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Review

Current Data on the Genetic Background of Impulse Control Disorders in Parkinson's Disease

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Abstract

Impulse Control Disorders (ICDs) are increasingly recognized non-motor complications in PD patients with multiple negative consequences for the individual and caregivers. ICDs are frequently observed in PD patients treated with dopaminergic agents, however not all patients develop these behavioral disorders, suggesting that other factors may increase susceptibility for PD-ICDs. This review aims to analyze current knowledge on the genetic background of ICDs. For this narrative review article, we searched PubMed and Scopus databases for peer-reviewed research, review articles, and meta-analyses regarding the role of genetics in ICDs, published in the English language with no time restrictions. References of the selected articles for possible additional articles were also screened in order to include most of the key recent evidence. This review pinpoints the critical role of genes that encode for enzymes, transporters and receptors that participate in the dopaminergic system, in ICD pathogenesis. Glutamate receptor, ionotropic, N-methyl-d-aspartate 2B (*GRIN2B*), involved in the glutamatergic pathway and hydroxytryptamine receptor 2A (*HTR2A*) and tryptophan hydroxylase 2 (*TPH2*) involved in the serotoninergic pathways, are also highlighted as important risk factors, as well as Opioid receptor kappa 1 (*OPRK1*) and Opioid receptor Mu 1 (*OPRM1*) that participate in the opioid system. Early recognition of genetic factors that increase susceptibility for ICDs in PD patients is awaited to increase diagnostic accuracy and expedite individualized treatment.

Keywords: Parkinson's disease; gene; dopamine; pathway; polymorphism; receptor; pathogenesis; serotonin; opioid; glutamine

1. Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder with a prevalence of about 1% in people over 60 years of age to about 4% in people over the age of 85 [1]. It is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies (LBs) in the surviving neurons. The motor symptomatology of the disease including resting tremor, bradykinesia, rigidity, postural instability, as well as its responsiveness to L-dopa therapy, are well known. However, the disease is also characterized by non -motor symptoms which usually arise before the diagnosis of the disease [2–4].

Impulse Control Disorders (ICDs) are an increasingly recognized non-motor complication in PD with multiple social, financial or legal consequences for the individual, as well as caregivers. They are defined as an inability to resist the impulse, drive or temptation to engage in repetitive, excessive and compulsive behaviors, despite their possible negative effects. ICDs include, among others, compulsive eating, shopping or medication use, pathologic gambling, hypersexuality and punding

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[5]. The prevalence of ICDs in PD patients varies from 3.5 to 42.8%, probably due to different study designs, assessment tools or ethnic background (5). Notably, PD patients with ICDs suffer more frequently from neuropsychiatric comorbidities, such as depression or anxiety and PD patients with multiple ICDs have been found to experience more severe dyskinesia problems [6]. Interestingly, ICDs are frequently observed in PD patients treated with dopaminergic agents, especially dopamine agonists [5]; however not all patients develop these behavioral disorders, suggesting that clinical, genetic or environmental factors may also have a crucial role in the pathogenesis of ICDs. Early recognition of these factors could improve diagnostic accuracy and lead to individualized therapeutic interventions. Recent data show that specific variants in genes implicated in different pathways such as dopaminergic, glutaminergic, serotoninergic etc may play a pivotal role in the genetic susceptibility of an individual to develop ICDs. This review discusses the role of a number of genes that have been found to participate in the pathogenesis of ICDs in PD patients in an attempt to elucidate the genetic background of these behavioral complications that have multiple personal, social and economic consequences (Table 1).

Table 1. Genes and pathways implicated in PD-ICDs.

Gene	Chromosome	Variant	Main pathway affected	Reference
DRD1	5q35.1	rs4532, rs4867798, rs5326	Dopaminergic pathway	[7–9]
DRD2	11q22-23	rs1800497, rs6275, rs12364283, rs1076560	Dopaminergic pathway	[8,10,11]
DRD3	3q13.3	rs6280	Dopaminergic pathway	[12]
DRD4	11p15.5	VNTRs (DRD4 7+)	Dopaminergic pathway	[13]
DDC	7p12.2-p12.1	rs1451375 rs3837091 rs4490786	Dopaminergic pathway	[9,14,15]
SLC22A1	6q25.3	rs628031	Dopaminergic pathway	[16]
DBH	9q34.2	rs1611115	Dopaminergic pathway	[11]
GRIN2B	12p13.1	rs7301328	Glutaminergic pathway	[8,17]
HTR2A	13q14–q21	rs6313	Serotoninergic pathway	[18]
TPH2	12q21.1	rs4290270, rs4570625	Serotoninergic pathway	[16]
OPRK1	8q11.23	rs702764	Opioid pathway	[9,15]
OPRM1	6q24–q25	rs677830, rs1799971	Opioid pathway	[15,19]
LRRK2	12q12	rs34637584	unknown	[20]
SNCA	4q21.3-q22	unknown	unknown	[21]
FBXO7	22q12-q13	c.1162C>T, c.80G>A	unknown	[22]

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GBA	1q21	unknown	unknown	[23]
APOE	19q13.32	*APOE* ε4 allele	unknown	[24]
BDNF	11p13–14	rs6265	unknown	[11]
ACE	17q23.3	rs4646994	unknown	[11]
NOS1	12q24.2-q24.31	rs2682826	unknown	[16,25]

2. Methods

For this narrative review article, we searched PubMed and Scopus databases for peer-reviewed research, review articles, and meta-analyses regarding the role of genetics in ICDs in PD patients, with no time restrictions. The keywords used were "Parkinson's disease", "impulse control disorders", "compulsive eating", "compulsive shopping", "compulsive medication use", "pathologic gambling", "hypersexuality", "punding" "gene", "genetic", "gene polymorphism", "SNP", "genetic variant" "genotype", "allele", "mutation", "mutation carriers", "familial PD", "sporadic PD", "risk factor", "genetic susceptibility", in various combinations. We also screened the references of the selected articles for possible additional articles to include most of the key recent evidence. Regarding the inclusion criteria, all studies were in the English language, performed on humans, and referred to genetics in PD-ICDs. Studies were excluded when the title and/or the abstract were not compatible with the aim of this narrative review.

3. Results and Discussion

3.1. Genes Involved in the Dopaminergic Pathway

Recent data indicate that the dopaminergic pathway is not only involved in PD pathogenesis but also in ICDs. Such behavioral addictions are frequently associated with dopamine agonist therapy of PD patients overstimulating the reward-seeking mesolimbic pathway [26]. A number of genes that encode for enzymes, transporters, and receptors that participate in dopamine synthesis, transport, degradation and signaling have been found to be associated with the development of ICDs in PD patients [9].

3.1.1. DRD1

Dopamine is synthesized in the dopaminergic neurons from Tyrosine. Levodopa produces dopamine via dopa decarboxylase (DDC). Dopamine binds to dopamine receptors on postsynaptic neurons or glial cells. There are five known dopamine receptors (DRs) subtypes; DR1 and DR5 which act as D1-like receptors and DR2, DR3 and DR4 which act as D2-like receptors. D2-like receptors have a 10- to 100-fold greater affinity for dopamine compared to the D1-like receptors. Moreover, DR1 and DR2 are the most abundant DR subtypes [27].

Dopamine receptor D type 1 (*DRD1*) gene is located on chromosome 5q35.1, has two exons and the encoded protein has 446 amino acids. The DR1 receptor is highly expressed in brain, especially in the caudate-putamen, the nucleus accumbens, the substantia nigra pars reticulata, as well as in the cerebral cortex, however it has lower expression in peripheral tissues [27].

The *DRD1* rs4532 and rs4867798 polymorphisms have been associated with ICDs in PD patients. These polymorphisms are located outside of the *DRD1* coding region. Interestingly, the rs4532 polymorphism in the 5′ untranslated region (5′-UTR) has previously been associated with compulsive addictive behavior [7]. In the study of Abidin et al, the T allele was significantly associated with an increased risk of ICDs in PD patients [8]. The *DRD1* rs4532 polymorphism has also been associated

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with neuropsychiatric diseases, like bipolar disorder and attention deficit hyperactivity disorder [28,29]. Regarding the rs4867798 variant, the C allele also increased the risk of ICDs in PD patients. However, the two variants showed no LD In the subsequent haplotype-based analysis. The two variants in the 5′-UTR and 3′- UTR of *DRD1* may affect mRNA stability, the binding site of microRNA (miRNA) or the secondary structure of mRNA, thus may have an impact on DRD1 expression [8].

Another polymorphism in the 5′-UTR of *DRD1*, rs5326 was recently associated with increased risk of ICDs [9] in PD patients, as well. This variant has been previously been associated with a decreased levels of DRD1, impaired cognitive function and an elevated risk of neuropsychiatric disorders [30–32]. Replication of these findings in larger studies are needed in order to draw more definite conclusions.

3.1.2. DRD2/ANKK1

Dopamine receptor D type 2 (*DRD2*) gene is located on chromosome 11q22-23, it consists of eight exons separated by seven introns and encodes for DRD2 which is highly expressed in the basal ganglia, including the caudate-putamen, the substantia nigra pars compacta and the cerebral cortex. DRD2 is a transmembrane G protein-linked receptor which regulates intracellular signalling by inhibiting cAMP synthesis, it is involved in the mesocorticolimbic pathway and affects motor control [27].

The *DRD2*/*ANKK1* rs1800497 polymorphism located close to the coding region of the ankyrin repeat and kinase domain containing 1 gene (*ANKK1*) adjacent to *DRD2* has been extensively studied. This polymorphism, also referred as Taq1A, causes an amino acid change (Glu713Lys) in ANKK1 [10] and occurs in two alleles (A1 and A2); thus, individuals can have 3 possible genotypes: A1/A1, A1/A2 and A2/A2. The Taq1 A (A1) allele has been associated with lower D2 receptor striatal density and reduced D2 binding in the striatum. More specifically, it has been observed that the D2 receptor density can be reduced by up to 30% in A1 carriers, especially in the ventral regions of the caudate and putamen [33,34]. Additionally, this variant has been implicated in conditions like pathological gambling [35], greater ventral striatal reactivity [36], dependence or polysubstance abuse [37]. The *DRD2*/*ANKK1* rs1800497 variant was recently found to be associated with PD-ICDs [8], which is consistent with a previous study in PD-ICD individuals [38]; however other studies have not replicated these findings [17,39]. Interestingly, in another study the rs1800497 Taq1A (A1) polymorphism (A1/ A1 or A1/A21) was found to display better ability to suppress impulsive actions when being on dopamine agonist medication. As the rs1800497 polymorphism produces a Glu713-to-Lys (E713K) substitution, thus a change from an amino acid group with a negatively charged side chain to one with a positively charged residue, a significant protein structure modification may affect the DRD2 expression and increase the risk of neuropsychiatric symptoms in PD patients [40].

Additionally, in the study of Fedosova et al, the TT genotype of the rs6275 substitution in exon 7 of *DRD2* was found to increase ICD risk [11]. The recessive T allele influences the stability and translation of the protein and the TT genotype may lead to overactivation of downstream dopamine receptors and an increased response to the released dopamine [41]. Also, the recessive A allele of rs12364283 substitution was found to be associated with ICD development, as well as the dominant A allele of the rs1076560 substitution in the Intron 6 of *DRD2*, suggesting of a possible role of *DRD2* in ICD development [11]. Further studies examining the role of the *DRD2*/*ANKK1* polymorphisms regarding the risk of ICDs in PD patients should be performed, for more definite conclusions to be drawn.

3.1.3. DRD3

Dopamine receptor D type 3 (*DRD3*) gene is located on chromosome 3q13.3. DRD3 is mainly expressed in the ventral striatum (nucleus accumbens, olfactory tubercle) and the globus pallidus where, with the aid of dopamine transporter, it regulates dopamine release and clearance. DR3 is also closely associated with the limbic system [27].

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The *DRD3* rs6280 polymorphism, a thymine (T) to cytosine (C) change that results to a Ser9-to-Gly substitution, has been examined regarding ICDs. The homozygous glycine variant has greater receptor binding affinity compared to the wild-type homozygous serine variant. Behavioral addictions in PD have been found to be associated with an early onset of PD disease, the rs6280 *DRD3* variant and the type of dopamine agonist used [42]. The role of this *DRD3* polymorphism has been highlighted in different ethnicities [17,43], however with variable results, due to ethnic variances or differences in the age at PD onset of the enrolled patients. Moreover, the rs6280 *DRD3* variant has been implicated in aberrant decision-making under uncertainty in PD patients without active ICDs, suggesting that it could affect impulsivity [12]. Apathy and the rs6280 *DRD3* polymorphism have also been found as interactive risk factors for ICD severity. Apathy has been associated with atrophy of the bilateral putamen and reduced dopamine synthesis in the limbic striatum and PD patients with the *DRD3* risk variant had also reduced dopamine synthesis in the putamen and limbic striatum [44]. Future studies are awaited to further examine the plausible mechanisms underlying the interaction between ICDs and the *DRD3* risk polymorphism, as well as the role of other genetic and environmental factors.

3.1.4. DRD4

Dopamine receptor D type 4 (*DRD4*) gene is located on chromosome 11p15.5 and encodes for DRD4 which is almost expressed in the same forebrain regions as the DR2 receptor and at lower levels in the cerebral cortex. *DRD4* contains a remarkable number of polymorphic regions. There is a hypervariable region in the third cytoplasmic loop with 2–11 imperfect 48 base pair repeats (48-bp VNTR) [27]. Individuals with 7 or longer VNTRs (DRD4 7+) exhibit a higher risk for compulsive or addictive disorders, neuropsychiatric diseases, increased gambling or other similar behaviors [45,46]. It has been proposed that the *DRD4* 7+ VNTR forms heteromers with DRD2, enhancing dopamine-mediated inhibition of glutamate, affecting the tendency for ICDs [47]. Torres et al highlighted the role of the DRD4 7+ polymorphism, as well as other demographic and clinical factors including male gender, early disease onset, moderate and severe dyskinesia symptoms, sleep behavior disorders and psychiatric comorbidities, in the development of ICDs in PD patients [13]. In another study, a gene-drug interaction on gambling behavior was examined. More specifically, carriers of the 4/7 *DRD4* genotype had increased gambling propensity after levodopa administration [46], highlighting the importance of assessing genetic data when investigating the impact of different pharmacological agents on patients' behavior.

3.1.5. DDC

*DDC i*s located on chromosome 7 and contains 15 exons and 14 introns. *DDC* encodes for the aromatic L-amino acid decarboxylase enzyme which is essential for dopamine synthesis via catalyzing the conversion of l-dihydroxyphenylalanine to dopamine. Moreover, DDC is involved in the synthesis of norepinephrine and serotonin via conversion of l-5 hydroxytryptophan to serotonin and l-tryptophan to tryptamine, respectively. Different mRNA transcripts, neuronal and non-neuronal, encoding the same proteins, are produced due to alternative splicing in the 5′ UTR [48]. In a recent study, the presence of allele C in *DDC* rs1451375 intron polymorphism was found to affect ICD susceptibility [14]. Another variant in the promoter region, rs3837091 and genotype AA was also found to be associated with ICDs in the group of patients that were under dopamine treatment [15]. Moreover, the *DDC*-rs4490786 intron polymorphism was also observed to increase the risk of ICDs [9], reinforcing the notion that polymorphisms in *DDC* probably alter the bioavailability of dopamine in the central nervous system (CNS) and regulate dopamine neurotransmission, especially in individuals under dopamine treatment [14].

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3.1.6. SLC22A1

Solute-like carrier family 22 member 1 (*SLC22A1*) gene also known as *OCT1*, is located on chromosome 6q25.3; it consists of 11 exons that span 37 kb [16]. *SLC22A1* encodes the organic cation transporter 1 (OCT1) protein, which transports endogenous compounds, including dopamine, contributing to the distribution and regulation of dopamine levels [49]. Redenšek et al found that carriers of the *SLC22A1* rs628031 AA genotype had higher odds for ICDs, suggesting a new predictive biomarker of ICDs in PD patients receiving dopaminergic treatment [16]. Replication of these results in independent PD cohorts are needed in order to clarify role of this genetic biomarker in the development of ICDs in PD patients treated with dopaminergic agents, facilitating a more individualized approach in PD management.

3.1.7. DBH

Dopamine beta-hydroxylase (*DBH*) gene is located on chromosome 9q34.2. It encodes for a copper-containing enzyme that converts dopamine to norepinephrine. DBH is crucial for neuronal health and its dysfunction has been linked to the development and progression of PD [50].

In a recent study evaluating genetic markers as risk factors for ICDs in PD patients under dopaminergic therapy, the *DBH* rs1611115 polymorphism and particularly the recessive allele C, was associated with ICD development. This substitution has been found to affect enzyme plasma activity [11]. Additional studies for the role of this or other *DBH* variants are needed to improve our understanding regarding the role of this gene in PD-ICDs.

3.2. Genes Involved in the Glutamatergic Pathway

The glutamatergic pathway is the primary excitatory neurotransmitter system in the CNS. It plays a critical role in the underlying pathophysiology of PD and ICDs, affecting how the brain handles reward, excitotoxicity and motor regulation. Glutamate, responsible for the majority of excitatory signals in the brain bind to ionotropic (N-methyl-D-aspartate, NMDA) and amino-3-hydroxy-5-methyl-4-isoxazolepropionic, AMPA) or metabotropic glutamate (mGluRs) receptors [51].

3.2.1. GRIN2B

Glutamate receptor, ionotropic, N-methyl-d-aspartate 2B (GRIN2B) gene is located on chromosome 12p13.1 and it encodes for the NR2B subunit of the NMDA receptor. NMDA receptors are ionotropic glutamate receptors that participate in in glutamate-mediated neurotransmission in the brain [8]. The NMDA receptor has been associated with PD, as alterations in the expression of NMDA receptor subunits or factors affecting NMDA receptor activation, influence glutamate release, leading to the death of dopaminergic neuron. The NMDA receptor is composed of two subunits NR1 (GRIN1) and NR2 (GRIN2). Regarding NR2 subunit, it has four subtypes: GRIN2A, GRIN2B, GRIN2C and GRIN2D [8]. The GRIN2B subunit of the NMDA receptor is highly concentrated in the striatum/basal ganglia.

The GRIN2B rs7301328 (C366G) polymorphism has been associated with an increased risk of developing ICDs in PD patients [8,17]. Notably, rs7301328 is a synonymous single nucleotide substitution, thus although it alters the DNA sequence it does not cause amino acid change. Interestingly, this variation has been previously been associated with schizophrenia and alcohol dependence [52–54], as well. Larger studies in different ethnicities are awaited to shed light regarding the role of GRIN2B rs7301328 in ICDs in PD patients. Gene-gene interactions especially between genes involved in the dopaminergic and glutamatergic pathways would be of particular interest, as well as the identification of miRNA binding site domains.

3.3. Genes Involved in the Serotoninergic Pathway

ICBs involve a kind of behavioral addiction and mesolimbic dopaminergic and serotonergic pathways are believed to be closely connected and implicated in these addictive behaviors. Serotonin

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is a main neurotransmitter in the CNS, but also an important signaling molecule in the periphery. Serotonergic neurotransmission is widely distributed in the brain and is mediated by serotonergic neurons in the raphe nuclei which project to the striatum. Serotonin homeostasis is mainly regulated by its receptors, transporter and enzymes of its biosynthetic pathway, including the 5-hydroxytryptamine receptor 2A (HTR2A) and tryptophan hydroxylase 2 (TPH2) [55].

3.3.1. HTR2A

5-Hydroxytryptamine receptor 2A (HTR2A) gene is located on chromosome 13q14–q21 and encodes the 5-HT2A serotonin receptor, which is a G protein-coupled receptor (GPCR) that regulates neurotransmitter release, including glutamate and dopamine release, neuropsychiatric processes and peripheral effects [56]. In a case-control study, the HTR2A c.102T > C (rs6313) polymorphism was examined in Korean PD patients, for the risk of ICDs. The T allele was marginally associated with impulse control and repetitive behaviors in PD and this effect was more profound in the lower levodopa-equivalent-dose PD patient group [18]. This variant has previously been associated with increased serotonin 2A receptor expression [57], increasing serotonin 2A receptor activity. In the study of Lee et al, the significant effect of the c.102T>C variant of HTR2A with ICD, in a dose-dependent manner, was also observed, suggesting a dose-dependent genetic susceptibility [18]. Additional studies with increased number of patients and studied HTR2A polymorphisms, are awaited to increase our understanding regarding its involvement of this gene in PD ICDs.

3.3.2. TPH2

Tryptophan hydroxylase 2 (TPH2) gene is located on chromosome 12q21.1, it consists of 11 exons, and it encodes a rate-limiting enzyme in serotonin synthesis, primarily expressed in the brain. In the study of Redenšek et al, TPH2 rs4290270 and TPH2 rs4570625 polymorphisms were studied. Carriers of the TPH2 rs4570625 GT genotype and carriers of at least one T allele were associated with ICDs in PD patients [16]. This allele has been shown to decrease serotonin synthesis [58]. Reduced serotonin levels may in turn reduce tonic inhibition of midbrain dopaminergic neurons, induce dopamine release, leading to ICDs [59]. Interestingly, specific TPH2 haplotypes have also been associated with increased risk of ICDs, as well as a higher tendency of risk-taking behavior, particularly in males [16]. Larger studies in different ethnicities are required to better understand the role of TPH in ICDs in PD.

3.4. Genes Involved in the Opioid Pathway

The opioid system can modulate dopaminergic pathways; opioids inhibit GABA production, thus releases inhibition of dopamine release, leading to increased dopamine levels [9]. Opioid receptors, include the mu1 receptor (OPRM1) and kappa1 receptor (OPRK1) which belong to the a 7-transmembrane GPCR family that regulate pain, mood and physiological responses by binding to endogenous ligands like endorphins, and exogenous drugs like fentanyl [60].

3.4.1. OPRK1 and OPRM1

OPRK1 which is located on chromosome 8q11.23 encodes the kappa-opioid receptor (KOR) and plays an important role in regulating the effects of endogenous opioids, as well as addiction-related behaviors, pain and stress. In addition, OPRM1 located on chromosome 6q24–q25, encodes the Mu-type opioid receptor that mediates the analgesic effects, reward and addictive properties of both endogenous and exogenous opioids. Opioids are fundamental factors in the addictive process, especially via the reward system and the reinforcement process. MORs are mainly associated with positive reinforcement, whereas KORs to negative reinforcement [61].

In a clinical–genetic study aiming to predict the incidence of ICDs in early-stage PD, a panel of genetic variants including OPRM1 rs677830 and OPRK1 rs702764, improved the prediction of ICDs, reinforcing the clinical utility of genetic testing. In fact, OPRM1 rs677830 and OPRK1 rs702764,

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together with GRIN2B rs1105581, rs7301328, Catechol-O-methyltransferase (COMT) rs4646318, TPH2 rs4290270, and Dopamine receptor D type 5 (DRD5) rs6283 polymorphisms were associated with a decreased risk of ICDs [15]. Thus, genetic panels of different genes can aid early identification of PD patients with increased risk of displaying ICDs. In another study, the results of clinical-genetic prediction model were more robust in patients initiating DA therapy. More specifically, variations in OPRK1, HTR2A and DDC had the strongest genetic predictive effect [9]. Moreover, Verholleman et al, examined the possible impact of OPRM1 rs1799971 polymorphism on the effectiveness of naltrexone on hypersexuality symptoms [19]. Naltrexone, a mu delta kappa antagonist, binds to the mu-opioid receptor (MOR), encoded by OPRM1. Interestingly, the A118G (rs1799971) OPRMR1 polymorphism in exon 1 causes an amino acid exchange at residue 40 of the MOR; the normal asparagine (Asn, A allele) is changed to an abnormal aspartic acid (Asp) residue (G allele) (Asn40Asp) which decreases its expression and binding ability in the brain [62]. The relationship between clinicogenetic and pharmacologic risk factors for ICD in PD needs to be further investigated, as well as the functional significance of specific genetic risk factors.

3.5. Genes Associated with Monogenic PD

A number of genes that have been associated with familial PD have been recognized as candidate genes implicated in ICD pathology, suggesting possible common pathogenic mechanisms. However, the exact pathways have not been identified.

3.5.1. LRRK2

The leucine-rich repeat kinase 2 (LRRK2) gene is located on chromosome 12q12. It encodes dardarin protein which is involved in crucial cellular processes, such as vesicular trafficking, autophagy and cytoskeleton maintenance. LRRK2 mutations have been recognized in familial, as well as in sporadic PD. The most prevalent LRRK2 mutation is G2019S (rs34637584) [63].

In the study of Sun et al, PD patients with LRRK2 G2019S mutation had a higher impulse control disorder score compared to PD patients without the mutation. However, although these PD patients were characterized by a more severe clinical presentation at the baseline, they had a slower rate of disease progression and a reduction in impulse control problems. Probably, these could be due to complex compensatory mechanisms and cellular restoration processes, environmental or other unknown yet factors that influence disease progression in LRRK2 G2019S carriers [20]. Additional studies examining G2019S and other LRRK2 variants are waited to add to the total pool of data investigating the role of LRRK2 in ICDs.

3.5.2. SNCA

The a-synuclein (SNCA) gene is located on chromosome 4q21.3-q22. It encodes for a 140 amino-acid-soluble protein, a-synuclein, which is mainly expressed in the CNS, especially in presynaptic terminals. SNCA was the foremost gene associated with PD genetic background, specifically autosomal dominant PD. Increased levels of a-synuclein expression have been shown to reduce PD age of onset and enhance PD severity. Notably, the insoluble a-synuclein fibrils are the fundamental component of LBs [64].

Pen˜ a-Oliver et al showed that the presynaptic protein alpha-synuclein is associated with ICDs. More specifically, in mice, a part of chromosome 6 was deleted leading to loss of SNCA and to lower impulsivity compared to the ancestral, suggesting that a-synuclein may be implicated in the regulation of impulsivity [21]. Mice lacking alpha-synuclein display altered dopaminergic neurotransmission in striatal areas [21], thus changes in dopamine levels due to altered a-synuclein expression might be associated with low impulsivity. The role of SNCA in ICDs remains elusive and should be further explored in future studies.

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3.5.3. FBXO7

F-box protein 7 (FBXO7) gene is located on chromosome 22q12-q13. It encodes a protein involved in ubiquitin-mediated degradation and is a rare monogenic cause of autosomal recessive PD with a variety of clinical symptoms. Variations in this gene were first detected in an Iranian family by genome-wide linkage analysis. Since then, only 7 types of pathogenic variants have been described. PD patients with FBXO7 mutations have been found to have early onset disease, ranging from 10 to 52 years and akinetic-rigidity dominant parkinsonism with variable response to levodopa. Atypical characteristics have also been observed, such as mental deficiency, supranuclear gaze palsy or chorea [65].

Recently, Yoo et al described a PD patient with early onset disease harboring two novel pathogenic FBXO7 variants, a nonsense (c.1162C>T, p.Gln388X) and a missense (c.80G>A, p.Arg27His) one. During treatment with levodopa and a small dose of dopamine agonist, serious ICDs arose limiting medical treatment [22]. Close monitoring for early manifestations of ICDs may be required in PD patients with FBXO7 mutations.

3.6. Other genes

A limited number of genes that have been previously recognized as risk factors of PD have been found to be associated with ICDs, however the implicated pathways remain to be elucidated.

3.6.1. GBA

Glucosylceramidase beta (GBA) gene is located on chromosome 1q21. It encodes for the lysosomal enzyme glucocerebrosidase (GCase), which catalyzes the hydrolysis of glucocerebroside into glucose and ceramide. GBA mutations are the most common genetic factor increasing susceptibility for PD. GBA mutation carriers have been associated with an earlier PD onset, rapid disease progression and an increased burden of non-motor symptoms, such as cognitive dysfunction, rapid eye movement sleep behavior disorder and hyposmia [66].

In the study of Amami et al, ICDs had a higher incidence in GBA-PD patients (52.2%) compared to non mutated-PD patients (13%), with hypersexuality and compulsive shopping being the most prevalent ones. Only one PD patient was on levodopa monotherapy and most of them were taking dopamine agonists [23]; other studies have also shown increased prevalence of ICDs in GBA -PD patients compared to sporadic PD, whereas some showed no difference [67–70]. Additional studies in different ethnicities are awaited to advance our knowledge regarding the role of GBA in ICDs.

3.6.2. APOE

Apolipoprotein E (ApoE) gene is located on chromosome 19q13.32 and it encodes a multifunctional protein involved in lipid transport, cholesterol metabolism and nerve repair. ApoE has three major isoforms: ApoE2, ApoE3, and ApoE4, which are expressed by the polymorphic alleles ε2, ε3, and ε4. The amino acid change within the ApoE isoforms affects protein stability and interactions, with the ApoE4 isoform being the least stable [71].

The APOE ε4 allele is the strongest genetic risk factor for Alzheimer's disease and is also associated with α-synuclein pathology and faster cognitive decline in PD patients [72,73]. Recently, Chen et al, found a strong connection between the APOE ε4 allele and accelerated ICDs progression in newly diagnosed PD patients who were followed by the time of disease diagnosis, suggesting a plausible relationship between the APOE ε4 allele and progression of ICDs in PD [24]. Further studies are needed to address the role of APOE in the development of ICDs in PD patients and possible underlying mechanisms of this association.

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3.6.3. BDNF

Brain-derived neurotrophic factor (BDNF) gene is located on chromosome 11p13–14. BDNF is essential for neuron survival, growth, and synaptic plasticity. BDNF encodes for a large promolecule (pro-BDNF) with a secretory signal peptide. The Val66Met (rs6265) polymorphism in the 50-pro-BDNF sequence changes the intracellular tracking and packaging of pro-BDNF, affecting the function and production of the mature BDNF protein [74]. The dominant Allele A of the rs6265 substitution has recently been found to increase the risk of ICD development in PD patients [11]. Additional larger studies in different ethnic backgrounds are required to clarify the implication of BDNF in PD -ICDs.

3.6.4. ACE

Angiotensin I converting enzyme (ACE) gene is located on chromosome 17q23.3 and encodes the angiotensin conversion enzyme peptidyl dipeptidase A. ACE has a fundamental role in role in the Renin-Angiotensin-Aldosterone System (RAAS) which regulates blood pressure and fluid and electrolyte balance in human body [75]. In fact, ACE acts as a dipeptidyl carboxypeptidase that converts the inactive decapeptide angiotensin I into the active octapeptide angiotensin II.

The common insertion/deletion (rs4646994) polymorphism in intron 16 of ACE is seen as an insertion (I) and/or deletion (D) of a sequence of Alu repeats with a length of 289 bp. The dominant allele I has been recently been associated with ICD in PD [11]. More studies investigating the role of ACE in ICD pathology are required.

3.6.5. NOS1

Nitric Oxide Synthase 1 (NOS1) gene is located on chromosome 12q24.2-q24.31 and encodes an enzyme that produces nitric oxide, which acts as a neurotransmitter in the brain and peripheral nervous system and is implicated in neurotoxicity, as well. Recently, The NOS1 rs2682826 A allele was found to increase the susceptibility for ICDs [16,25]. Notably, NOS1 polymorphisms were previously implicated in other psychiatric disorders [76]. The role of NOS1 in ICD development should be further studied.

3.7. Research Gaps and Future Prospects

ICD is a complex process the pathophysiology of which remains currently elusive. Dopaminergic treatment, especially with dopaminergic agonists, has been associated with the development of ICDs, however not all PD patients suffer from these behavioral addictions. The reported prevalence of ICDs varies, as there are no standard screening tools, often many cases are undiagnosed, and also no long-term universal management guidelines are followed. The socioeconomic burden of ICDs is also understudied. Moreover, usually there is a lack of multidisciplinary approach which is essential, as ICDs are characterized by many psychiatric comorbidities. ICDs are often treated as a single entity, however multiple ICD subtypes exist and the role of genetic and other biomarkers seems to be crucial in this discrimination. Thus, there is a need to identify specific genetic, epigenetic or protein biomarkers for certain ICDs subtypes in order to follow a more personalized PD treatment approach. The exact pathological mechanisms leading to ICDs remain currently elusive, however the combined effects of individual polymorphisms in genes that participate in different pathways could provide useful information regarding ICD pathology. Future gene-gene, gene-environmental studies, as well as functional studies are awaited to further improve our understanding regarding the pathophysiology of ICDs in PD. Moreover, larger studies in different ethnicities are needed to be carried out in order more definite conclusions to be drawn. Exome sequencing information is required to clarify which genes are involved and which pathways are implicated, followed by well-designed replication studies. Functional neuroimaging data will also enhance our understanding in ICDs' pathology. Thus, in future studies the combination of clinical, genetic, pharmacologic and imaging data is awaited to lead to a better stratification of PD patients, improve predictability of ICDs and hopefully facilitate tailored treatment of PD patients.

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4. Conclusions

ICDs are an increasingly recognized non-motor complication in PD. Notably, ICDs are often seen in patients treated with dopaminergic agents, especially dopamine agonists, however this is not the case for all PD patients. Specific clinical, genetic or environmental factors seem to have a pivotal role in ICD pathogenesis. The genetic jigsaw of ICDs is complicated, however a number of genes that encode for enzymes, transporters and receptors that participate in dopamine synthesis, transport, degradation and signaling have been found to be associated with the development of ICDs in PD patients, underlying a fundamental role of the dopaminergic pathway in ICD pathology. *GRIN2B* that is involved in the glutamatergic pathway may also have a critical role in the underlying pathophysiology of PD-ICDs, affecting mainly the reward system. The serotonergic neurotransmission is believed to be closely related to these behavioral addictions, as well; notably, variations in *HTR2A* and *TPH2* have already been found to increase susceptibility for PD-ICDs. Moreover, the opioid system that is known to interact with the dopaminergic system is another potential crucial factor in ICD pathogenesis, with *OPRK1* and *OPRM1* been recognized as susceptibility genes. These and other currently unknown pathways need to be further investigated in order to better understand the genetic background of ICD pathology, recognize which pathways and pathogenic mechanisms are implicated in these behavioral disorders and finally follow a more patient-targeted therapeutic plan.

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Abbreviations

The following abbreviations are used in this manuscript:

ICDs	Impulse Control Disorders
PD	Parkinson disease
LBs	Lewy bodies
DDC	dopa decarboxylase
5′-UTR	5′ untranslated region
ANKK1	ankyrin repeat and kinase domain containing 1
DRD3	Dopamine receptor D type 3
DRD4	Dopamine receptor D type 4
SLC22A1	Solute-like carrier family 22 member 1
CNS	central nervous system
DBH	Dopamine beta-hydroxylase
NMDA	N-methyl-D-aspartate
AMPA	amino-3-hydroxy-5-methyl-4-isoxazolepropionic

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mGluRs	metabotropic glutamate receptors
GRIN2B	Glutamate receptor, ionotropic, N-methyl-d-aspartate 2B
HTR2A	hydroxytryptamine receptor 2A
TPH2	tryptophan hydroxylase 2
GPCR	G protein-coupled receptor
OPRK1	Opioid receptor kappa 1
OPRM1	Opioid receptor Mu 1
COMT	Catechol-O-methyltransferase
DRD5	Dopamine receptor D type 5
LRRK2	leucine-rich repeat kinase 2
SNCA	a-synuclein
FBXO7	F-box protein 7
GBA	Glucosylceramidase beta
APOE	Apolipoprotein E
BDNF	Brain-derived neurotrophic factor
NOS1	Nitric Oxide Synthase 1

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