

PSYCHIATRIC COMORBIDITIES IN PARKINSON'S DISEASE SEEN THROUGH THE PRISM OF GENOMICS AND EPIGENETICS

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SUMMARY

Parkinson's disease (PD) is a neurodegenerative disorder clinically characterized by motor dysfunctions due to progressive loss of dopaminergic neurons and a broad spectrum of non-motor symptoms. Interestingly, non-motor symptoms like depression, anxiety and psychosis are often present several years before the occurrence of classic motor features seriously affecting patient quality of life. Their presence is often misleading, delaying the correct diagnosis of PD. Despite its high incidence, the pathophysiology and aetiology of neuropsychiatric symptoms associated with PD remains unclear. Currently, a lot of interest lays in research looking for genetic predictors of motor and non-motor symptoms in PD. The availability of next-generation sequencing technology for genome, epigenetic and transcriptional analysis opens the door to a new way of studying multifactorial diseases like PD and their comorbidities. In this review we will present new insights in the genomic and epigenetic background of psychiatric comorbidity in Parkinson's disease.

Key words: Parkinson's disease - neuropsychiatric symptoms – genomics - epigenetics

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INTRODUCTION

Parkinson's disease (PD) is clinically characterized by motor dysfunctions due to progressive loss of dopaminergic neurons in the substantia nigra, pars compacta (Weng et al. 2018). However, most patients also develop different, non-motor, symptoms including mood disorders, cognitive decline, hallucinations and delusions, autonomic dysfunction and/or sleep disturbances. In most cases, different non-motor symptoms are present several years before the occurrence of classic motor features seriously affecting patient quality of life. Motor symptoms are mainly a consequence of dopamine deficiency, while non-motor symptoms are considered to be related to changes in levels of serotonin and noradrenaline (Politis et al. 2012, Delaville et al. 2011). In PD the nigrostriatal system is primarily damaged but in cases of cognitive impairment neurodegeneration is more extended, including neuronal loss in the striatum, hippocampus and neocortex (McKeith et al. 2004). Although the aetiopathogenesis of PD is not completely clear, studies point to a variety of prominent causes, including deficit in mitochondria, oxidative stress, accumulation of aberrant proteins, ubiquitin-proteasome system dysfunction as well as autophagy lysosomal pathway dysfunction (Tan et al. 2007).

Only a small portion of PD cases, about 10%, is monogenic inherited in recessive or dominant manner and is associated with mutations in genes such as *SNCA*, *LRKK2* and *PINK1* (Tan et al. 2007; Verstraeten et al. 2015). Mutations in these genes can also act as risk factors for sporadic PD, suggesting a common pathological background of sporadic and inherited forms. In addition, penetration of some recurrent mutations is not complete

and may vary depending on age (Tan et al. 2007). There are also various genetic polymorphisms that affect dopamine as a risk factor for PD related complications, such as dyskinesias and hallucinations. Currently, a lot of interest lays in research looking for genetic predictors of motor and non-motor symptoms in PD. However, most genomic related studies are limited to genetic risk factors with poorly understood consequences of genetic variability in clinical phenotype, as well as undefined interaction between genetic and environmental substrates. As part of our research, in order to characterize underlying genetic mechanisms leading to accumulation of alpha synuclein due to lysosomal dysfunction, we performed a comprehensive analysis of genetic variants using a custom targeted next-generation sequencing (NGS) panel, containing a set of 440 genes related to lysosomal pathways as well as genes previously implicated in familial forms of PD (unpublished data). Apart from the genes associated with autophago-lysosomal pathways, the variants obtained have also profiled damaged pathways leading to neurodegeneration (unpublished data). PD is a multifactorial disease considered to be a result of complex interactions between environmental toxins, genetic changes and other cellular processes. The role of genetic abnormalities and environmental factors in PD pathogenesis has been the subject of discussion for many years. In recent years there has been a shift of focus to epigenetic changes as a link of environmental influences and genetic predisposition. These epigenetic changes could also be part of the explanation of the differences in psychiatric comorbidity in patients with PD.

In this article we will review the present state-of-the-art concerning the genomic and epigenetic background of psychiatric comorbidity in Parkinson's disease.

ANXIETY AND DEPRESSION IN PARKINSON'S DISEASE

Mood and anxiety disorders are frequently observed in PD patients, yet the understanding of the underlying mechanisms of those symptoms in PD is limited. Depression is the most common psychiatric disorder occurring in PD and can cause a significant reduction in daily functioning. It is associated with worsening of motor function and a more severe clinical picture of PD (Palhagen et al. 2008). About 30-50% of patients with PD also have depression (Perez-Lloret & Rascol 2012). Depression is already present in 29% of newly diagnosed patients and more than half of PD patients with depressive disorder meet the criteria for major depressive disorder (Starkstein et al. 1990). Some studies suggest depressive disorders as a result of neuropathology of PD (Starkstein et al. 1990), while other claim that depression is a consequence of psychological and physical limitations of the patient (Gotham et al. 1986). Petkus and al showed that worse performance across all cognitive domains was associated with subsequently higher anxiety and depressive symptoms, while the reverse direction was not significant, concluding that worse cognitive performance is a risk factor for increased symptoms of anxiety and depression (Petkus et al. 2018). In addition to depressive disorders, there is a great number of anxiety disorders observed in the PD population. In some cases anxiety symptoms may precede typical symptoms of PD suggesting a common neurobiological substrate (Kummer & Teixeira 2009), also a wide range of anxiety disorders can be induced by dopaminergic therapy (Nuti et al. 2004). The most common forms of anxiety disorders in PD include panic disorders, generalized anxiety disorders and social phobia. Their incidence in PD varies in the range of 3.6% to 40%, with a peak incidence of around 20% (Lentjeens et al. 2005; Dissanayaka et al. 2010; Nuti et al. 2004; Menza et al. 1993). Nuti and al showed that mood disorders and anxiety disturbances were more frequent in PD patients compared with the control population, with no correlation of psychiatric disorders with age, sex, clinical features, severity of disease, age of onset and PD duration nor anti-parkinsonian therapy (Nuti et al. 2004). There are conflicting data on the relationship between anxiety and severity of PD symptoms. While some studies do not show a significant relationship between anxiety and severity of motor symptoms (Nuti et al. 2004, Menza et al. 1993), other studies point to more severe subjective motor disturbances in people with comorbid anxiety and a worse treatment outcome with more complications in people with symptoms of anxiety (Henderson et al. 1992; Giladi & Hausdorff 2006; Dissanayaka et al. 2010). On the other hand, there was no significant association between anxiety and duration of PD. However, PD patients with a younger age of disease

onset have a higher risk of anxiety regardless of the severity of PD symptoms. In PD population as well as in the general elderly population, there is a trend of reducing symptoms of anxiety with age (Dissanayaka et al. 2010).

Depression and anxiety in PD are diagnosed through standardized criteria for major depression and generalized anxiety disorder such as DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) criteria (Starkstein & Brockman 2017). The main problem of using these criteria is in overlapping of symptoms of depression and anxiety with PD symptoms (Starkstein & Brockman 2017) making it insufficiently diagnosed in the PD population. According to one study, anxiety in PD was undetected in 50% of cases, making it imperative to find a biomarker for early detection (Shulman et al. 2002). Despite its high incidence, the pathophysiology and aetiology of depression and anxiety associated with PD remains unclear. However, dysfunction of dopaminergic, serotonergic and norepinefrinergic pathways in the limbic system undoubtedly contributes to their development. A polymorphism in the regulatory region of the serotonin transporter (5-HTTLPR; 5-HTT-linked polymorphic region) is of particular interest as the serotonin transporter plays an important role in regulating serotonergic tone and may represent a significant risk factor for anxiety and depression in elderly patients with PD (Menza et al. 1999). Furthermore, studies showed that abnormal brain-derived neurotrophic factor (BDNF) has an important role in the development and progress of various neurological and psychiatric disorders (Boulle et al. 2012). The neurotrophic hypothesis of depression states that low levels of BDNF are linked to the clinical picture of depression (Pishva et al. 2017). It is described that a common polymorphism in the *BDNF* gene, Val66Met (rs6265) is contributing to the appearance of depression and anxiety in PD (Cagni et al. 2017). BDNF is a member of the neurotrophin family of growth factors and binds to tropomyosin-related kinase B (TrkB) receptor promoting neuronal growth, survival, differentiation, and synaptic plasticity (Cagni et al. 2017). Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene are the most common genetic cause of PD (Bonifati 2014). Recent studies showed a significant causal role of *LRRK2* in the development of anxiety and depression. Lim et al. showed that mice carrying G2019S variant of *LRRK2* gene were displaying anxiety/depression-like behaviour before motor dysfunction (Lim et al. 2018). The mutation G2019S is very common and is found in 5-6% of cases of familial PD and in 1-2% of sporadic PD (Gilks et al. 2005). The prevalence of this mutation depends on the population and our analysis of 50 patients with PD from Croatian has not revealed the presence of this mutation (unpublished data).

PSYCHOSIS IN PARKINSON'S DISEASE

Psychosis is a common non-motor symptom in PD. Since it involves a large spectrum of symptoms, the frequency of psychosis in the PD population is unclear. For example, studies estimate the incidence of complex visual hallucinations ranged from 22–38%, compared to an incidence of 0–22% for auditory hallucinations (Ffytche et al. 2017, Fenelon & Alves 2010). There is a difference between symptoms of psychosis spectrum in early and later stages of PD. Symptoms in early stages present as passage and presence hallucinations, illusions, and formed hallucinations (Ffytche et al. 2017). As PD progresses, auditory, tactile and olfactory hallucinations occur alongside visual hallucinations (Ffytche et al. 2017). Psychosis in PD is associated with higher rates of mortality, caregiver distress, and nursing home placements (Lenka et al. 2016). Known risk factors for psychosis in PD include long duration of PD, older age of patients and sleep disturbances (Lenka et al. 2016). The influence of dopaminergic therapy on development of psychosis is questionable because some studies show an increased rate of psychosis while others show no correlation (Papapetropoulos & Mash 2005; Aarsland et al. 1999) suggesting to a more complex background of hallucinations than a simple dependency on serum levels of levodopa. Interindividual genetic differences in dopamine transporter controlling presynaptic dopamine in dopaminergic neurons of the nigrostriatal system may also play a role in the emergence of psychotic symptoms due to PD therapy. Also, there are several functional variants of dopamine receptors D2, D3, and D4, major sites of dopaminergic drug activity. It is considered that in addition to dopamine, one of the important neurochemical substrates of psychosis in PD is the imbalance of serotonin (Lenka et al. 2016). That being said, it is no surprise that the interest of some studies has focused on the research of gene coding polymorphisms for these neurotransmitters and their receptors in PD patients with psychosis (Lenka et al. 2016). Lim and al have shown that *LRRK2* mutant phenotype is followed by the age-dependent upregulation of the 5-HT1A receptor in the hippocampus, amygdala and dorsal raphe nucleus, pointing to the potential mechanism for psychotic symptoms within the *LRRK2* mutation phenotype (Lim et al. 2018). In addition, there is emerging interest in other risk genes for the development of psychosis in PD patients but with equivocal results. The most common studied genetic factor is the apolipoprotein E $\epsilon 4$ (*APOE* * $\epsilon 4$) allele but with conflicting results (Lenka et al. 2016). Consistent evidence links *GBA* with psychosis in PD (Ffytche et al. 2017). Creese and al showed that *GBA* mutations are associated with increasing risk of psychosis by 1.83 times, which confirms the relationship highlighted in earlier studies (Creese et al. 2018, Ffytche et

al. 2017). Genetic etiology of psychosis in PD is complex and involves many small effect size genes. As such, genome-wide association studies (GWAS) greatly contribute to the illumination of the genetic background of the appearance of these comorbidities. So far, only cholecystokinin (*CCK*) polymorphism studies have yielded consistent results showing a significant association of *CCK-45C>T* polymorphisms with hallucinations (Lenka et al. 2016; Goldman et al. 2011). Variants of *CCK* gene are also involved in other psychiatric disorders such as schizophrenia and panic disorder. *CCK* is present in dopaminergic neurons in the nucleus accumbens and amygdala and modulates the dopaminergic release and potent dopamine mediated behaviour (Crawley et al. 1985). Identification of various factors related to psychosis in PD is clinically important because of poor functional outcome of PD patients with psychosis. Genetic biomarkers for psychosis in PD are of immense importance because of their potential of early detection of the disease even before onset of first symptoms.

GENOMIC VIEW OF PD ASSOCIATED PSYCHIATRIC SYMPTOMS- WHAT CAN WE LEARN FROM MONOGENIC FORMS?

Recent genome-wide association studies (GWAS) are identifying novel candidate genes for Parkinson's disease. Identification of new candidate genes is important for a better understanding of the aetiology and pathology of PD as well as for understanding overlapping biological mechanisms leading to psychiatric comorbidities. Most variants that contribute to PD sensitivity are described in genes coding for microtubule-related protein (*MAPT*), leucine rich reuptake kinase (*LRRK2*), and alpha-sinuklein (*SCNA*) (Simón-Sánchez et al. 2009). It has been shown that PD cases with identified Mendelian genetic causes have an excess of additional rare variants of current unknown significance of PD genes (Lubbe et al. 2016). There is also a significant polygene contribution to the overall hereditary risk of PD suggesting that juvenile forms are not solely caused by highly malignant Mendel mutations but may arise as a result of accumulation of frequent alleles with a relatively low effect size (Escott-Price et al. 2015). In our study, we included only patients with idiopathic PD, however, we found a considerable number of heterozygous variants of these genes associated with juvenile forms of PD. This implies that the genetic architecture of PD is likely to be reflected in a large number of susceptibility genes and a complex set of biological pathways opening the door for multiple complex interactions with psychiatric disorders. However, the genotype does not necessarily determine the neurological phenotype due to epigenetic modulation of gene expression in response to endogenous and exogenous regulators.

Although only about 10% of Parkinson's disease cases are caused by clearly defined monogenic causes, these forms greatly illuminate the genetic basis of PD (Verstraeten et al. 2015). PD related genes can be changed by point mutations, duplication or triplication and there are more than 500 variants described in the PARK gene family that currently consists of 20 genes (Pavlou & Outeiro 2017, Nuytemans et al. 2010). Furthermore, studying genetic forms of PD brought a new insight in the association of PD genes *SNCA*, *LRRK2*, *VPS35*, *Parkin*, *PINK1*, *DJ-1*, and *GBA* risk factor with motor and non-motor PD symptoms. It has been shown that non-motor symptoms are different in various genetic forms of PD (Kasten et al. 2017). For example, despite a comparable age of PD onset there is a different frequency of psychiatric symptoms in carriers of *Parkin* and *PINK1* mutations. While cognitive decline and presence of psychotic symptoms are commonly associated with *SNCA* triplications, dementia and depression are more common in *GBA* mutation carriers (Kasten et al. 2017). *SNCA* duplication and *GBA* mutations carriers have a higher risk of dementia, hallucinations, and depression, while *LRRK2* mutation carriers have a lower risk of dementia (Kasten et al. 2017). It is known that heterozygous mutations in the *GBA* gene are an important genetic risk factor for Parkinson's disease (Nalls et al. 2013). Recent studies have focused significantly on the relationship between *GBA* mutations and the appearance of cognitive and neuropsychiatric symptoms in PD (Creese et al. 2018). Creed et al. showed that *GBA* mutations are associated with a 2.4-fold increased risk of cognitive disorders and a 1.8- to 2.2-fold increased risk of psychosis and depression (Creese et al. 2018). *GBA* mutations are associated with a distinct profile of cognitive impairment but in *Parkin* associated PD the frequency of cognitive decline falls within the range of the general population above the age of 65 years (Kasten et al. 2017). Oeda and al showed that PD patients with *GBA* mutations developed dementia and psychosis significantly earlier than those without mutations (Oeda et al. 2015).

EPIGENETICS OF PSYCHIATRIC COMORBIDITY IN PARKINSON'S DISEASE IN A NUTSHELL

The term epigenetics refers to reversible changes in gene expression that can be inherited or are a result of environmental factors (Portela & Esteller 2010). Epigenetic modulation of gene expression as an integrator of environmental factors is an important mechanism in PD and other neurodegenerative disorders as well as in neuropsychiatric disorders. Epigenetic mechanisms imply methylation of DNA, histone modification, and changed in expression of microRNA (miRNA). These mechanisms are responsible for the development and

adaptation to the environment by inducing differential gene expression. A number of cognitive and neurobiological functions of the central nervous system are regulated by epigenetic processes, while dysregulation of gene expression is associated with various neurological and psychiatric diseases. Recent studies have shown that in the development of depression epigenetic mechanisms are as important as genetic predisposition (Roth 2013, Sullivan et al. 2000). Since we do not yet fully understand the aetiopathogenesis of PD, it is considered that epigenetic regulation may be the missing part of the puzzle.

Genome-wide methylation studies of blood and brain samples revealed significant dysregulation of methylation in PD patients. It has been found that many of the PD-risk genes are hypo- or hypermethylated (Masliah et al. 2013). Furthermore, there are more than 20 genes identified that were differently methylated in blood samples from PD patients compared with controls (Moore et al. 2014). As already mentioned, the development of depression and other neuropsychiatric diseases is greatly affected by both genetic and environmental factors. The explanation why external factors affect the risk of depression development is partly based on the response of the glucocorticoid receptor (GR) encoded by *NR3C1* gene (Deussing & Jakovcevski 2017). Changes in *NR3C1* gene methylation levels caused by environmental factors are presented both, in the brain and periphery. *NR3C1* can also act as a transcription factor allowing a direct effect on the epigenome. The pivotal role of *NR3C1* in response to external factors may be its impact on many different genes associated with depression (Deussing & Jakovcevski 2017). Another interesting gene in this context is *FKBP5* (FK506-binding protein 5) gene. *FKBP5* is a member of an immunophilic protein family associated with environmental response that affects the susceptibility to depression. The binding of cortisol to GR induces expression of *FKBP5*, while *FKBP5* decreases glucocorticoid binding affinity (Pishva et al. 2017). The aforementioned *BDNF* gene is also modulated by epigenetic changes. In fact, some risk factors can cause permanent changes in the regulation of the *BDNF* gene increasing the susceptibility to psychopathology (Boulle et al. 2012). Such stable imprints on the *BDNF* gene could partly explain the different treatment efficacy as well as the high degree of recurrence in psychiatric disorders (Boulle et al. 2012). Studies have shown that in patients with depression there are elevated levels of methylation at different locus within the *BDNF* gene, confirming the neurotropic hypothesis which claims that reduced *BDNF* levels are associated with clinical depression (Pishva et al. 2017). The value of epigenetics is not only in the understanding of the disease, but also in potential therapeutic and diagnostic applications. Hypomethylation of *SNCA* and *LRRK2*

gene that can be detected in peripheral blood leukocytes was proposed as a potential non-invasive biomarker for early detection of PD (Tan et al. 2014). DNA methylation of candidate genes has an excellent diagnostic potentials as biomarkers of various diseases and their susceptibility to comorbidity. Furthermore, some of candidate genes described also exhibit epigenetic changes due to antidepressant treatment, and antidepressant drugs can directly affect the specific epigenetic mechanisms (Menke & Binder 2014).

Apart from an evident significance of methylation, an important role of histone modification was also demonstrated, suggesting that chromatin remodelling could be highly involved in PD pathogenesis. There are increased levels of acetylation of H2A, H3 and H4 in comparison with age-specific control subjects (Park et al. 2016). Histone deacetylase (HDACs) removes acetyl groups in amino-terminal tails of histone nuclei and other proteins, having the opposite effect of histone acetyltransferase (HAT) (Abel & Zukin 2008). Deacetylation of histone proteins moves the balance to chromatin condensation and thereby suppresses gene expression (Abel & Zukin 2008). In this context, the interest aroused around HDAC inhibitors as new therapeutic approaches to the treatment of neurodegenerative disorders (Abel & Zukin 2008). Studies have shown that HDAC inhibitors can be a promising therapeutic strategy to alleviate the progressive neurodegeneration associated with PD (Kontopoulos et al. 2006). Histone acetylation represents also a valid therapeutic target in treatment of depression and anxiety. It is interesting that HDAC inhibitors reverse behavioral changes that are the result of epigenetic reprogramming during development, altering the susceptibility to psychiatric comorbidities.

Due to their pleiotropic effects in biological cells, miRNA also contributes to neurodegeneration in PD (Pavlou & Outeiro 2017). A total decrease in miRNA was demonstrated in tissue samples isolated from PD patients compared to healthy subjects (Cardo et al. 2014). Taking into account the involvement of miRNA in several aspects of neural plasticity, neurogenesis and stress response, it is concluded that miRNAs play an important role in the pathogenesis of depression and that they may open new platforms for development of precise therapeutic agents (Dwivedi 2014).

CONCLUSION

Linkage and GWAS studies have already revealed the importance of various variants of PD related genes with a higher risk of neuropsychiatric symptoms. On the other hand, epigenetics may provide new insight into the pathophysiology of psychiatric comorbidity in PD and its better understanding opens the door to new biomarkers for early diagnostics. With the help of high-throughput genomic techniques, a number of causative genes will be discovered in the future contributing to the

understanding of genetic susceptibility of non-motor symptoms associated with PD. Better understanding of the pathophysiology of genetic causes of psychiatric comorbidities in PD may lead to the development of more specific therapies. Accurate diagnosis of progressive diseases such as Parkinson's disease and prediction of comorbidity risk by simple non-invasive measures is a critical requirement for the purpose of using more appropriate procedures for early diagnosis and precise treatment.

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Contribution of individual authors:

Antonela Blažeković: acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

Fran Borovečki: study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

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