“Dopamine receptor (DRD3) polymorphism (rs6280) is associated with risk for Impulse Control Disorders and related behaviors in Parkinson's disease in India”

Thesis submitted in partial fulfilment of the rules and regulations for DM Degree Examination of Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

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2012-2014
DECLARATION

I, Dr. Hardeep Kumar, hereby declare that the projects in this book were undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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Date:

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The candidate, Dr. Hardeep Kumar, has carried out the minimum required project.

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Date:

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Date:

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Dr. Hardeep Kumar
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Introduction

Impulse control disorders (ICDs) are characterized by the failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or to others (1). Impulse control and related behaviors (ICRB) has been recently recognized as a long term complication of dopamine replacement therapy (DRT) in patients with Parkinson’s disease (PD). The proposed category of ICRB in PD includes addictive behaviors, such as problem/pathological gambling, compulsive shopping, hypersexuality, compulsive eating, and punding. Punding, is an aimless repetitive stereotyped performance of complex tasks and is not a true ICD but is included under ICRB (2). The lifetime prevalence of ICRB in PD is not known, but several hospital-based surveys have suggested that they are not rare and range from 2–31% (3,4,5,6). In a study conducted among 3090 patients with treated idiopathic PD receiving routine clinical care in United States and Canada, an ICD was identified in 13.6% of patients and it was more common in patients treated with a dopamine agonist (5). We recently reported that among 305 patients of PD seen in the movement disorder clinic of SCTIMST in a cross sectional study, 31.6% had at least one ICRB. The risk of ICRB was found to be significantly associated only with the dopamine agonist therapy, alone or in combination with levodopa and not with levodopa alone (4). Not all patients exposed to dopamine agonist exhibit such behavior pointing to other risk factors in the development of ICRB. Various studies has reported that certain personality traits such as impulsivity and novelty seeking behaviors are more common in PD patients on dopaminergic drugs (7). Genetic variation in components of neurotransmitter systems, may alone or in conjunction with other factors such as personality traits predispose to ICRB. In a study conducted by Lee et al., in Korea in 404 patients, they found that AA genotype of DRD3 p.S9G and the CC genotype of GRIN2Bc.366C>G were more frequent in patients with ICRB and PD than in PD patients without ICRB (8). In another study conducted by same authors, they found a genetic variation in the serotonin type
2A receptor gene (HTR2A) to be related to ICRB in PD (9). There are very few studies on genetic risk factors for ICRB reported in literature and no reports in Indian patients so far, to the best of our knowledge. We therefore undertook a study in the PD patients from our centre diagnosed with ICRB to investigate the role of genetic polymorphisms in dopamine, Serotonin and glutamate receptor systems in causing ICRB.
Review of literature

Prevalence

Various studies has reported that prevalence of ICRBs in PD patients on dopamine agonist therapy ranges from 2%–31%.(3,4,5,6). In study conducted among 3090 patients with treated idiopathic PD receiving routine clinical care in United States and Canada, an ICD was identified in 13.6% of patients.(5). We recently reported that among 305 patients of PD, 31.6% had at least one ICRB (based on validated criteria) and the risk of ICRB was found to be significantly associated with only the use of dopamine agonist therapy.(4). Compared with patients without an ICRB, those with an active ICRB were younger and more likely to be unmarried, have more formal education, smoke cigarettes, report familial gambling problems (both historical and current), and acknowledge alcohol abuse in first-degree relatives.(5).

Types of ICRB: The proposed category of ICRB in PD includes addictive behaviors, such as problem/pathological gambling, compulsive shopping, hypersexuality, compulsive eating, and punding (2).

Pathological gambling

Pathological gambling (PG) is defined as failure to resist gambling impulses despite severe personal, family, or vocational consequences (DSM IV). The prevalence of pathological gambling is 2.2% to 7% in treated PD patients (10,11). Prevalence of pathological gambling in our study was 4.5%(4). The large majority of PD patients with PG have never gambled before the onset of dopamine agonist therapy, and it is this single factor that contributes by far the greatest risk(12). Male sex, a previous history of alcohol or substance abuse, a history of depression, and high novelty-seeking personality traits have all been identified as risk factors in PD(2). PD patients with pathological gambling and other treatment-related
behavioral disorders show enhanced novelty seeking (13). They also make highly risky choices while taking dopaminergic medication. Dopaminergic overstimulation of orbitofronto-striatal networks may underlie these responses (14). In PD there is an uneven distribution of dopaminergic cell loss, with the dorsal striatum being much more severely damaged than the ventral striatum (15). This has led to the hypothesis that exogenous dopaminergic medication, necessary to correct the depleted dopamine levels in the putamen, might over stimulate the ventral circuitry (cognitive overdose hypothesis), leading to adverse behavioral and cognitive consequences (16). Those PD patients with a relatively more intact ventral striatum could pose a risk of or developing PG.

In PD patients, only a few studies have investigated the role of genetic polymorphisms of the dopaminergic system in PG and other ICRBs. Some relevant polymorphisms investigated in general population have not been assessed in PD patients (i.e., DRD1 and DRD4), whereas other polymorphisms have been assessed in PD patients with PG or other ICRBs without finding any significant association i.e. DRD2 Taq 1A variants (8). Notably, the homozygous variant Ser9Gly (AA genotype) of DRD3 is possibly associated with lower binding affinity to dopamine and seemed to be associated with a two-fold increase in the risk of PG and ICRBs in PD patients (8), but not in general population. As regards serotoninergic systems, the serotonin transporter gene (5-HTTLP) “S” allele has been shown to be more frequent in PD patients with pathological gambling and ICRBs, although neither dominant nor recessive model revealed any associations (8). More recently, a genetic variant affecting serotonin 2A receptor (HTR2A) pathway has been found to be associated with ICRBs in PD patients receiving dopamine replacement therapy, mainly under low-dopaminergic dose conditions (9). Last, the CC genotype of the 2B subunit (GRIN2B) of the glutamate N-methyl-D-aspartate (NMDA) receptor, mainly expressed in the striatum (17), has been found to be more frequent in PD patients with pathological gambling and ICRBs than in non-affected patients.
(8). In summary, studies on genetic susceptibility for ICRBs in PD patients are quite limited and often included a relatively small number of patients (18). Available data seem to suggest an association of pathological gambling with DRD3 and with polymorphisms of serotoninergic and glutamatergic pathways, but these results await to be confirmed in further independent studies on larger samples of PD patients.

**Punding**

Punding describes a heterogeneous set of aimless, stereotyped behaviors performed for long periods of time at the expense of other activities (19). Patients often display a fascination with repetitive manipulations of a familiar object for example, collecting, sorting or habitual disassembly, and reassembly of objects (20). Prevalence of punding has been reported to be 0.34% to 15% (3,4) in PD patients. The link between high doses of dopaminergic therapy and punding has already been established (19,20). A study by Evans et al. found that patients with both compulsive L-dopa use and punding had higher dopamine levels in the ventral striatum after L-dopa ingestion than those without (21). This could suggest that punding is due to sensitization of ventral striatal circuitry in humans (22).

**Hypersexuality**

Hypersexuality in PD was first described by Vogel and Schiffer (23). The behavioral manifestations of hypersexuality include increased libido, increase in erection frequency and increased sexually demanding behavior sometimes accompanied by aggressiveness and compulsive masturbation (2004). Prevalence of hypersexuality in PD patients was reported to be 3.5% by Weintraube et al. (5), and was reported to be 7.5% in our previous study (4). There are several potential theoretical explanations for the development of increased libido as a result of disturbances in the impulse control system. One such explanation is a primary
degeneration of the reward system, and another is functional and possibly structural changes secondary to long-term, continuous, non-physiological, stimulation of the dopaminergic system with medications. It is possible that the combination of the two leads to the clinical syndrome (25).

**Compulsive buying**

Compulsive buying is defined by the presence of repetitive impulsive and excessive buying leading to personal and family distress. Compulsive buying is more frequent in patients with an obsessive–compulsive disorder than in normal individuals. Maia et al. published the first report on uncontrolled buying in PD. Compulsive buying was found in 5.7% of PD patients in DOMINION study (5) and was reported to be 8% in our previous study (4).

**Compulsive eating**

Nirenberg and Waters (26) described seven patients with a compulsive eating disorder that had developed in the context of treatment with the dopamine agonist, Pramipexole. All the affected patients had significant, unwanted weight gain; four had other comorbid compulsive behaviors. The dose of Pramipexole was either lowered or the dopamine agonist treatment was discontinued in five of the patients, whereupon the behavior ceased and there was no further weight gain. Compulsive eating has been identified in 4.3% PD patients in a multicentre DOMINION study (5) and 7.8% in our previous study (4).

**Neural substrates for ICRBs in Parkinson’s disease:**

Parkinson’s disease is characterized by degeneration of substantianigra pars compacta dopaminergic neurons, with a resulting deficiency of striatal dopamine. With the progressive loss of the nigrostriatal dopaminergic neurons, there is a corresponding decrease of dopamine
content in both the nigra and the striatum. Dopamine replacement therapy using L-DOPA is the major medical approach to treating PD. The alternative to L-dopa treating PD symptoms is the use of a dopamine agonist (27). Dopamine agonists are synthetic analogues of dopamine. Bromocriptine was found to be effective in PD in 1974. Other ergotamine dopamine agonists including lisuride, pergolide, and cabergoline were subsequently found to be effective. In the 1990s, two nonergot dopamine agonists (DA), pramipexole and ropinirole, were granted approval for use. The dopamine agonists ropinirole, pramipexole, and pergolide exhibit high affinity for the D3 receptors (28). The older dopamine agonist, bromocriptine, does not share this specificity and appears to have greater affinity for the D2 receptor (28). Evidence suggests uneven distribution of these dopamine receptor subtypes within different brain regions: D1 and D2 receptors are found to be abundant in the dorsal striatum whilst D3 receptors are found in abundance in the ventral striatum. Action of dopamine within the dorsal striatum may improve motor symptoms (29) whereas activation of D3 receptors of the ventral striatum may induce impulsive behavior. Although virtually all PD patients are treated with dopaminergic drugs, only a minority will develop hyperdopaminergic states, suggesting predisposing and/or protecting factors. Recent genetic studies have investigated associations between ICRB and polymorphisms of genes involved in the dopamine metabolism pathway (COMT, DAT), dopamine receptors (DRD1, DRD2, DRD3, DRD4), serotonin receptors and its transporter (HTR2A, 5HTT), and glutamate receptors (GRIN2B) (18). To date, only a few studies have examined genetic susceptibility to ICRB in PD patients. Lee et al. (8) found a higher frequency of allele AA of DRD3 Ser9Gly polymorphism among 58 PD patients with ICRB as compared to 346 PD patients without ICRB. In the same cohort, an association was found between the presence of ICRB and the c.102T>C variant of the HTR2A gene, coding the serotonin 2A receptor (9).
The present study was designed to test the role of genetic polymorphisms in receptors of important neurotransmitters in the striatum in the causation of ICRBs in our PD cohort diagnosed to have ICDRB
AIMS AND OBJECTIVES

To assess whether the following genetic polymorphisms are associated with impulse control disorders in Parkinson's disease patients exposed to DRT:

1. Dopamine receptor (DRD3 rs6280)
2. Glutamate receptor (GRIN2B rs1806201)
3. Serotonin transporter (5HTTLPR rs6313)
MATERIALS AND METHODS

Patients diagnosed to have PD on the basis of UKPDS Brain Bank Criteria (30) by an experienced movement disorder specialist and detected to have ICRBs as per standard diagnostic criteria (2) were recruited for the study from the Movement disorders clinic of our University hospital. All the patients who were detected to have ICRBs, in our previous (4) study (n =77) were included; additional patients diagnosed in the 2 years after completion of the previous study using the same criteria (n = 22) were also recruited. Patients with PD without any ICRBs (n= 100) from the same cohort negative for ICRBs formed the comparator groups. 100 healthy volunteers were screened to study the distribution of these polymorphisms in general population. All demographic, clinical and treatment data were collected and verified with the patient’s medical records. All patients provided written informed consent for participation in the study. The study was approved by the institutional ethics committee.

Inclusion criteria (for PD patients):

1. Diagnosis of PD, as per standard UKPDS criteria.
2. Only patients who had received at least 1 year of DRT and whose treatment had not been modified, based on prior reporting of ICRB were included.
3. A psychiatrist confirmed diagnosis of ICRB/no ICRB after satisfying criteria 1 and 2.
4. Ability to read, understand and write well.
5. Ability to provide written informed consent.
Inclusion criteria (for Controls)

1. No known neurological disorders.
2. Normal neurologic examination.
3. Ability to read, understand and write well.
4. Ability to provide written informed consent.

Exclusion criteria (for PD patients and Controls)

1. Patient’s scoring less than 24 in MMSE in the screening visit were excluded.
2. Significant neurological, psychiatric or medical co-morbidity interfering with ICRB testing.

There was no gender, class, caste, ethnicity or racial considerations in the inclusion / exclusion criteria.

Assessments

Patients were diagnosed to have PD using UKPDS Brain Bank Criteria. The modified Minnesota Impulsive Disorders Interview (MIDI) was used for screening for ICRBs (31). Those who screened positive were subjected to an elaborate test battery consisting of DSM IV-RT criteria for pathological gambling and compulsive eating (7), operational diagnostic criteria for hypersexuality (7), McElroy’s criteria for compulsive shopping (7), operational criteria for punding (7). Patients with PD who were screened positive in the MIDI and in whom ICRBs were confirmed by the test battery were classified as PD-ICRB. Those with PD who screened negative in the MIDI were classified as PD-controls. Healthy volunteers were also for verifying whether the disease population was in equilibrium with general population.

Levodopa equivalent daily dosages (LED) calculation: Levodopa equivalent daily dosages of drugs were calculated using the formula: 100mg of regular L-DOPA =133 mg of
controlled release L-DOPA, =1mg of pramipexole, =5mg of ropinirole, =1mg of rasagiline, =100mg of amantadine, =0.33 x L DOPA dose of entacapone (32).

**Genetic methodology:**

**Sample Collection and Genomic DNA Isolation**

6mL of peripheral blood was collected from patients in K2EDTA Vacutainer tubes and the genomic DNA isolated as per manufacturer’s protocol (*FlexiGene DNA Kit, Qiagen*).

**PCR amplification**

Primers were designed in silico using PrimerZ software contiguous to their respective SNPs. The reaction volume comprised 2ng of genomic DNA, 200µM of dNTPs (Genei), 1mM of each primer (Sigma-Aldrich), 1X PCR buffer and 1 unit of Taq DNA polymerase enzyme (Invitrogen, Brazil). Amplification of the specific sequence comprising the SNP was set up according to the PCR conditions: initial denaturation at 94°C for 1 min followed by 35 cycles of denaturation for 15s, annealing at 64°C for 15 s, extension at 72°C and a final extension at 72°C for 7 minutes in an Applied Biosystems® Veriti® Thermocycler (Life Technologies).

**Genotyping**

Restriction Fragment Linked Polymorphism (RFLP) analysis of DRD3 polymorphism was conducted by digesting the PCR products with MscI restriction endonuclease (NEB, Inc., USA). The products were visualized on a 3% agarose gel (Sigma-Aldrich), stained with ethidium bromide. The undigested product was 172 bp in size and the digested fragments were of sizes 86 and 92 bps.

Genotyping of HTR2A and GRIN2B polymorphisms was done using *KASP*ar _SNP Genotyping System_ (LGC Genomics, UK) following manufacturer’s protocols.
Statistical analysis

The genotypic and allelic frequencies of case and control samples were computed and verified for any deviation from the Hardy-Weinberg equilibrium. Statistical differences were determined using Pearson’s $\chi^2$ test and Fischer’s exact test (two-tailed) was used to compare the allelic frequencies between cases and controls. A "P" value of <0.05 was considered to be statistically significant.
Clinical characteristics of whole cohort: Total 199 PD patients (99 ICRB positive and 100 ICRB negative), participated in study of which 149 were males and 50 were females. Their mean age was 57 years (S.D = 10.68, range=22-84 years). The mean age of onset of disease was 48.8 years (S.D = 10.89, range=13-74 years). The mean duration of disease was 8.3 years (S.D = 4.9, range=0.6-28 years).

Figure 1.
Clinical characteristics of ICRB positive versus ICRB negative patients

The mean age of ICRB positive patients was 54.58 years (SD = 10.54, range=22-74 years), ICRB negative patients was 59.58 (SD = 10.27, range=31-84 years). The ICRB positive patients were younger than the negative group (p <0.001). The mean age of onset of symptoms was 46.12 years (SD = 10.14, range=13-65 years) in ICRB positive patients versus 51.58 years (SD = 10.9, range=24-74) and this difference was significant (p <0.001). The duration of disease was 8.46 years (SD = 4.46, range= 1- 24 years) in ICRB positive patients versus 8.14 years in (SD = 5.45, range=0.6-28 years) ICRB negative patients and this difference was not significant (p value was 0.6).

Figure 2.

Treatment characteristics of whole cohort: Mean LEDD dose was 527.13 mg (SD=321.14, range 0.0-2080 mg). Mean L-DOPA dose was 345.34 mg (SD=242.77, range 0.0-1200mg) and mean duration was 4.93 years (SD=4.83, range 0.0-22years). Mean dose of
pramipexole was 1.45 mg (SD=1.68, range 0.0-4.5mg) and mean duration of exposure to pramipexole was 1.24 years (SD=1.83, range 0.0-8.0 years). Mean ropinirole dose was 0.77 mg (SD=1.89, range 0.0-12mg) and mean duration was 0.68 years (SD=1.78, range 0.0-11years).

**Treatment characteristics of ICRB positive versus ICRB negative patients:**

The Mean LEDD dose in ICRB positive group was 603.38 mg (SD=346.47, range 0.0-2080mg) was higher than in ICRB negative group (51.65 mg, SD=275.43, range 0.0-1400mg) (p < 0.001). Mean L-DOPA dose in ICRB positive group was 363.42 mg (SD=243.71, range 0.0-1100) versus 327.45 (SD=241.72, range 0.0-1200) and was not significantly different (p =0.29). The mean duration of L-DOPA in ICRB positive patients was 5.3 years (SD=4.89, range 0.0-22) versus 4.58 years (SD=4.77, range 0.0-19) and not significantly different (p= 0.295). Mean dose of pramipexole in ICRB positive group was 1.98 mg (SD=1.74, range 0.0-4.5mg) versus 0.93 mg (SD=1.44, range 0.0-4.5) in non ICRB group and p value was <0.001. The mean duration for pramipexole treatment in ICRB positive group was 1.66 years (SD=2.05, range 0.0-8.0years) and was significantly longer than in the negative group of 0.82 years (SD=1.49, range 0.0-7.0 years) (p < 0.001). The mean ropinirole dose in ICRB positive group was 0.73 mg (SD=1.81, range 0.0-8.0) versus 0.80 mg (SD=1.97, range 0.0-12) in ICRB negative group and was not significantly different (p =0.80). The mean duration for ropinirole treatment was 0.70 years (SD=1.90, range 0.0-11) in ICRB positive group versus 0.67 (SD=1.66, range 0.0-8.0) in non ICRB group and not significantly different (p =0.9).
Figure 3. LEDD comparison

![LEDD Comparison Graph](image)

Figure 4. Dopamine agonist dose comparison:

![Dopamine Agonist Dose Comparison Graph](image)
Table 1. Clinical characteristics of all patients and those with and without ICRBs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICRB(n=99)</th>
<th>Non- ICRB(n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>74(74.7)</td>
<td>75(75%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.58</td>
<td>59.58</td>
<td>0.001</td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>46.12</td>
<td>51.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of disease(years)</td>
<td>8.46</td>
<td>8.14</td>
<td>0.6</td>
</tr>
<tr>
<td>L-dopa Dose (mg)</td>
<td>363.42</td>
<td>327.45</td>
<td>0.2</td>
</tr>
<tr>
<td>L-dopa Duration (years)</td>
<td>5.3</td>
<td>4.58</td>
<td>0.2</td>
</tr>
<tr>
<td>Pramipexole Dose (mg)</td>
<td>1.98</td>
<td>0.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pramipexole duration(years)</td>
<td>1.66</td>
<td>0.82</td>
<td>0.001</td>
</tr>
<tr>
<td>Ropinirole Dose(mg)</td>
<td>0.73</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Ropinirole duration(years)</td>
<td>0.7</td>
<td>0.67</td>
<td>0.9</td>
</tr>
<tr>
<td>Amantadine dose(mg)</td>
<td>33.33</td>
<td>29</td>
<td>0.6</td>
</tr>
<tr>
<td>Entacapone dose(mg)</td>
<td>163.63</td>
<td>116</td>
<td>0.3</td>
</tr>
<tr>
<td>Pacitane dose (mg)</td>
<td>1.54</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Pacitane duration(years)</td>
<td>1.44</td>
<td>1.42</td>
<td>0.9</td>
</tr>
<tr>
<td>LEDD (mg)</td>
<td>603.38</td>
<td>451.65</td>
<td>0.001</td>
</tr>
<tr>
<td>Rasagiline dose(mg)</td>
<td>0.14</td>
<td>0.18</td>
<td>0.5</td>
</tr>
<tr>
<td>Rasagiline duration(years)</td>
<td>0.16</td>
<td>0.16</td>
<td>0.9</td>
</tr>
</tbody>
</table>
**Frequency and pattern of ICRBs:**

Total 199 PD patients participated in the study of which 99 patients were ICRBs positive. Compulsive gambling was present in 6 (6.1%), hypersexuality in 21(21.2%), compulsive buying in 26(26.3%) patients, compulsive eating in 19(19.2%), and punding 43(43.4%) of patients. Other ICRBS such as, compulsive medication use was seen in 7 patients(7.1%). Hyperphagia was present in 1 patient(1%), IED(impulsive eating disorder) was present in 7 patients (7.1%), premorbid ICRB was seen in 18 patients (18.2%), which exacerbated after starting DRT in 11 of them(11.1%).

**Genotypic characteristics:**

Genotype distributions of the three variants in the patients and control subjects were all in Hardy-Weinberg equilibrium. Genotype distributions for various SNPs among the patients is shown as follows:

**Dopamine receptor D3 (DRD3)rs6280**: CC, CT and TT genotype was present in 16.2%,51.5% and 32.3 % patients respectively in ICRB positive patients when compared to 19%,33% and 47% patients respectively in ICRB negative patients group. CT genotype was more common in ICRB positive group versus ICRB negative group (p=0.03).
Table 2. Genotype distribution of Dopamine receptor D3 (DRD3) rs6280:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>ICRB</th>
<th>Non ICRB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC count</td>
<td>16</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>CC % within group</td>
<td>16.2%</td>
<td>19.0%</td>
<td>17.6%</td>
</tr>
<tr>
<td>CT count</td>
<td>51</td>
<td>33</td>
<td>84</td>
</tr>
<tr>
<td>CT % within Group</td>
<td>51.5%</td>
<td>33.0%</td>
<td>42.2%</td>
</tr>
<tr>
<td>TT count</td>
<td>32</td>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>TT % within Group</td>
<td>32.3%</td>
<td>48.0%</td>
<td>40.0%</td>
</tr>
</tbody>
</table>

Figure 5.

![Pie chart showing genotype distribution of DRD3 (rs 6280) in ICRB group](image-url)
Serotonin receptor (HTR2A) rs6313: CC, CT and TT genotype was present in 30.3%, 55.6% and 14.1% patients respectively in ICRB positive group as compared to 35%, 46% and 19% patients respectively in non ICRB group. There was no significant genotypic difference between the two groups (p = 0.3).

Table 3. Genotype distribution of Serotonin receptor (HTR2A) rs6313:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>ICRB</th>
<th>Non ICRB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC count</td>
<td>30</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>CC % within group</td>
<td>30.3%</td>
<td>35.0%</td>
<td>32.7%</td>
</tr>
<tr>
<td>CT count</td>
<td>55</td>
<td>46</td>
<td>101</td>
</tr>
<tr>
<td>CT % within Group</td>
<td>55.6%</td>
<td>46.0%</td>
<td>50.8%</td>
</tr>
<tr>
<td>TT count</td>
<td>14</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>TT % within Group</td>
<td>14.1%</td>
<td>19.0%</td>
<td>16.6%</td>
</tr>
</tbody>
</table>
Figure 7

HTR2A in ICRB GROUP

Figure 8.

HTR2A (rs6313) in ICRB versus non ICRB group

22
Glutamate receptor (GRIN 2B) rs1806201: AA, AG and GG genotype was present in 26.3%, 46.5% and 27.3% patients respectively in ICRB positive group as compared to 17%, 49% and 34% patients respectively in non ICRB group. There was no significant genotypic difference between the two groups (p = 0.2).

Table 4. Genotype distribution of Glutamate receptor (GRIN 2B) rs1806201:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>ICRB</th>
<th>Non ICRB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA count</td>
<td>26</td>
<td>17</td>
<td>43</td>
</tr>
<tr>
<td>AA % within group</td>
<td>26.3%</td>
<td>17.0%</td>
<td>21.6%</td>
</tr>
<tr>
<td>AG count</td>
<td>46</td>
<td>49</td>
<td>95</td>
</tr>
<tr>
<td>AG % within Group</td>
<td>46.5%</td>
<td>49.0%</td>
<td>47.7%</td>
</tr>
<tr>
<td>GG count</td>
<td>27</td>
<td>34</td>
<td>61</td>
</tr>
<tr>
<td>GG % within Group</td>
<td>27.3%</td>
<td>34.0%</td>
<td>30.7%</td>
</tr>
</tbody>
</table>

Figure 9.
Figure 10. GRIN 2B rs1806201 in ICD versus non ICRB group.
Discussion

This was 1st study from Indian subcontinent evaluating the risk of genetic polymorphisms for developing ICRB impulse control disorders in PD during DRT. In our study we found significant allelic difference in PD patients with ICRB as compared to without ICRB. DRD3 rs6280 CT genotype was significantly more common in PD ICRB group when compared to ICRB negative group. Clinical characteristics that were significantly associated with ICRBs as compared to non ICRB group were younger age at study, younger age of onset of disease, higher dose of pramipexole, higher duration of exposure to pramipexole duration and total LEDD dose. Fewer patients were on ropinirole and that may explain the lack of association with its dose or duration of exposure. Multivariate analysis of clinical factors revealed that only dopamine agonist use was associated with ICRB.

The exact mechanism by which dopamine agonist use triggers impulsive behavior is not well established. Dopamine derived from exogenous levodopa (D1, D2 receptor agonist) leads to amelioration of the motor symptoms of the PD without any behavioral side effects. Non ergot dopamine agonists activate D2 and D3 receptors. It is well known that stimulation of D2 receptors leads to amelioration of the motor symptoms. It is speculated that the stimulation of D3 receptors, which are predominantly distributed in the ventral striatum, might lead to impulsive behavior. Dopaminergic projection from the ventral tegmental area via the nucleus accumbens and ventral striatum to the ventromedial prefrontal and orbitofrontal cortex, is a major anatomical substrate for the reward learning. D3 receptors located in the ventral striatum are an important component of this reward learning system. Alteration in this reward learning system has been proposed to lead to impulse control disorders (33). Christopher et al. postulated two distinct response types in dopamine neurons. Brief, phasic activations
occurred monotonically with increasing reward probability, whereas slower, more sustained activations developed with increasing reward uncertainty. Under normal conditions, phasic release of dopamine from the ventral tegmental area to the nucleus accumbens occurs at the time of anticipating a reward and receiving an unanticipated reward. Conversely, phasic suppression occurs when a reward is expected but not received. In PD, impaired dopaminergic stimulation at the D3 receptors may result in a loss of the normal physiologic suppressing response when reward is not received and loss of hedonic (pleasurable) effect. This may generate the compulsion to do the particular act repeatedly to receive gratification. Lee et al. reported that homozygous variant Ser9Gly (AA genotype) of DRD3 is possibly associated with lower binding affinity to dopamine and seemed to be associated with two-fold increase in the risk of PG and ICRBs in PD patients (8). In the present study we demonstrated heterozygous variant Ser9Gly genotype can also increase the risk to develop PD ICRB. Seymour in 2012 highlighted converging behavioral and neural evidence that serotonin modulates (is necessary for) distinct behavioral and anatomical components of decision-making. Both neurotransmitter systems (serotonin and dopamine) may play opponent roles as dopamine activity can be reduced by serotonin in certain brain regions and serotonin decreases dopamine release in the nucleus accumbens and the striatum. Lee et al found a possible contribution of genetic variation in the serotonin receptor (HTR2A) and susceptibility to ICRB in PD. In this study we did not find any significant difference in genetic polymorphism for serotonin receptor (HTR2A) between ICRB positive and negative PD patients.

In our study we could not find significant association of glutamate receptor polymorphism and ICRBs. N-methyl-D-aspartate (NMDA) receptors strongly influence dopaminergic function, it is conceivable that the glutamatergic system is also involved in
decision-making. Ness et al (34) examined whether polymorphisms in the N-methyl-D-aspartate receptor 2B subunit gene (GRIN2B) influence decision-making using the Iowa Gambling Task (IGT). They found that two SNPs in exon 13, rs1806191 (H1178H) and rs1806201 (T888T) showed the strongest association with aspects of IGT performance and concluded that healthy individuals with certain GRIN2B variations respond differently to ambiguous conditions, possibly by altered perception of wins and losses. In a study done by Lee et al, they found that CC genotype of GRIN2B c.366C>G were more frequent in patients with ICRB PD patients as compared to non ICRB group. However, we could not identify a similar risk from these polymorphisms in the glutamate receptor.
Conclusion

In this study on genetic risk factors for the development of ICRBs in Indian PD patients on DRT, we found that a heterozygous DRD3 polymorphism (rs6280) was associated with a higher risk for ICDRB. Genetic polymorphism involving DRD3 receptor, even in the heterozygous form, may affect dopaminergic signalling in the ventral striatum and interfere with the reward learning system to cause ICRBS during dopamine agonist treatment. There was no risk posed to Indian patients by the serotonin receptor (HTR2A) rs6313polymorphisms and glutamate receptor (GRIN 2B) rs1806201 polymorphisms that were tested in this study.
Bibliography:


ANNEXURES

PROFORMA

“Dopamine receptor (DRD3) polymorphism (rs6280) is associated with risk for Impulse Control Disorders and related behaviors in Parkinson's disease in India”

Serial No:
Name:
Age: Sex: male/female Hospital no:
Level of Education Marital status:
Address:
Telephone No: occupation:
Age at onset: year of onset: duration of disease
Side of onset: Stable/fluctuating:
Type of PD: sporadic/familial No of family members affected:
Duration of drug therapy

Medication:
Levodopa
Levodopa + agonist
Levodopa + Amantadine
Agonist only
Levodopa + agonist + (artane or Amantadine)
LEDD
DA Dose
**Stage of disease:**

- **H&Y (ON):**
- **OFF:**

**UPDRS (at ON):**

Premorbid personality:

Premorbid habits:

- **Alcohol:** yes/no  years of intake:  Occasional/moderate/severe/dependent
- **Smoking:** yes/no  Pan chewing: yes/no

**QOL- PQDRS**

<table>
<thead>
<tr>
<th>MMSE</th>
<th>mMIDI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>I</td>
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<tr>
<td>II</td>
<td>II</td>
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<tr>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>V</td>
<td>V</td>
</tr>
</tbody>
</table>

**Impulse control disorder**

1. Problem/pathological gambling  yes/no
2. Compulsive shopping  yes/no
3. Compulsive eating  yes/no
4. Hyper sexuality  yes/no
5. Punding  yes/no
6. Compulsive medication use  yes/no

**Genetic association**

1. **DRD2 Taq1A**  yes/no
2. **DRD3p.S9G**  yes/no
3. **GRIN2B c.366C>G**  yes/no
   - **c.2664C>T**  yes/no
   - **c.200T>G**  yes/no
4. **Serotonin transporter gene (5HTTLPR)**  yes/no
## Mini-Mental State Examination (MMSE)

Patient's Name: ____________________________ Date: _______________

**Instructions:** Ask the questions in the order listed. Score one point for each correct response within each question or activity.

<table>
<thead>
<tr>
<th>Maximum Score</th>
<th>Patient’s Score</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>“What is the year? Season? Date? Day of the week? Month?”</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>“Where are we now: State? County? Town/city? Hospital? Floor?”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient’s response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: ________</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>“I would like you to count backward from 100 by sevens.” (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: “Spell WORLD backwards.” (D-L-R-O-W)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“Earlier I told you the names of three things. Can you tell me what those were?”</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Repeat the phrase: ‘No ifs, ands, or buts.’”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“Take the paper in your right hand, fold it in half, and put it on the floor.” (The examiner gives the patient a piece of blank paper.)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Please read this and do what it says.” (Written instruction is “Close your eyes.”)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Make up and write a sentence about anything.” (This sentence must contain a noun and a verb.)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Please copy this picture.” (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)</td>
</tr>
</tbody>
</table>

30 TOTAL

(Adapted from Rovner & Folstein, 1987)
Jay Modified Minnesota Impulsive Disorders Interview (mMIDI)

Module 1: Buying Disorder Screen
1. Do you or others think that you have a problem with buying things too often or with spending too much money? ☐ Yes (score = 1), complete Questions 2 and 3 below  ☐ No (score = 0), end this module and go to the next module
2. Do you ever experience an irresistible urge or uncontrollable need to buy things or mounting tension that can only be relieved by buying?

<table>
<thead>
<tr>
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<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td>__________</td>
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</table>

3. Has problem buying led to social, marital, family financial or work problems or caused you to experience significant distress?

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<tr>
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<th>3</th>
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</thead>
<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td>__________</td>
</tr>
</tbody>
</table>

Module 2: Compulsive Gambling
1. Do you gamble? ☐ Yes (score = 1), complete Questions 2 and 5 below  ☐ No (score = 0), end this module and go to the next module
2. Do you or others think that you have ever had a problem with gambling?

<table>
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<tr>
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<th>3</th>
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<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td>__________</td>
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</tbody>
</table>

3. Have you ever felt guilty about the way you gamble or what happens when you gamble?

<table>
<thead>
<tr>
<th></th>
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<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td>__________</td>
</tr>
</tbody>
</table>
4. Have you been preoccupied with gambling or obtaining money to gamble?

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td></td>
</tr>
</tbody>
</table>

5. Have you gambled larger amounts of money or over longer period of time than you intended to?

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<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td></td>
</tr>
</tbody>
</table>

**Module 3: Compulsive Sexual Behaviour Screen**

1. Do you or others that you know think that you have a problem with being overly preoccupied with some aspect of your sexuality or being overly sexually active?
- ☐ Yes (score = 1), complete Questions 2 and 4 below
- ☐ No (score = 0), end this module and go to the next module

2. Do you have repetitive sexual fantasies which you feel are out of your control or cause you distress?

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<thead>
<tr>
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<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td></td>
</tr>
</tbody>
</table>

3. Do you have repetitive sexual urges which you feel are out of your control or cause you distress?

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<thead>
<tr>
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<th>0</th>
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<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td></td>
</tr>
</tbody>
</table>

4. Do you engage in repetitive sexual behavior which you feel is out of control or causes you distress?:

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<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td></td>
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</tbody>
</table>
Module 4: Compulsive Eating Screen

1. Do you or others that you know think that you have a problem with being, overly preoccupied with food or actively overeating?
   □ Yes (score = 1), complete Questions 2 and 4 below
   □ No (score = 0), end this module and go to the next module

2. Do you have repetitive fantasies about eating which are out of your control or cause you distress?
   0  1  2  3
   No  Rarely  Occasionally  Frequently

3. Do you have repetitive urges to eat which you feel are out of your control or cause you distress?
   0  1  2  3
   No  Rarely  Occasionally  Frequently

4. Do you engage in constant or overly frequent eating which you feel is out of control or causes you distress?
   0  1  2  3
   No  Rarely  Occasionally  Frequently

Module 5: Punding Behaviour Screen

1. Do you find yourself fascinated with or performing repetitive and/or mechanical tasks such as taking apart and putting back together simple mechanical objects, or picking at oneself, or sorting and arranging common objects?
   □ Yes (score = 1), complete Questions 2 and 4 below
   □ No (score = 0), end this module and go to the next module

2. Do you collect things such as rocks, coins or books and line them up together?
   0  1  2  3
   No  Rarely  Occasionally  Frequently
3. Do you disassemble mechanical things such as doorknobs, watches, radios or other objects and then re-assemble them?

<table>
<thead>
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<th>3</th>
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<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td></td>
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</table>

4. Do you find performing such repetitive tasks comforting?

<table>
<thead>
<tr>
<th></th>
<th>0</th>
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<th>3</th>
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<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
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</table>

5. Do you get frustrated if you are unable to perform such repetitive tasks?

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
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</table>

6. Have you ever taken amphetamines?

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<thead>
<tr>
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<tbody>
<tr>
<td>No</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
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</tbody>
</table>
Diagnostic Criteria for Various Impulse-Control Disorders

Diagnostic Criteria for Pathological Gambling (DSM IV)

A. Persistent and recurrent maladaptive gambling behavior as indicated by five or more of the following:

1. Is preoccupied with gambling (eg preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble)

2. Needs to gamble with increasing amounts of money in order to achieve the desired excitement

3. Has repeated unsuccessful efforts to control, cut back or stop gambling

4. Is restless or irritable when attempting to cut down or stop gambling

5. Gambles as a way of escaping from problems or of relieving a dysphoric mood (eg, feelings of helplessness, guilt, anxiety, depression)

6. After losing money gambling, often returns another day to get even (“chasing” one’s losses)

7. Lies to family members, therapist or others to conceal the extent of involvement with gambling

8. Has committed illegal acts such as forgery, fraud, theft, or embezzlement to finance gambling

9. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling

10. Relies on others to provide money to relieve a desperate financial situation caused by gambling

B. The gambling behavior is not better accounted for by a manic episode
**Proposed Diagnostic Criteria for Hedonistic Homeostatic Dysregulation Syndrome Due to DRT Misuse (Giovannoni et al., 2000)**

A. Parkinson’s disease with documented levodopa responsiveness

B. Need for increasing doses of DRT in excess of those normally required to relieve Parkinsonian symptoms and signs

C. Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias despite being “on,” drug-hoarding or drug-seeking behavior, unwillingness to reduce DRT, or absence of painful dystonias

D. Impairment in social or occupational functioning: fights, violent behavior, loss of friends, absence from work, loss of job, legal difficulties, arguments, or difficulties with family

E. Development of hypomanic, manic, or cyclothymic affective syndrome in relation to DRT

F. Development of a withdrawal state characterized by dysphoria, depression, irritability, and anxiety on reducing the level of DRT

G. Duration of disturbance of at least 6 months

**Proposed Diagnostic Criteria for Compulsive Buying (McElroy et al 1994)**

A. Maladaptive preoccupation with buying or shopping, or maladaptive buying or shopping impulses or behavior, as indicated by at least one of the following:
   1. Frequent preoccupation with buying or impulses to buy that is/are experienced as irresistible, intrusive and/or senseless
   2. Frequent buying of more than can be afforded, frequent buying of items that are not needed, or shopping for longer periods of time than intended

B. The buying preoccupations, impulses, or behaviors cause marked distress, are time-consuming, significantly interfere with social or occupational functioning or result in financial problems (eg, indebtedness or bankruptcy)
C. The excessive buying or shopping behavior does not occur exclusively during periods of hypomania or mania
**Proposed Diagnostic Criteria for Pathological Hypersexuality (Voon Vet al., 2006)**

A. The sexual thoughts or behaviors are excessive or an atypical change from baseline marked by one or more of the following:

1. Maladaptive preoccupation with sexual thoughts
2. Inappropriately or excessively requesting sex from spouse or partner
3. Habitual promiscuity
4. Compulsive masturbation
5. Telephone sex lines or pornography
6. Paraphilias

B. The behavior must have persisted for at least one month

C. The behavior causes at least one of the following:

1. Marked distress
2. Attempts to control thoughts or behavior are unsuccessful or result in marked anxiety or distress
3. Are time consuming
4. Interfere significantly with social or occupational functioning

D. The behavior does not occur exclusively during periods of hypomania or mania

F. If all criteria except C are fulfilled, the disorder is subsyndromal