Genetic Architecture of Psychosis in Parkinson's Disease

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Psychosis in Parkinson's disease (PDP) represents a common and debilitating condition that complicates Parkinson's disease (PD), mainly in the later stages. The spectrum of psychotic symptoms are heterogeneous, ranging from minor phenomena of mild illusions, passage hallucinations and sense of presence to severe psychosis consisting of visual hallucinations (and rarely, auditory and tactile or gustatory) and paranoid delusions. PDP is associated with increased caregiver stress, poorer quality of life for patients and carers, reduced survival and risk of institutionalization with a significant burden on the healthcare system. The pathophysiology of psychosis in PD is complex and still insufficiently clarified.

psychosis Parkinson's disease genetics

1. Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative movement disorder associated with progressive disability and characterized by both motor and non-motor symptoms [1]. PD represents the second most common age-associated neurodegenerative disorder after Alzheimer's disease (AD) [2]. Patients experience motor features, including resting tremor, bradykinesia and muscular rigidity with postural instability, often appearing as the disease progresses [3]. Pathologically, these symptoms are mostly attributed to the extensive degeneration of striatal dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) projecting to the dorsal striatum [4], resulting in a loss of dopamine transmission throughout the brain. At the histological level, the progressive SNpc degeneration correlates with the accumulation of large intra-cytoplasmic inclusions, namely Lewy bodies (LBs) containing misfolded α-synuclein (α-syn), neurofilaments and ubiquitin [5], although α-syn deposition occurs years before motor presentations begin. PD patients also suffer from non-motor symptoms, such as autonomic dysfunction, pain, olfactory deficits, sleep disorders, cognitive impairment and psychiatric disturbances [6]. The underlying mechanisms of PD-related non-motor manifestations are far less clear than motor features and still very difficult to treat.

Among the different non-motor symptoms of PD, psychosis in PD (PDP) is one of the most common, complex and disabling non-motor features, with an estimated prevalence of 43–63% in later stages of the disorder [7][8][9]. PDP prevalence increases with disease progression and it is associated with poorer quality of life, disability and caregiver stress, as well as accelerated cognitive decline, hospitalization or institutionalization, morbidity and mortality [10]. Importantly, the clinical features observed in PDP have a different pattern as compared to other psychotic diseases such as schizophrenia or mood disorders associated with psychotic phenomena, so the current

diagnostic criteria applied to other psychiatric illnesses may be unsatisfactory when describing the diversity of PDP [11]. The spectrum of psychotic symptoms experienced by PD patients consist of hallucinations (mainly visual, but also auditory, tactile or gustatory) and delusions, which simplistically define psychosis. Additionally, there are also minor psychotic phenomena, which include passage hallucinations, sense of presence and illusions [12]. Once psychotic features develop, they tend to become progressive and persistent. Although PDP has some common mechanisms to other psychotic disorders, the neurobiology is different, complex and still insufficiently known [11]. Neuroimaging and neuropathological studies have implicated executive function and visual processing deficits in neocortex and limbic structures, with an imbalance between dopamine, acetylcholine and serotonin neurotransmission [13]. Moreover, PDP therapeutic strategies still continue to be a challenge as dopaminergic treatment for PD motor symptoms, such as levodopa or dopaminergic agonists, exacerbates the condition [8] and the administration of antipsychotic drugs in vivo have revealed a high rate of mortality and morbidity [14]. Apart from exogenous factors, including dopaminergic treatment, several intrinsic factors have been associated with PDP development, including ageing, a more advanced stage of the disease, depression, cognitive impairment, female sex and REM sleep behavior disorder and daytime sleepiness [13][15]. However, not all PD patients develop psychosis, and dopaminergic drugs only partially contribute to the PDP risk. PDP has also been observed in drug naïve PD patients [16]. Although an increasing number of studies has investigated the relationship between several genetic factors and psychotic symptoms in PD, their role in PDP is still unclear.

2. The Genetic Landscape of Parkinson's Disease

The vast majority of PD cases are idiopathic (also defined as sporadic or sometimes "non-genetic") with a multifactorial etiology, whereas only approximately 5–10% are the so-called monogenic forms (sometimes called Mendelian, familial or genetic), caused by pathogenic variants in single genes inherited with Mendelian transmission pattern [17][18] (summarized in **Table 1**).

Table 1. Established Parkinson's disease-causing genes and risk factors.

Gene	Function	Main Types of Mutations/Variants
Autosomal dominant		
SNCA	Synaptic vesicle trafficking and neurotransmitter release	Genomic multiplications (duplications, triplications) and missense mutations
LRRK2	Neuronal vesicular trafficking and autophagic protein degradation	Missense mutations
VPS35	Retromer and endosomal trafficking	Missense mutations

Gene	Function	Main Types of Mutations/Variants
Autosomal recessive		
PRKN	Mitochondrial homeostasis	Structural variants (genomic multiplications and deletions in exons or gene promoter), missense, nonsense, splice-site and frameshift mutations
PINK1	Mitochondrial homeostasis	Structural variants, missense, nonsense and frameshift mutations
DJ-1	Mitochondrial homeostasis	Deletions, missense and frameshift mutations
Risk factors		
SNCA	Synaptic vesicle trafficking and neurotransmitter release	Polymorphic variants, often in non-coding regions
LRRK2	Neuronal vesicular trafficking and autophagic protein degradation	Polymorphic variants
MAPT	Microtubules assembly and stabilization	Polymorphic variants
GBA	Lysosomal	Biallelic (homozygous or compound heterozygous) mutations
X-linked		
RAB39B	Vesicular trafficking	Whole gene deletion, missense, splicing and frameshift variants

DJ-1, protein deglycase; GBA, glucosylceramidase beta; LRRK2, leucine-rich repeat kinase 2; MAPT, microtubule-associated protein tau; PINK1, PTEN-induced putative kinase 1; PRKN, parkin; RAB39B, Ras Analogue in Brain 39b; SNCA, α-synuclein; VPS35, vacuolar sorting protein 35.

3. Genetic Architecture of Psychosis in Parkinson's Disease

3.1. Potential Association between APOE Genotype and PDP

Apolipoprotein E (APOE) is a lipoprotein abundantly found in the brain, being implicated in several cellular processes including the metabolism and clearance of β-amyloid [19]. *APOE* gene has three alleles, named ε2, ε3 and ε4. *APOE* ε3 is the most frequent allele, whereas the ε4 allele is the most common genetic risk factor for AD, leading to an earlier onset of the disease as well [19]. Furthermore, *APOE* ε4 has been linked to hallucinations and

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delusions in AD patients [20] and may be also an age-related risk factor for the worsening of delusions and hallucinations in patients with schizophrenia [21]. In PD, the *APOE* ε4 allele has been associated with earlier disease onset [22][23] and a greater risk of dementia [24], although there is also evidence that does not confirm these relationships [23][25]. Moreover, hallucinations have been shown to be more common in patients with dementia with LBs carrying *APOE* ε4 [26]. Given the well-established association between psychosis and dementia in PD [27], as well as the relationship between advanced disease and the manifestation of psychotic symptoms, it has been suggested that *APOE* ε4 may increase the risk of PDP.

3.2. Dopamine Transporter (DAT) Gene Polymorphisms and PDP Development

Dopamine transporter (DAT) modulates the reuptake of dopamine in the presynaptic dopaminergic neurons, being highly involved in the temporal and spatial regulation of dopamine recycling [28]. VNTR is the most commonly studied polymorphism in the *DAT* gene, located in the non-coding 3′ untranslated region (3′ UTR), consisting of 40 base pairs (bp), which are repeated from three to eleven times. The most common alleles are those with nine and ten repeats, whereas the number of repeats might regulate gene expression and the subsequent retrieval of dopamine in the synapsis [29]. *DAT* polymorphisms have been linked to neuropsychiatric diseases, including bipolar disorder and attention deficit hyperactivity disorder [28]. In addition, the A9 allele of the *DAT* gene increases the risk of visual hallucinations in alcohol-dependent women during alcohol withdrawal [30]. The 40-bp VNTR of the *DAT* gene has been associated with increased susceptibility to PD [31][32][33].

DAT gene polymorphisms have been associated with a greater frequency of PDP in some but not all studies. More specifically, the nine-copy allele of the 40-bp VNTR of the *DAT* gene was more commonly identified in levodopa-treated PD patients of Caucasian descent with psychosis compared to those without psychosis [34]. Preclinical evidence has demonstrated that compared to the ten-copy allele of the *DAT* gene, the nine-copy allele could promote the transcription of the gene, even though it is located in a non-coding region [35].

Further, the −839 C > T allele of the 5′ UTR of the *DAT* gene has been associated with visual hallucinations in levodopa-treated PD patients [36]. It has been speculated that this polymorphism may affect *DAT* gene expression, although its exact functional consequences are unclear [36]. Concerning *DAT1* rs28363170, a recent study in Brazilian PD patients showed that carrying the 10/11, 10/8 and 10/9 genotypes was more frequently associated with visual hallucinations, but no association was found for *DAT1* rs28363170 [37]. In addition, a recent study in Slovenia demonstrated that the haplotype of the *SLC6A3* gene was associated with the development of levodopa-induced visual hallucinations in PD patients [38]. Taken together, the role of *DAT* genes in PDP still remains obscure.

3.3. Dopamine Receptor (DRD) Gene Polymorphisms and the Risk for PDP

Dopaminergic therapy is one of the most significant risk factors for PDP; hence, dopaminergic receptor-related pathways might be an appropriate target for exploring PDP pathophysiology. Dopaminergic agonists act by directly stimulating the postsynaptic dopamine receptors in the striatum, with a relative selection for the dopamine D2-like

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receptors, including D2, D3, and D4 ones, compared to dopamine D1-like ones, including DRD1 and DRD5 [39].

The use of dopaminergic agonists significantly increases the risk for PDP: in particular, apomorphine, which has a higher affinity for DRD4 compared to DRD2 and DRD3, displays modest hallucinogenic effects, and pergolide, which has greater affinity for DRD2 and DRD3 compared to DRD4, is significantly associated with hallucinations [40]. Therefore, the tendency of dopaminergic agonists to induce psychotic symptoms may be DRD2- and DRD3-mediated. In addition, neuroleptic drugs used for the treatment of schizophrenia mainly target against DRD2. In PD, the neurodegenerative process leads to a denervation-induced hypersensitivity, and DRD2 upregulation has been demonstrated in vivo [39]. DRD2 is found in various brain areas including the striatum and limbic system, whereas DRD3 and DRD4 are mainly located in the limbic system [40]. It has been suggested that hypersensitivity of the dopaminergic mesocorticolimbic system could be implicated in the development of hallucinations in PD, especially those early in the course of the disease not generally related to cognitive decline [40].

DRD gene polymorphisms have already been investigated for schizophrenia and AD-related psychosis. In particular, the *DRD3* Ser-9 allele has been associated with higher risk for schizophrenia [41], although there is also evidence not confirming this hypothesis [42]. In AD, psychotic symptoms and aggressive behavior have been associated with homozygosity for *DRD1*.B2, whereas *DRD*3 1/1 or 2/2 homozygotes AD patients were more likely to develop psychosis [43]. In addition, the risk for psychotic manifestations was higher in the case of co-presence of *DRD1* and *DRD3* polymorphisms compared to these gene polymorphisms alone in this study, suggesting a possible interaction. There is also evidence that in PD, the *DRD3* gene Ser9Gly polymorphism may be associated with the severity of depressive symptoms in PD patients [44].

3.4. Genetic Polymorphisms of the Cholecystokinin System and PDP

Cholecystokinin (CCK) is a neuropeptide with a critical role in dopaminergic modulation, which is found in both the gastrointestinal and central nervous system (CNS). There are two types of CCK receptors (CCKRs), A and B (*CCKAR* and *CCKBR*, respectively). CCKRs are G protein-coupled receptors with varying affinity for CCK forms, including CCK4 and sulfated and unsulfated CCK8. CCK regulates dopamine release in the mesolimbic pathway, thereby modulating behavior. Dopamine and CCK also coexist in dopaminergic neurons [45], and dopamine can stimulate *CCK* gene expression [46]. In addition, decreased CCK8 immunoreactivity has been demonstrated in the SN of PD patients [47]. CCKAR is mainly implicated in the CCK-mediated dopamine release in the posterior nucleus accumbens, whereas CCKBR is responsible for the CCK-mediated inhibition of dopamine release in the anterior nucleus accumbens [48]. The *CCK* -45 Ins/Ins C/T genotype has been more frequently found in PD patients compared to age-matched controls [49], although this finding has not been confirmed in other studies [50].

Given the fact that CCK is majorly implicated in dopamine-related behavior, it has been hypothesized that *CCK* gene polymorphisms could affect the risk for several psychiatric conditions. In this regard, it has been shown that *CCK* and *CCKAR* polymorphism may be associated with panic disorder, alcoholism and delirium tremens, bipolar disorder and schizophrenia [51]. Given the molecular differences in PDP and schizophrenia pathogenesis, and the mainly auditory hallucinations in schizophrenia, these findings are not directly comparable with PDP. Therefore, it

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has been suggested that *CCK* and *CCKAR* gene polymorphisms may be also related to PDP development, and several studies have investigated this relationship.

3.5. Relationship between HOMER1 Gene and PDP

Apart from impaired dopaminergic neurotransmission, glutamatergic imbalance has been proposed to play a major role in PDP pathophysiology. In this context, metabotropic glutamate receptors (mGluRs) critically regulate synaptic activity and neuronal function, and they have also been related to drug-induced neuroplasticity in the nucleus accumbens [52]. The Homer family, encoded by *HOMER1*, *-2* and *-3* genes, is a group of postsynaptic density proteins interacting with the intracellular domain of mGluR1, thereby regulating several signaling pathways [53]. HOMER1 is highly expressed in the brain, and they are implicated in glutamatergic neurotransmission and synaptic plasticity [54]. Homer1a isoform is implicated in several neurological and psychiatric disorders, such as epilepsy, drug abuse and schizophrenia [55]. Homer1 knockdown can also protect dopaminergic neurons by modulating calcium homeostasis in in vitro models of PD [56]. In 6-hydroxydopamine (6-OHDA)-treated rat models of PD, deep brain stimulation of the subthalamic nucleus was associated with downregulation of *HOMER1*, potentially leading to decreased sensitivity to glutamate in basal ganglia [57]. Further in vivo evidence has revealed that Homer1a is overexpressed after the use of dopaminergic agonists [58], suggesting its possible role in treatment-related symptoms in PD.

3.6. Catechol-O-Methyltransferase (COMT) Gene Polymorphisms and PDP

Catechol-O-methyltransferase (COMT) plays a critical role in the metabolism of dopamine. It has been indicated that the *COMT* rs4680 genotype is associated with depressive symptoms [59] and the *COMT* Val158Met polymorphism is related to MDMA-induced psychotic symptoms [60].

Dopamine is produced in the dopaminergic neurons from levodopa by the enzyme dopa decarboxylase (DDC). Interestingly, *COMT-DDC* gene–gene interaction has been shown to affect the risk of levodopa-induced visual hallucinations in PD patients [38]. *DDC* rs921451 has been shown to reduce the enzyme activity, possibly resulting in lower dopamine levels [61]. Therefore, the effects of *COMT-DDC* interaction with PDP risk might explained by the alterations in dopamine concentrations [38].

3.7. Angiotensin I-Converting Enzyme and PDP

Emerging evidence highlights the role of angiotensin I-converting enzyme (ACE), which is the main enzyme of the renin-angiotensin system (RAS), in the pathogenesis of neurological and psychiatric disorders. The D allele of *ACE* has been associated with psychotic symptoms in bipolar disorder, whereas the I allele may protect against the development of schizophrenia and bipolar disorder [62]. In PD, dopaminergic treatment has been shown to affect ACE levels in the cerebrospinal fluid (CSF) [63], and perindopril,-an ACE inhibitor- treatment, may improve motor symptoms in levodopa-treated PD patients [64]. A very recent study has also shown that angiotensin II receptor blockers with blood—brain barrier penetrating capacity reduce the risk for PD among patients with ischemic heart

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disease [65], *ACE* gene polymorphisms have been demonstrated to increase the risk for PD [66], and the rs4646994 polymorphism in *ACE* has been recently associated with impulsive control disorders in PD patients [67].

3.8. ANKK1 Gene Polymorphisms and PDP

Ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene polymorphisms have been associated with alcoholism and other neuropsychiatric disorders, including PD [68]. The GG rs2734849 *ANKK1* gene polymorphism has been associated with the development of PDP in levodopa-treated PD patients in another recent study [69]. rs2734849 polymorphism is in the coding region of *ANKK1* gene and it is able to regulate DRD2 density by changing NF-kB expression levels [70].

3.9. Serotoninergic System Genes and PDP

Serotoninergic dysfunction plays a critical role in PD pathophysiology. A significant serotoninergic neuronal loss is observed in the raphe nucleus of the brainstem, accompanied by reduced serotoninergic terminals in the putamen, frontal and temporal cortex [71]. A repeat polymorphism of the promoter region of the serotonin transporter (*5-HTT*) gene, 5-HTTLPR, has been associated with depression and anxiety in PD patients in some — but not all — studies [72][73][74]. In addition, 5-HT2A receptor gene polymorphisms have been associated with negative symptoms in schizophrenia [75] and psychotic manifestations in AD [76]. Pimavanserin, a 5-HT2AR inverse agonist and antagonist, has been approved by the FDA for PDP, further strengthening the hypothesis that serotoninergic system is critically implicated in PDP [77].

3.10. Microtubule Associated Protein Tau (MAPT) Gene Polymorphisms and PDP

As mentioned above, the *MAPT* gene exists in three genotypes (H1/H1; H1/H2 and H2/H2). A postmortem study showed that PD cases with the H1/H1 genotype had significantly more frequently hallucinations compared to non-carriers, independent of the disease stage [78]. However, no link was revealed between *MAPT* gene polymorphisms and psychotic manifestations in PD patients in another study [16].

3.11. SNCA Gene Polymorphisms and PDP

No association has been found between psychotic symptoms and genetic polymorphisms in the *SNCA* gene [16]. In particular, the *SNCA*-REP1 261 allele, which has been shown to increase the risk for PD [79], was not associated with psychotic manifestations in PD patients [16].

3.12. IL-6 Gene Polymorphisms and PDP

Neuroinflammation is one of the core pathophysiological mechanisms underlying PD pathogenesis. It has been proposed that it may contribute to the development of non-motor symptoms of PD, although its specific role in PDP still remains elusive [80]. Increased plasma interleukin-6 (IL-6) levels were identified as a major contributor to mortality in PD patients [81]. In addition, elevated plasma CRP levels were associated with the occurrence of

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hallucinations or illusions in PD patients, suggesting that excessive systemic inflammation might increase the risk for PDP [82].

3.13. GPX1 Gene Polymorphisms and PDP

Oxidative stress plays a critical role in PD pathophysiology, and lower levels of glutathione peroxidase-1 (GPX1), an enzyme with anti-oxidant activity, have been shown in the SNpc of PD patients [83]. *GPX-1* polymorphisms rs1050450 and rs1800668 have been associated with schizophrenia in the Chinese population [84], suggesting a potential role of *GPX-1* gene in psychosis.

3.14. MAOB Gene Polymorphisms and PDP

MAOB gene polymorphisms have been related to the development of schizophrenia [85][86]. *MAOB* rs1799836 polymorphism has been shown to protect against PDP development in a recent study [87]. It has been proposed that this effect may be due to the lower turnover of dopamine in carriers of the G allele [88].

3.15. BIRC5 Gene Polymorphisms and PDP

It has been shown that *BIRC5* rs8073069 polymorphism may lower the risk of the development of visual hallucinations in PD patients [87]. One potential explanation might be the subsequent higher expression of survinin, which inhibits apoptosis, neuroinflammation and oxidative stress [89].

3.16. BDNF Gene Polymorphisms and PDP

A recent preclinical study demonstrated that chronic methamphetamine use may interact with brain-derived neurotrophic factor (*BDNF*) Val66Met to remodel psychosis-related pathways in the mesocorticolimbic circuitry [90]. The same polymorphism has been associated with the onset age of schizophrenia [91]. The Met allele has been associated with cognitive impairment in patients with PD [92]. This substitution can reduce the extracellular release of BDNF [93], resulting in its decreased availability to the neuronal cells.

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