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# Relation between serum prolactin levels and antipsychotic response to risperidone in patients with schizophrenia

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ABSTRACT

***Background:*** Hyperprolactinemia is commonly seen in patients with schizophrenia on risperidone. Dopamine receptor blockade plays a major role in risperidone induced hyperprolactinemia. However, limited studies are available with inconsistent results on antipsychotic response to risperidone and prolactin elevation. Therefore, we aimed to study the change in serum prolactin levels and response to risperidone and to test the association between DRD2 genetic variants and prolactin levels in schizophrenic patients treated with risperidone.

***Methods:*** A prospective study comprising of 102 patients with schizophrenia were recruited. Prolactin levels and Positive and Negative Syndrome Scale (PANSS) score were recorded at baseline and after four weeks of risperidone treatment. Prolactin concentrations were measured by standard method Advia-Centaur® Chemiluminescence immuno assay method. Taq1A DRD2 genotyping was performed by qRT-PCR.

***Results:*** The mean±SD prolactin levels (ng/ml) were increased after four weeks of treatment in both responders (males 21.66±15.15 to 41.63±18.73; $p < 0.01$ females 51.92±40.89 to 122.35±52.16; $p < 0.01$) and non-responders group (males 23.89±14.85 to 37.45±13.5; $p < 0.01$ females 39.25±26.94 to 91.13 ±54.31; $p < 0.01$). Patients with increased prolactin concentration were 4.6 fold higher in responders (OR 4.60; 95%CI 1.376-15.389; p-value 0.01) compared to non-responders. Ninety-six patients were genotyped for Taq1A DRD2 gene (AA=9, AG=46, GG=41) and found no association (p=0.6) between genetic variants and response to risperidone.

***Conclusion:*** Patients were showing more than 20% increase in prolactin levels had a better chance of responding to risperidone therapy. *Taq1A DRD2* gene did not show any association with prolactin elevation and response to risperidone.



## 1. Introduction

Schizophrenia is a severe psychiatric illness, often requiring long time therapy with antipsychotics (Prior et al., 2001). Presently, atypical antipsychotics have become the most commonly used drugs in the treatment of schizophrenia. Among the atypical antipsychotics risperidone is a widely used medication for schizophrenia. Dopamine (D2) receptor blockade has been reported to play a predominant role in response to antipsychotics, and genesis of extrapyramidal symptoms and drug-induced hyperprolactinemia (Milano et al., 2011).

The degree of prolactin elevation varies with the antipsychotic prescribed (Fitzgerald and Dinan, 2008). The degree of prolactin elevation depends upon the binding affinity of antipsychotics to the dopamine receptors. Dopamine receptor blockade by antipsychotics and hyperprolactinemia has been well reported in various studies. Therefore, prolactin elevation may be considered as a central marker for antipsychotics function on dopamine receptors (Pérez-Iglesias et al., 2012). Several authors have reported the positive correlation and few studies were with no correlation between prolactin levels and symptoms amelioration due to antipsychotic medication (Akhondzadeh et al., 2006; Lieberman et al., 1994; Markianos et al., 1991; Newcomer et al., 1992; Otani et al., 1994; Tsuboi et al., 2013; Van Putten et al., 1991). Additionally, genetic epidemiological studies have also reported that D2 receptor gene (Taq1A,-141Ins/Del, ser311Cys) polymorphisms is associated with variation in prolactin levels, etiology

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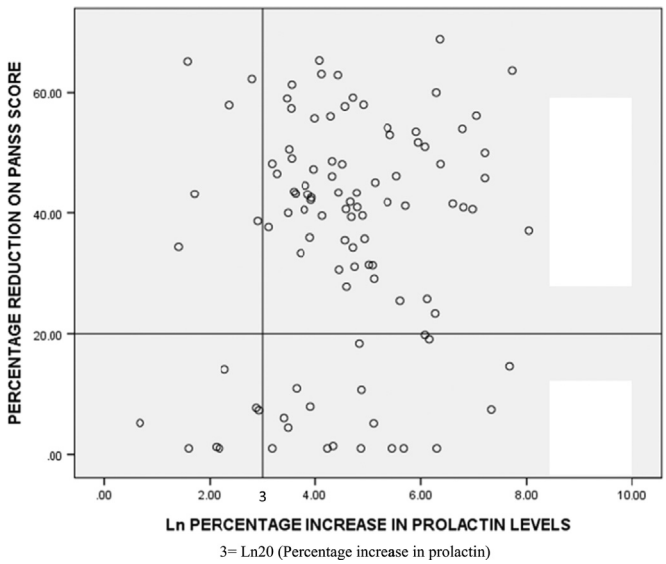


**Fig. 1.** Prolactin levels distributions in responders and non-responders after four weeks of treatment (PANSS score reduction (%) verses Ln Percentage increase in prolactin) 3=Ln20 (Percentage increase in prolactin).

of schizophrenia and response to antipsychotic medication (Kwon et al., 2008; López-Rodríguez et al., 2011; Young et al., 2004).

Prolactin secretion is regulated under the dopamine, both the first generation and second generation antipsychotics can cause the elevation in prolactin levels. Available evidence suggests that genetic polymorphism in dopamine receptor is associated with reduced binding affinity to antipsychotic agents which may modulate the prolactin secretion (Ritchie and Noble, 2003). Taq1A is one of the most extensively studied polymorphism in schizophrenia and other major psychiatric disorders, located on novel kinase gene downstream of DRD2 gene (chromosome11q23). Few studies also reported the association of Taq1A with prolactin levels, but no study has reported the role of Taq1A on prolactin modulation in the patients with schizophrenia in the population of South India. So far reported studies are with limited sample size and inconsistent results. Hence, the present study aimed at finding the change in prolactin levels and response to risperidone in patients with schizophrenia and to investigate the effect of DRD2 gene Taq1A polymorphism on prolactin level variation. The study hypothesis was serum prolactin levels will associate with antipsychotic response to risperidone in patients with schizophrenia Fig. 1.

## 2. Methods

Patients with acute episodes of schizophrenia as per DSM-IV TR criteria who were treated at the Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, South India were recruited for the study. All the patients were enrolled in the study between August 2013 to August 2015 at special clinic for psychosis and schizophrenia. Patients were recruited consecutively during the screening procedure, each patient history and clinical symptoms assessed on PANSS score. Patients were excluded if they had history of medical illness or substance abuse. Further, women who were pregnant and lactating were excluded from the study. The study protocol was approved by Institute Ethics Committee. Informed consent was obtained from the patients or their LAR (Legally Acceptable Representative) after explaining the study procedure and methodology.

### 2.1. Study design

All the patients above 18 years who were diagnosed with schizophrenia and received risperidone therapy (4–8 mg/day) for their treatment for a minimum of four weeks were recruited. The patients were either medication naïve or free from any treatment for at least three weeks. The Positive And Negative Symptoms Scale (PANSS) scores were assessed at baseline and after the minimum of 4 weeks of risperidone therapy. PANSS score assessments were performed by trained medical personnel. Same practitioner was rated for each patient throughout the study and blinded to patients' serum prolactin levels and genotype. Patients taking other antipsychotics other than risperidone were excluded from the study.

### 2.2. Prolactin measurement

Five ml of venous blood was collected between 9 A.M to 12A.M from all the patients at baseline and after 4 or more weeks of treatment with risperidone. Serum was separated and stored at −40 °C until assay; prolactin concentration was measured by standard method Advia-Centaur® Chemiluminescence (Advia-Centaur CP, Siemens healthcare diagnostics, Germany) immunoassay method (Margari et al., 2015). Intra assay and inter assay coefficients of variation were less than 7% and 9% respectively.

### 2.3. Genotyping

DNA was extracted from peripheral leukocytes cells by standard phenol-chloroform method. Genotyping for DRD2 gene Taq1A polymorphism was performed by real-time thermocycler (ABI Prism 7300, Foster City, CA, USA) using Taqman SNP probe (Applied Biosystems, Foster City, CA, USA).

### 2.4. Response criteria

After four weeks of risperidone treatment, patients who showed more than 20% decrease in PANSS score were considered as responders and others were considered as non-responders (Haas et al., 2009).

### 2.5. Statistical analysis

Patients' details were expressed in Mean ± Standard deviation. Paired *t*-test was used to compare the prolactin levels at baseline and after four weeks of treatment. Unpaired *t*-test was used to compare the prolactin levels between responders and non-responders groups. Percentage increases in prolactin values converted to LN (Natural Logarithm) values verses % decrease in PANSS on scatter diagram. Spearman's correlation test was used to find the relationship between percentage reduction in PANSS score and percentage increase in prolactin levels. Fisher's exact test was used to compare the prolactin distribution between responders and non- responders. Kruskal - Wallis test was used to find the association between genotypes and prolactin level difference. Chi-square test was used to find the association between genotype and response to risperidone. P value $<0.05$ was considered as significant and missing value imputation was not done. Statistical analysis was performed by using Graph Pad In stat version 3.06 and SPSS (IBM PASW statistics;Ver 19.0) software.

## 3. Result

A total of 122 patients were recruited for the study, though 20 patients were excluded as they did not turn up for follow-up. Hence