYP2D6 in the brain: genotype effects on resting brain perfusion. Mol Psychiatry 2011; 16: 333–41.

39 Stingl JC, Esslinger C, Tost H, Bilek E, Kirsch P, Ohmle B, Viviani R, Walter H, Rietschel M, Meyer-Lindenberg A. Genetic variation in CYP2D6 impacts neural activation during cognitive tasks in humans. Neuroimage 2012; 59: 2818–23.

40 LLerena A, Dorado P, Peñas-LLedó EM, Cáceres MC, De la Rubia A. Low frequency of CYP2D6 poor metabolizers among schizophrenia patients. Pharmacogenomics J 2007; 7: 408–10.

41 Dahl AA, Løwert A, Asserson S, Bjarking L, Berglund J, Kristensen F, Norum D, Tønseth S, Bayer L, Mæhlum E. Hydroxylation polymorphism of debrisoquine hydroxylase (CYP2D6) in patients with schizophrenia in Norway and Denmark. Hum Psychopharmacol 1998; 13: 509–11.

42 Brockmöller J, Kirchheiner J, Schmider J, Walter S, Sachse C, Müller-Oerlinghausen B, Roots I. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clin Pharmacol Ther 2002; 72: 438–52.

43 Dawson E, Powell JF, Nothen MM, Crocq MA, Lanczik M, Korner J, Rietschel M, van Os J, Wright P, Gill M. An association study of debrisoquine hydroxylase (CYP2D6) polymorphisms in schizophrenia. Psychiatr Genet 1994; 4: 215–8.

44 Daniels J, Williams J, Asherson P, McGuffin P, Owen M. No association between schizophrenia and polymorphisms within the genes for debrisoquine 4-hydroxylase (CYP2D6) and the dopamine transporter (DAT). Am J Med Genet 1995; 60: 85–7.

45 Pirmohamed M, Wild MJ, Kitteringham NR, O'Brien K, Buchan IE, Back DJ, Park BK. Lack association between schizophrenia and the CYP2D6 gene polymorphisms. Am J Med Genet 1996; 67: 236–7.

46 Jonsson EG, Dahl ML, Roh HK, Jerling M, Sedvall GC. Lack of association between debrisoquine 4-hydroxylase (CYP2D6) gene polymorphisms and schizophrenia. Psychiatr Genet 1998; 8: 25–8.

47 Chen CH, Hung CC, Wei FC, Koong FJ. Debrisoquine 4-hydroxylase (CYP2D6) genetic polymorphisms and susceptibility to schizophrenia in Chinese patients from Taiwan. Psychiatr Genet 2001; 11: 153–5.

48 Bijl MJ, Luijendijk HJ, van den Berg JF, Visser LE, van Schaik RH, Hofman A, Vulto AG, van Gelder T, Tiemeier H, Stricker BH. Association between the CYP2D6*4 polymorphism and depression or anxiety in the elderly. Pharmacogenomics 2009; 10: 541–7.

49 Josefsson A, Sydsjö G, Berg G, Dahl ML, Wadelius M, Nordin C. CYP2D6 genotypes and depressive symptoms during late pregnancy and postpartum. Nord J Psychiatry 2004; 58: 61–4.

50 Stingl JC, Viviani R. CYP2D6 in the brain: impact on suicidality. Clin Pharmacol Ther 2011; 89: 352–3.

51 Peñas-LLedó EM, Trejo HD, Dorado P, Ortega A, Jung H, Alonso E, Naranjo ME, López-López M, LLerena A. CYP2D6 ultrarapid metabolism and early dropout from fluoxetine or amitriptyline monotherapy treatment in major depressive patients. Mol Psychiatry 2013; 18: 8–9.

52 Dorado P, Peñas-LLedó EM, González AP, Cáceres MC, Cobaleda J, LLerena A. Increased risk for major depression associated with the short allele of the serotonin transporter promoter region (5-HTTLPR-S) and the CYP2C9*3 allele. Fundam Clin Pharmacol 2007; 21: 451–3.

53 Sim SC, Kacevska M, Ingelman-Sundberg M. Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects. Pharmacogenomics J 2013; 13: 1–11.

54 Peñas-LLedó E, Gonzalez I, Dorado P, Perez B, Calzadilla LR, Alvarez M, Naranjo MEG, LLerena A, CEIBA RIBEF. eating disorder symptoms and CYP2D6 variation in cuban healthy females: a report from the ibero-american network of pharmacogenetics. Curr Pharmacog Person Med 2012; 10: 288–92.

55 Peñas-LLedó EM, Dorado P, Agüera Z, Gratacós M, Estivill X, Fernández-Aranda F, LLerena A. CYP2D6 polymorphism in patients with eatingdisorders. Pharmacogenomics J 2012; 12: 173–5.

56 Peñas-LLedó EM, Dorado P, Agüera Z, Gratacós M, Estivill X, Fernández-Aranda F, LLerena A. High risk of lifetime history of suicide attempts among CYP2D6ultrarapid metabolizers with eating disorders. Mol Psychiatry 2011; 16: 691–2.

57 Zackrisson AL, Lindblom B, Ahlner J. High frequency of occurrence of CYP2D6 gene duplication/multiduplication indicating ultrarapid metabolism among suicide cases. Clin Pharmacol Ther 2010; 88: 354–9.

58 Peñas-LLedó EM, Blasco-Fontecilla H, Dorado P, Vaquero-Lorenzo C, Baca-García E, LLerena A. CYP2D6 and the severity of suicide attempts. Pharmacogenomics 2012; 13: 179–84.

59 Blasco-Fontecilla H, Peñas-LLedó E, Vaquero-Lorenzo C, Dorado P, Saiz-Ruiz J, LLerena A, Baca-García E. CYP2D6 Polymorphism and Mental and Personality Disorders in Suicide Attempters. J Personal Disord 2013 (in press).

60 LLerena A, Cobaleda J, Benítez J. Debrisoquine hydroxylation phenotypes in healthy volunteers. Lancet 1989; 8651: 1398.

61 Lasagna L, Von Felsinger JM. The volunteer subject in research. Science 1954; 120: 359–61.

62 Pollin W, Perlin S. Psychiatric evaluation of 'normal control' volunteers. Am J Psychiatry 1958; 115: 129–33.

63 Halbreich U, Bakhai Y, Bacon KB, Goldstein S, Asnis GM, Endicott J, Lesser J. The normalcy of self-proclaimed 'normal volunteers. Am J Psychiatry 1989; 146: 1052–5.

64 Thaker GK, Moran M, Lahti A, Adami H, Tamminga C. Psychiatric morbidity inresearch volunteers. Arch Gen Psychiatry 1990; 47: 980.

65 Shtasel DL, Gur RE, Mozley PD, Richards J, Taleff MM, Heimberg C, Gallacher F, Gur RC. Volunteers for biomedical research. Recruitment and screening of normal controls. Arch Gen Psychiatry 1991; 48: 1022–5.

66 Tishler CL, Apseloff G, Bartholomae S, Reiss NS, Rhodes AR, Singh A. Are normal healthy research volunteers psychologically healthy? A pilot investigation. Exp Clin Psychopharmacol 2007; 15: 539–45.

67 Schechter D, Lebovitch R. Normal controls are expensive to find: methods to improve cost-effectiveness of the screening evaluation. Psychiatry Res 2005; 136: 69–78.

68 Gustavsson JP, Asberg M, Schalling D. The healthy control subject in psychiatric research: impulsiveness and volunteer bias. Acta Psychiatr Scand 1997; 96: 325–8.

69 Almeida L, Kashdan TB, Nunes T, Coelho R, Albino-Teixeira A, Soares-da-Silva P. Who volunteers for phase I clinical trials? Influences of anxiety, social anxiety and depressive symptoms on self-selection and the reporting of adverse events. Eur J Clin Pharmacol 2008; 64: 575–82.

70 Maliepaard M, Nofziger C, Papaluca M, Zineh I, Uyama Y, Prasad K, Grimstein C, Pacanowski M, Ehmann F, Dossena S, Paulmichl M. Pharmacogenetics in the evaluation of new drugs: a multiregional regulatory perspective. Nat Rev Drug Discov 2013; 12: 103–15.

71 Rodríguez-Antona C, Gurwitz D, de Leon J, LLerena A, Kirchheiner J, de Mesa EG, Ibarreta D. CYP2D6 genotyping for psychiatric patients treated with risperidone: considerations for cost-effectiveness studies. Pharmacogenomics 2009; 10: 685–99.

72 Berecz R, Dorado P, De La Rubia A, Cáceres MC, Degrell I, LLerena A. The role of cytochrome P450 enzymes in the metabolism of risperidone and its clinical relevance for drug interactions. Curr Drug Targets 2004; 5: 573–9.

73 Peñas-LLedó EM, Dorado P, LLerena A. Pharmacogenomics and personality: role of CYP2D6 and implications for psychopathology. In: Pharmacogenomics in Psychiatry, eds Schwab M, Kaschka WP, Spina E. Adv Biol Psychiatry. Basel: Karger, 2010; 25: 30–45.

74 Höfer P, Schosser A, Calati R, Serretti A, Massat I, Kocabas NA, Konstantinidis A, Linotte S, Mendlewicz J, Souery D, Zohar J, Juven-Wetzler A, Montgomery S, Kasper S. The impact of Cytochrome P450 CYP1A2, CYP2C9, CYP2C19 and CYP2D6 genes on suicide attempt and suicide risk-a European multicentre study on treatment-resistant major depressive disorder. Eur Arch Psychiatry Clin Neurosci 2013; 263: 385–91.

75 Peñas-LLedó EM, Naranjo ME, LLerena A. Impact of cytochrome P450 genes on suicide attempt and risk. Eur Arch Psychiatry Clin Neurosci 2013; 263: 703–4.