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Review article

# The influence of Serotonin Transporter Promoter Polymorphism (SERTPR) and other polymorphisms of the serotonin pathway on the efficacy of antidepressant treatments

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**Abstract**

The definition of a genetic liability profile for specific antidepressant treatment will soon be available offering considerable help in early detection of effective therapy in affective disorders. The search for genetic factors predisposing to drug response or side-effects in affective disorders started only in the last few years. The efficacy of antidepressant action was associated with several polymorphisms, located on coding genes of proteins thought to be involved in the different mechanisms of action of antidepressant treatments. Among these, gene variants in sequences of serotonin pathway proteins were candidate, both for the well known evidence of its involvement in the development of depressive symptomathology and for the wide-world use of selective serotonin reuptake inhibitors as first choice treatment of depression. A polymorphism in the promoter region of the serotonin transporter (SERTPR) was independently associated with efficacy for a range of treatments, other polymorphism located on the tryptophan hydroxylase gene, 5-HT2a receptor and G-protein beta 3 showed some association, while other candidate genes were not associated with treatment efficacy. Possible liability genes controlling at least to some extent both acute and long-term treatment were identified, and the further objective is to identify other candidate genes in order to define individualized treatments according to genetic profile in a future. The present paper reviews the pharmacogenetic studies published to date, focusing the attention on the serotonergic pathway.


*Keywords:* Affective disorders; Antidepressant treatments; Depression; Pharmacogenetics; Serotonin

**Contents**



*Abbreviations:* AD, antidepressant drug; GNB3, G beta3 subunit; HAMD, Hamilton Rating Scale for Depression; AADC, L-Aromatic amino-acid Decarboxylase; MAOA, monoamine oxydase A; MAOI, MAO inhibitors; MDE, *N*-ethyl-3,4-methylenedioxyamphetamine; SD, sleep deprivation; SSRI, selective serotonin reuptake inhibitor; 5HT, Serotonin; 5HT1–7, serotonin receptors 1–7; SERT, serotonin transporter; SERTPR, serotonin transporter promoter polymorphism; TPH, triptophan hydroxylase; TPH-P, TPH promoter; VNTR, variable number tandem repeat; VAS, visual analogue scale.

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## 1. Introduction

Affective disorders have a large impact on social health, with considerable both direct and indirect costs (Bauwens et al., 1991; Pincus and Pettit, 2001; Rice, 1999).

Pharmacologic treatment of mood disorders reduced morbidity of depressive disorder and improved mental health for millions of individuals worldwide. Antidepressant drugs (AD), available since the early 1950s, improved well-being and increased the chance of a good long term outcome. From the late eighties, also other non-pharmacological treatments, such as sleep deprivation (SD), have proved their efficacy, both as the only and as augmentation therapy, in addition to ADs (Benedetti et al., 1997, 1999a, 2001; Smeraldi et al., 1999; Szuba et al., 1994; Vogel et al., 1980; Wirz-Justice and Van den Hoofdakker, 1999; Wu and Bunney, 1990). Unfortunately, not all subjects benefit from treatments, 30–40% of all patients do not respond sufficiently to the initial treatment and it takes up to 6 weeks for them to be identified (Doris et al., 1999). Efficient clinical predictors have not yet been established, but there is some evidence suggesting that genetic factors play a substantial role (Berrettini, 1998; Franchini et al., 1998; O'Reilly et al., 1994; Orsini, 1987; Pare and Mack, 1971; Sederer, 1986; Serretti et al., 1998).

Pharmacogenetics is the use of genetic information to guide pharmacotherapy by providing individualized and science-based treatment decisions. This field gained increasing attention and holds great promises for clinical medicine in the latest years (Dettling et al., 2001; Pickar and Rubinow, 2001; Roses, 2000; Segman et al., 1999). The emerging field of pharmacogenetics holds great potential, particularly in psychiatry, for refining and optimizing psychopharmacology, given the lack of biologically based treatment guidelines (American Psychiatric Association, 1994, 1997, 2000).

Beyond clinical factors, individual's variability in treatment response may be a result of the combination of polymorphisms in metabolic enzymes and in targeted receptors, in fact single gene mutations are unlikely to cause the continuous variability observed in response to psychiatric treatment (Pickar and Rubinow, 2001).

5HT is found in clustered neuronal cell bodies specifically located in the brainstem. The axons of these cells, however, innervate almost every area of the central nervous system, where 5HT has a variety of functions. Beside its fundamental role in mood tone, in fact, it is also involved in eating, sleeping, sexual behavior, the circadian cycle, and other neuro-endocrine functions, all involved in the clinical presentation of mood disorders. Levels of serotonergic neurotransmission in the forebrain are a key to mood: high activity are associated with euphoria, low activity with dysphoria (Jacobs and Fornal, 1995; Maes and Meltzer, 1995). ADs are known to act on monoamine systems; in particular, the majority of them has shown some association with the increase of serotonin (5HT) levels in the inter-synaptic cleft or an interaction with 5HT receptors (Jacobs and Fornal, 1995; Maes and Meltzer, 1995). Moreover, the serotonergic pathway is the main target of SSRIs, the most widely used AD compounds. They interfere with the activity of the serotonin transporter (SERT), a reuptake molecule that removes serotonin from the synaptic cleft (Schafer, 1999). The most current versions of the serotonin model hypothesize that selective serotonin reuptake inhibitors are effective against depression not only for their acute effects on serotonergic transmission, but also for the long-term adaptive changes in monoamine neurotransmission arising from the chronic inhibition of serotonin reuptake (Leonard, 1996). In particular, while the acute effects could be ascribed to the inhibition of serotonin reuptake in dorsal raphe nucleus, to the activation of somatodendritic autoreceptor 5-HT1A and to the decrease of serotonin release, the long-term effects could be linked to the desensitization of the same 5-HT1A autoreceptor, with an increasing serotonin release, and consequently the higher serotonin concentration in terminal areas (Artigas et al., 1996; Bel and Artigas, 1993). Moreover, molecular and pharmacological studies showed that SSRIs are involved in the modification of cellular mechanisms following receptor activation. In particular, changes in protein kinase C, protein Kinase A and in other postsynaptic substrates have been observed (Bel and Artigas, 1993; Perez et al., 1991, 1995).

The present paper reviews the pharmacogenetic studies published to date, focusing the attention on the serotonergic pathway.

### 1.1. Serotonin metabolism: synthesis and catabolism

5HT is synthesized from tryptophan, after the active uptake of this amino-acid into the serotonergic neurons. Tryptophan is transformed in 5-hydroxy-tryptophan via tryptophan hydroxylase (TPH), then the enzyme L-aromatic amino-acid Decarboxylase (AADC) synthesizes 5HT.

The TPH gene, which codes for the rate-limiting enzyme of 5HT biosynthesis, has been cloned (Boularand et al., 1990) and mapped on 11p15.3–p14 (Craig et al., 1991). Studies on administration of *N*-ethyl-3,4-methylenedioxyamphetamine (MDE) to rats showed a significant concentration decline of 5-HT and of TPH activity in the hippocampus (Johnson et al., 1989). In addition, long-term treatment of rats with sertraline has shown to up-regulate mRNA and protein levels of the TPH (Kim et al., 2002b). These findings suggest a role of TPH in AD action.

Four genetic variants of the TPH promoter (TPH-P), which could modulate TPH gene transcription, were identified: −7180T>G, −7065C>T, −6526A>G, and −5806G>T (Rotondo et al., 1999). The expression of the TPH gene is tightly regulated both at the transcriptional and at the post-transcriptional levels (Cote et al., 2002). For this reason, polymorphisms in the promoter region of TPH gene could be interesting candidates for pharmacogenetic studies, which were not yet performed to our knowledge.