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Genetic susceptibility to Tardive Dyskinesia in chronic schizophrenia subjects: Role of oxidative stress pathway genes

Arun K Tiwari[1], **Smita N Deshpande**[2], **Bernard Lerer**[3], **Vishwajit L Nimgaonkar**[4], and **BK Thelma**[1,*]

1*Department of Genetics, University of Delhi South Campus, New Delhi 110021 India*

2*Department of Psychiatry, Dr. RML Hospital New Delhi 110001, India*

3*Department of Psychiatry, Hadassah-Hebrew University Medical Center, Ein Karem, Jerusalem 91120, Israel*

4*Department of Psychiatry, University of Pittsburgh, PA 15213, USA*

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Tardive Dyskinesia (TD) is a severe debilitating movement disorder with a potentially irreversible course developing in schizophrenia patients under long term treatment with classical neuroleptics. Its development in a subset of patients (~20-25%), familial nature, and concordance amongst twins indicate a possible genetic basis (for review see Muller et al. 2004). In addition to the classical dopaminergic pathway genes, oxidative stress mediated neurotoxic damage is also an important hypothesis proposed to explain the development of TD. Considerable support to OS hypothesis comes from the observations of increased lipid peroxidation in cerebrospinal fluid in patients with TD and antioxidants such as vitamin E alleviate TD symptoms (Adler et al. 1999; for review see Lohr, 2003). Recently a novel antioxidant AD4 has been reported to reduce haloperidol induced vacuous chewing moments in rats (Sadan et al. 2005).

In this study, genes involved in the maintenance of cellular redox balance namely, superoxide dismutase 2 (SOD2; MnSOD; Ala9Val), Uncoupling protein 2 (UCP2; 45bp del/ins), neuronal nitric oxide synthase (nNOS; NOS1; His902His, rs2682826), endothelial NOS (eNOS; NOS3; 27bp ins/del), glutathione S transferase (GST; GSTMI, TI; Presence/Null; GSTPI, Ile105Val) and NADPH: quinone oxidoreductase 1 (NQO1, Pro187Ser) were analysed. Schizophrenia patients with TD (n=96) and without TD (n=239) were recruited for the study. SNPs were genotyped using PCR-RFLP and allelic, genotypic and haplotypic association was tested using χ^2 test. Further, to test whether severity of TD was influenced by genotype, mean AIMS score was compared across the genotypic categories for each of the polymorphism using Kruskal Wallis H test.

*To whom correspondence should be addressed. Tel: 91-11-24118201, Fax: 91-11- 24115270, email: humgen@vsnl.com.

None of the SNPs tested were associated with the development of this iatrogenic disorder ($p>0.05$). However, an increased severity of TD in subjects homozygous for NOS3 27bp ins allele (4b) was observed ($p=0.03$) and reduced severity of TD in carriers of the TT genotype of NQOI Pro187Ser C>T polymorphism ($p=0.025$) was observed though they did not withstand corrections for multiple comparisons (Table1). The possible reason for the above observation could be as follows. The cellular milieu determines whether NO is neuroprotective or neurotoxic. Under conditions of oxidative stress the NO produced can react with superoxide to produce peroxynitrite ($ONOO^-$). Peroxynitrite can oxidize lipids and proteins or alternatively it gets protonated to form nitrate or decomposes to nitrogen dioxide and hydroxyl radical. Uncoupling of NOS3 due to oxidative stress causes production of superoxide instead of NO (Fostermann and Munzel, 2006). Thus carriers of the ins allele (4b) would tend to have more disruption of normal cellular functions. Severity of TD was significantly reduced in the patients homozygous for the TT genotype of NQO1. Although the primary function of NQO1 is reduction of quinones to hydroquinones, it is also involved in the detoxification of superoxide radical to H_2O_2. The detoxification of H_2O_2 formed is carried out by catalase and glutathione peroxidase, a reaction that is considerably slower. NQO1 expression is also induced by free radicals; therefore, under conditions of oxidative stress increased H_2O_2 coupled with slow removal will lead to more H_2O_2 remaining in the system (Siegel et al. 2004). This in presence of electron donors such as NADPH / GSH and transition metals (Cu2+ or Fe2+) can form hydroxyl radical, a more toxic ROS. Thus more severe TD may be observed in patients expressing NQO1 (pro/pro or pro/ser) compared to those with complete absence of the protein (ser/ser).

We previously demonstrated the contribution of some of the genes from the dopaminergic pathway in the genesis of TD (DRD4 120bp dup; COMT 408C>G and Val158Met; Srivastava et al. 2006). The CYP450 family of genes modified only the severity (CYP1A2*1C and CYP2D6*4; Tiwari et al. 2005a, 2005b, 2006) and genes from the serotonergic pathway are not involved in either the development or severity of TD (Deshpande et al. 2005). In the present study, the antioxidant genes investigated are not associated with the genesis of TD but influence the severity of the phenotype (NOS3 27bp duplication and NQO1 Pro187Ser). Thus we may conclude that in our sample set the genes from the dopaminergic pathway govern the development of TD and cytochrome P450 family of genes together with the oxidative stress pathway genes modify the severity of the disease. However, a replication of these observations in an independent sample set from the same or another population is warranted.

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Table 1

Distribution of mean AIMS score according to genotype in patients with TD.

Polymorphism[#]	AIMS score (mean±SD)			p-value[*]
	11	12	22	
SOD2 Ala9Val C/T	7.12±4.16	6.17±3.29	5.67±2.89	0.436
UCP2 45bp del/ins	6.35±3.21	5.93±3.70	--	0.287
NOS1 rs1047735 C/T	6.12±3.43	5.76±2.96	7.00±3.63	0.730
NOS1 rs2682826 C/T	5.84±3.24	6.03±3.40	7.17±3.43	0.591
NOS3 27bp ins/dup	6.81±3.63	5.13±3.20	7.50±2.12	**0.038**
GSTM1 Presence/Null	6.00±3.29		6.33±3.46	0.643
GSTT1 Presence/Null	6.27±5.27		5.27±2.28	0.580
GSTPI Ile105Val A/G	5.68±2.57	6.49±3.63	6.11±4.51	0.595
NQO1 Pro187Ser C/T	6.20±3.40	6.80±3.40	3.57±0.54	**0.061**[ψ]

[#] The 11 genotype corresponds to the first allele e.g. Ala9Val C/T 11=CC, 12=CT,22=TT genotypes;

[*] Kruksal Wallis H test;

[ψ] CC+CT vs TT 6.42 ± 3.44 vs. 3.57 ± 0.54; p=0.025