Austin Journal of Clinical Neurology

Open Access

Austin Publishing Group

Special Article - Parkinson's Disease & Movement Disorders

Impulse Control Disorders in Parkinson's Disease: Pathophysiology, Effect of Genetic Polymorphism and Future Research Directions

Bhattacharjee S*

Department of Neurology, Plymouth Hospital NHS Trust, UK

***Corresponding author:** Bhattacharjee S, Department of Neurology, Plymouth Hospital NHS Trust, PL68DH, UK

Received: December 21, 2016; **Accepted:** January 25, 2017; **Published:** January 27, 2017

Abstract

Impulse control disorder is a common non- motor feature observed in Parkinson's disease. Impulse control disorders were reported in up to 13.6% of Parkinson Disease patients. Though there are multiple theories to explain the generation of Impulse control disorders in Parkinson's disease but the most recent theory suggests that it happens due to the overstimulation of Dopamine type 3 (D3) receptor in the limbic area. Though Dopamine Agonists are well known risk factors for impulse control disorders but recently few studies explored the influence of genetic polymorphism in the generation of impulse control disorders. The existing evidences suggest that genetic polymorphism in Dopamine receptor D1, D2, D3 and the N-Methyl D Aspartate receptor GRIN2Bare the risk factors for the development of impulse control disorders in Parkinson's disease. Other genetic polymorphism which were found to be associated with ICDs includes Hydroxytryptamine receptor (HTR2A), Dopa Decarboxylase (DDC) and Dopamine Transporter 1 (DAT1) genes. However, the cumulative dose of Levodopa and the ethnicity probably influence the genetic polymorphism in the development of impulse control behaviours. In future large studies involving multiple genes of the dopaminergic and glutamatergic pathways are needed.

Keywords: Dopamine; Glutamate; Impulse; Disorders; Gene; Polymorphism

Introduction

Impulse Control Disorders (ICD) is characterized by the failure to resist an urge or temptation to perform an act which is detrimental to one self or others. Impulse Control Disorder (ICD) is a common non-motor feature observed with a frequency up to 13.6% in Idiopathic Parkinson's Disease (PD) population [1]. Common ICDs reported in PD includes pathological gambling, hypersexuality, compulsive eating, excessive buying, excessive intake of Levodopa despite dyskinesia (Dopamine dysregulation syndrome) and punding. Pathological gambling and hypersexuality are more commonly reported in male while excessive buying and binge eating are more common in female PD patients [2].

The neurobiology and pathophysiology of impulse control disorders in parkinson's disease

The Nigrostriatal, Mesocortical and Mesolimbic Dopaminergic pathways play a crucial role in the pathophysiology and pathogenesis of ICD in PD. The Mesocortical pathway is a connection between the Ventral tegmentum (VTA) of the midbrain and the prefrontal cortex while the Mesolimbic pathway is a connection between the VTA and Nucleus Accumbens (NA) of the limbic system through amygdala and Hippocampus [2]. The NA is important for the reward system and Amygdala is important for the conditioned response.

The exact mechanism of impulse control disorder in PD is not clear. Long term use of Dopamine agonists, a well- known risk factor for the development of ICD leads to down regulation of D2 receptors expression [2]. Consequently, the PD patients seek higher than normal stimuli to obtain sufficient rewards. The second possible reason will be the greater tonic Dopamine release and reduced phasic release. The tonic Dopamine release occurs with any action of greater uncertainty like gambling etc. The phasic Dopamine release happens when a reward is anticipated and is suppressed when the reward is not granted. The greater tonic release of Dopamine will lead to a relative Dopamine deficit and reduced reward sensation. Another possible cause is the over activity of the brain areas involved in reward based learning and impulse control behaviours. The limbic area including the NA area which controls the reward and emotions have greater concentration of dopamine 3 (D3) receptors. Dopamine agonist drugs preferentially act on these D3 receptors instead of D1/D2 receptors and increases the risk of ICDs. D1 and D2 receptors that are more abundant in Caudate nucleus and Putamen are more selectively targeted by Levodopa. As the Caudate Nucleus and Putamen have no major role in impulse control and reward seeking behaviours the risk of ICD with Levodopa is much less. However, ICD is a complex process emanating from the interaction among dopaminergic, Glutamatergic, Serotonergic and Opioid pathways and there are conflicting evidences about the role of various neurotransmitter pathways in the pathogenesis of ICD.

Impact of Genetic polymorphism on the risk of developing ICD in PD and the review of related literature

The influence of genetic polymorphism on ICD in patients with PD is poorly studied. Genetically, the two most widely studied

Bhattacharjee. © All rights are reserved

Citation: Bhattacharjee S. Impulse Control Disorders in Parkinson's Disease: Pathophysiology, Effect of Genetic Polymorphism and Future Research Directions. Austin J Clin Neurol 2017; 4(1): 1100.

Table 1: Literature review on genetic variations and the risk of Impulse Control Disorders in Parkinson's disease patients.

Authors (with references)	Receptor types and subtypes	Gene/polymophism	Risk of Impulse control disorders (if statistically significant)
[3]	Dopamine receptor type (DRD)1	DRD1rs4867798, rs4532	Increased
	Dopamine receptor type 2	DRD2/ANKK1 rs1800497	
	Glutamate receptor (GRIN) 2B	GRIN2B rs7301	
	Ankyrin repeat and kinase domain containing 1 (ANKK1) enzyme works closely with DRD2	Ankyrin repeat and kinase domain containing 1 (ANKK1)	
[4]	Dopamine receptor type (DRD)3	DRD3 p.S9G(rs6280) CT*	Increased
	Glutamate	GRIN2B	No association
[6]	Opioid Receptor Kappa (OPRK1)	OPRK1 rs702764: TC & rs702764: CC	Increased
	Hydroxytryptamine receptor(HTR2A) 2A	HTR2Ars6313: GA** & rs6313: AA	increased
	Dopamine	Dopa Decarboxylase (DDC) rs383709: -/AGAG DDC: rs3837091: -/- rs1451375: AA	Increased
	Hydroxytryptamine	Tryptophan Hydroxylase (TPH2) rs7305115	No impact
	Dopamine (DRD2)	rs1800497 G/A	No impact
[7]	Monoamine transporters	Catechol-O-Methyl Transferase (COMT) gene Val158 Met	No impact
[8]	Dopamine receptors 3	DRD3 rs6280	Increased
	Glutamate receptor (GRIN) 2B	GRIN2B rs7301328	Increased
[9]	Hydroxytryptamine (HTR2A) 2A	HTR2Ac.102T>C	Increased in lower dopamine equivalent dose group
[10]	Dopamine	DRD2 Taq1A Dopamine Transporter (DAT1)	No impact
[12]	Glutamate	GRIN2B c.2664C>T genotype AG	Increase risk taking behaviour in Iowa Gambling task

**AG-Adenine and Guanine: *CT-Cytosine and Thymine

pathways in ICD are the Dopaminergic and Glutamatergic pathways. The Dopamine receptors where genetic polymorphism was found to be associated with the increased risk of ICD are D1, D2 and D3 [2] (Table 1). N-Methyl-D -Aspartate (NMDA) is a Glutamate receptor. The NMDA receptor subunit NR2 has 4 subtypes namely GRIN2A, 2B, 2C and 2D. The GRIN 2B is the most important of the NR2 subtypes where single nucleotide polymorphism was found to have an association with the risk of ICD [3]. GRIN 2B is more commonly expressed in Striatum. Other polymorphism which were found to be associated with ICDs include Hydroxytryptamine receptor (HTR2A), Dopa Decarboxylase (DDC) and Dopamine Transporter 1 (DAT1) genes.

Krishnamoorthy S, et al. found a novel association between the Dopamine receptortype3 (DRD3)p. S9G (rs6280)CT genotype and the impulse control disorders (ICD) trait in a cohort of Parkinson's Disease patients in India [3]. This study included 70 cases of PD with ICD, 100 PD without ICD and 285 controls. It found no association between Glutamate (GRIN 2B) and serotonin (HTR2A) polymorphism and the generation of ICD. This study showed that enhanced D3 receptor affinity due to the gain of function could impair the reward-risk assessment in the mesolimbic pathways in the DRD3p. S9G (rs6280) CT genotype. However, the study was performed in a predominantly South Indian population. A large prospective study concluded that the role of DRD3 polymorphism on the risk of ICD in the Caucasian PD population is low [5]. Kraemmer J, et al. conducted a comprehensive study on 15 candidate genes involved in the metabolism of the monoaminergic system. In addition to the Hydroxytryptamine, Dopamine receptor genes this study also involved Alpha 2 adrenergic receptor (ADRA2C) gene, Dopamine Transporter gene (*SLC6A3*) and Catechol -O-Methyltransferase gene. Kraemmer J, et al. suggested the role of Opioid Receptor Kappa (OPRK1) rs702764: TC genotype with increased risk of ICD in the whole PD population [6]. However, among the Dopamine Agonist users, Opioid receptor Kappa 1 (OPRK1) genotypes rs702764: TC & rs702764: CC, Hydroxytryptamine receptor 2A (HTR2A) genotype rs6313: GA & rs6313: AA, Dopa Decarboxylase (DDC) genotype rs383709: -/AGAG, rs3837091: -/- and rs1451375: AA all increased the risk of ICD in PD. This study could identify no significant association of ICD with the *ADRA2C* and *DRD2* variants. Napier TC, et al. reviewed the existing literature and found no association between the COMT gene Val158 Met or Dopamine Transporter gene SLC6A4 gene and ICD in PD [7].

A study from Malaysia revealed DRD1 rs4867798, DRD1 rs4532, DRD2/ANKK1 rs1800497 and GRIN2B rs7301 were associated with an increased risk of developing ICD among 91 PD patients [3]. This study found no role of genetic polymorphism in D4 or D5 receptors in the development of ICD though D4 receptor polymorphism was previously blamed for Schizophrenia and addiction in non-PD population. A South Korean group of researchers genotyped variants of the DRD3 p.S9G, DRD2 Taq1A, GRIN2B c.366C>G, c.2664C>T and c.-200T>G, and the promoter region of the serotonin transporter gene (5-HTTLPR) to analyze their association with ICD. They found that Variants of DRD2 and 5-HTTLPR were not associated with the risk of developing ICD but the DRD3 rs6280 or GRIN2B rs7301328 variant were independent risk factor for the ICD [8]. Another Korean group suggested a possible contribution of genetic variation in the HTR2A to the susceptibility to impulse control and repetitive behaviours in PD patients. The impact of the c.102T>C variant was significantly enhanced in the lower Levodopa Equivalent Dose (LED) group, increasing the risk of ICDs by 2.8 and 6.9 times in CT and TT

carriers, respectively whereas in the higher-LED group the c.102T>C variant had no statistically significant effect on the development of ICDs [9]. There is reportedly a possible synergistic effect of *HTR2A* and Serotonin Transporter gene (5-HTTLPR) variants on the susceptibility to heroin dependence in non PD population but this study failed to find any significant synergistic action in PD patients. Though COMT Met/Met genotype may be a genetic risk factor that contributes to the development of both gambling and drinking problems in normal population but an Italian study found Variants of COMT not to be associated with the risk of developing ICD in PD patients. The same study found no association among DRD2 Taq1A and DAT1 polymorphism and the risk of developing ICDs in PD patients [10]. Hoenicka J, et al. analysed the role of addiction related gene Ankyrin repeat and kinase domain containing 1 (ANNK1) in PD patients with ICD and found no association between the Taq1A SNP and ICD in PD patients [11]. However, when PD patients were categorized according the diagnosis of any ICD with a potentially addictive reinforcement, ANNK1-TaqIA genotype showed significant association. Recently Rajan R, et al. showed that PD patients with GRIN2B c.2664C>T genotype 'AG' preferred the high-frequency-of-gain disadvantageous deck of the Iowa Gambling Task (test for ICD) while those with at least one 'C' allele in the DRD3 p.S9G gene preferred the low-frequency-of-gain advantageous deck of the Iowa Gambling Task test [12].

Limitations and future directions for genetic research for ICD in PD patients

Even in general population genetic factors can explain only up to 20% on inheritance in cases of pathological gambling [13]. There are a lot of shortcomings of the current ICD studies involving genetic factors. The ICD needs strong defining criteria. ICD in PD is not only restricted to pathological gambling or binge eating or hyper-sexuality but cyber addiction can also be an ICD behaviour in PD patients [14]. However cyber addiction or excessive creative addiction as ICD has not yet been studied in detail. It is not always easy to draw a line between the accentuation of impulsivity and the development of ICD. Another major problem with ICD is that lack of self-reporting by the patients. A recent study found that self- reporting by the PD patients in ICD is only 2% whereas the investigators found around 27% prevalence in PD patients [15]. Moreover, the selection of control in ICD must be strict for all genetic studies. ICD is generally taken a as a hyperdopaminergic state so both the test and the control group must have the same Dopaminergic levels. In fact, almost all Dopamine agonists have been implicated in the generation of ICD. The effect of genetic polymorphism can only be accurately assessed when the controls are also the PD patients treated with similar doses of Dopamine agonists as the cases with ICD. Several polymorphisms influencing impulsive behaviour have been discovered, but it remains unclear whether synergistic or antagonistic effects between the specific polymorphisms exist or not. A South Korean study showed that genetic polymorphism is significant in the generation of ICD in lower Levodopa equivalent dose PD group but not in the higher dose group. There seems to be a relationship between the dose of Levodopa and genetic polymorphism which is not yet studied. Moreover, there has been clear variability of genetic polymorphism and its effects on the generation of ICD in multiple ethnic groups [13]. Finally genetic polymorphism study must be conducted in association with functional neuroimaging to improve the accuracy of ICD risk assessment.

Conclusion

The most commonly described polymorphisms associated with ICD are found in the Dopamine receptor D1, D2, D3 and NMDA receptor GRIN2B. A large, well-designed whole genome association study of genes involving the Dopaminergic and Glutamatergic pathways would be helpful to reveal any unknown genetic factors involved in the pathogenesis of ICD.

References

1. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010; 67: 589-595.
2. Marechal E, DenoiseuxB, Thys E, Crosiers D, Pickut B, Cras P. Impulse control disorders in Parkinson's disease: an overview from neurobiology to treatment. J Neurol. 2015; 262: 7-20.
3. Abidin SZ, Tan EL, Chan SC, Jaafar A, Lee AX, Abd Hamid MH, et al. DRD and GRIN2B polymorphisms and their association with the development of impulse control behaviour among Malaysian Parkinson's disease patients. BMC Neurol. 2015; 15: 59.
4. Krishnamoorthy S, Rajan R, Banerjee M, Kumar H, Sarma G, Krishnan S, et al. DopamineD3 receptor Ser9Gly variantis associated with impulse control disorders in Parkinson's disease patients, Park. Relat. Disord. 2016; 30: 13-17.
5. McGuire V, Van Den Eeden SK, Tanner CM, Kamel F, Umbach DM, Marder K, et al. Association of DRD2 and DRD3 polymorphisms with Parkinson's disease in a multi-ethnic consortium. J. Neurol Sci. 2011; 307: 22-29.
6. Kraemmer J, Smith K, Weintraub DL, Guillemot V, Nalls MA, Cormier-Dequaire F, et al. Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. J. Neurol Neurosurg Psychiatry. 2016; 87: 1106-1111.
7. NapierTC, CorvolJC, GraceAA, Roitman JD, Rowe J, Voon V, et al. Linking neuroscience with modern concepts of impulse control disorders in Parkinson's disease. Mov Disord. 2015; 30: 141-149.
8. Lee JY, Lee EK, Park SS, Lim JY, Kim HJ, Kim JS, et al. Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. Mov Disord. 2009; 24: 1803-1810.
9. Lee JY, Jeon BS, Kim HJ, Park SS. Genetic variant of HTR2A associates with risk of impulse control and repetitive behaviors in Parkinson's disease. Parkinsonism Relat Disord. 2012; 18: 76-78.
10. Vallelunga A, Flaibani R, Formento-Dojot P, Biundo R, Facchini S, Antonini A, et al. Role of genetic polymorphisms of the dopaminergic system in Parkinson's disease patients with impulse control disorders. Parkinsonism Relat Disord. 2012; 18: 397-399.
11. Hoenicka J, García-Ruiz PJ, Ponce G, Herranz A, Martínez-Rubio D, Pérez-Santamarina E, et al. The addiction-related gene ANKK1 in Parkinsonian patients with impulse control disorder. Neurotox Res. 2015; 27: 205-208.
12. Rajan R, Krishnamoorthy S, Krishnan S, Sarma G, Kishore A. A Gene for Risk Taking: Effect of Genotypic Variants on Decision Making, Response Inhibition and Impulsivity in Parkinson's Disease. Neurology. 2016; 86: 325.
13. Bhattacharjee S, Talbot J, Vijayashankar P. Dopamine D3 receptor Ser9Gly variant is associated with impulse control disorders in Parkinson's disease patients. Parkinsonism Relat Disord. 2016; 30: 13-17.
14. Cormier F, Julia Muellner J, Corvol JC. Genetics of impulse control disorders in Parkinson's disease. J Neural Transm.2013; 120: 665-671.
15. Perez-Lloret S, Rey MV, Fabre N, Ory F, Spampinato U, Montastruc JL, et al. Do Parkinson's disease patients disclose their adverse events spontaneously. Eur J Clin Pharmacol. 2012; 68: 857-865.