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CYP2D6 Ultrarapid Metabolism and Suicide

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An increased frequency of individuals with multiplication of the CYP2D6 active gene (ultrarapid metabolizers –UMs- related to very fast enzyme activity) has been described among people who die by suicide [1], as well as among eating disordered patients with a lifetime history of suicidal behavior [2]. Furthermore, UMs have been found to present an elevated risk of high scores on one item of the Hamilton Depression Rating Scale that measures suicidality among inpatients experiencing unipolar or bipolar depression [3]. Finally, an increased number of UMs have been found among individuals who have survived a suicide attempt [4].

Since the polymorphic CYP2D6 enzyme is mainly studied in terms of its involvement in the metabolism of about half of the most of the commonly prescribed psychotropic drugs to prevent suicide or to treat mood disorders (i.e. fluoxetine, paroxetine, fluvoxamine, venlafaxine, citalopram) [5], the first and most likely explanation would be therapeutic failure in UM patients taking such CYP2D6 substrates. In support of this, a greater frequency of UMs was observed among patients with mood disorders that did not respond to antidepressant treatment with CYP2D6 substrates [6]. However, with regard to this first hypothesis, there are several studies that did not find any relationship between CYP2D6 and response to antidepressant drugs [7].

A second explanation could be via the implication of the polymorphic CYP2D6 in the endogenous metabolism, which is lately receiving more scientific attention. CYP2D6 is expressed in brain regions like basal ganglia, substantia nigra, hippocampus, diencephalon, cerebellum, and neocortex [8]. CYP2D6 is shown to play a role in neurotransmitter biotransformation. CYP2D6 transforms 5- methoxytryptamine into serotonin [9] and UMs have been shown to present different serotonin levels in platelets [10]. Additionally, CYP2D6 seems to be involved in the synthesis of dopamine from tyramine [11], and it has been shown to slightly influence dopaminergic tone, possibly due to the regulation of dopamine neurotransmission by serotonin [12]. Moreover, CYP2D6 participates in the metabolism of progesterone [13] and anandamide [14]. Consistently, in the early studies an association between CYP2D6 and psychological functioning (personality traits) was described in Swedish [15], Spanish [16,17] and Cuban [18] healthy volunteers. Furthermore CYP2D6 polymorphism has been associated with differences in neurocognition and vulnerability to psychopathology [19] including eating disorders [20]. Neuroimaging studies also support this second hypothesis [21]. The relationship between CYP2D6 personality and psychiatric disorders like schizophrenia has been also found in other studies [22] although is controversial [23].

In the light of present information the association between CYP2D6 ultrarapid metabolism and suicide seems to be proved. Two hypotheses could explain the relationship between CYP2D6 and suicide among eating disorder patients and severity of suicide. Therefore further research is warranted to determine the functional implications of polymorphic CYP2D6 enzymes in interindividual variability of both vulnerability to psychiatric diseases and drug response [24].

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