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REVIEW PAPER

Genetic and Epigenetic Collaboration in Parkinson's disease

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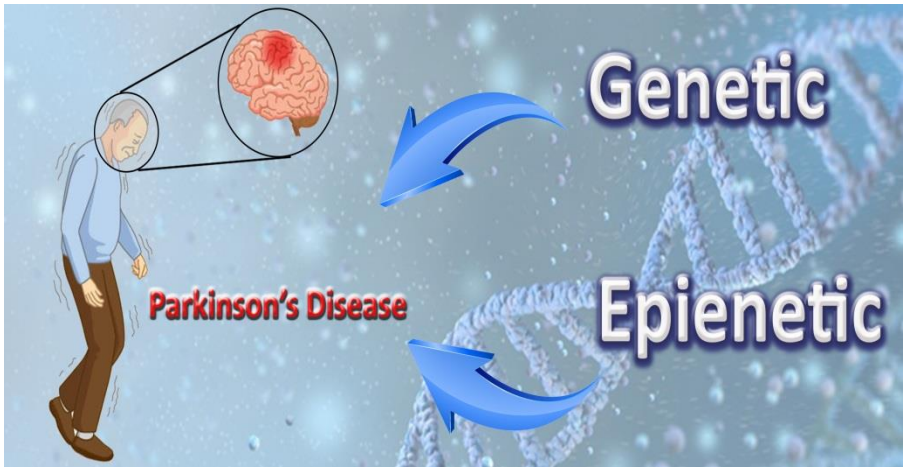
Highlights

- Parkinson's disease (PD) is a common neurodegenerative syndrome.
- The reduced activity of dopamine (DA) in Substantia Nigra is linked to PD.
- Epigenetics and genetics are highly interconnected in PD.
- Just 10–15% of Parkinson's disease are family-oriented.
- SNCA has a role in the pathogenesis of Parkinson's disease.

Graphical Abstract



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Abstract

Parkinson's disease (PD) is a common neurodegenerative syndrome that progreses with age and presents in many forms. Some efforts to understand PD development include regulation of epigenetic mechanisms, which usually include minor molecular modifications of DNA and histones which are essential to regulate genetic activity. We have highlighted the problems associated with the development of genetic and epigenetic processes and reviewed several studies. None of these led to stronger conclusions about the autonomous roles of epigenetic pathways. Data from the current standpoint suggests that SNCA, one of the hallmark genes implicated in PD, is more prevalent than pathways that directly require DNA methylation, as a consequence of complicated DNA hydroxymethylation, global hyperacetylation, and histone deacetylase (HDAC). Without current epigenetic clinical goals to delay PD progression, we hypothesize how PD neurons, with the potential therapeutic objectives, can affect local and global epigenetics via inflammation, oxidative stress, autophagy and DNA repair mechanisms.

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Introduction

Parkinson's (PD) disease is a common neurodegenerative syndrome with various motor and non-motor symptoms (1). The reduced dopamine (DA) activity in Substantia Nigra compacta (SNc) causes the gradual loss of spontaneous motions in Parkineson's patients, particularly loss of transmission to the dorsal striatum. Since these symptoms were first described in 1817 by James Parkinson, much progress has been made in determining the root causes. The word pathology applies to the research, for this reason, neuronal pathways, pathological features, and compromised anatomical regions are all well described (2). At this time, experts concentrate on the forms in which Parkinson's disease progresses and evolves (3).

Given the scarcity of genetic PD, stochastic events in nuclear and mitochondrial DNA, such as environmental signals, viruses and life-long somatic mutations, can all play a part; these theories were also used to understand why monozygotic twins have very low PD match when they germinate from a single seed. Furthermore, an increasing number of studies have found similarities between PD and activities that could cause differences in PD concordance in certain situations, such as the possible preventive consequences of smoking, Extraordinary signs, homeostasis protein, metabolism, and other aspects play a role part (4).

Epigenetics and genetics are highly interconnected. In the contemporary century, neuroscience has taken priority in untangling these factors, making more decisive conclusions regarding healthy lifestyles or therapies for Parkinson's disease possible. As a result, we'll see how much progress in genetics and epigenetics has progressed and how various epigenetic pathways can help individuals with Parkinson's disease. In the next step, we also take into consideration how PD shares some traits with ageing, such as DNA and mitochondrial damage, and a rise in (neuro) inflammation (5) and an increased incidence with age (6). Processes may affect the PD epigenome to summarize potential therapeutic epigenetic targets to delay PD production.

Parkinson's pathology

PD is also the second most prevalent diagnosis of neurodegeneration behind Parkinson's disease, which Dr. James Parkinson first documented in 1817. With a frequency of 1-2% over 65 years of age (7, 8) and 4-5% over 85 years of age (9) 6.3 million people worldwide are estimated to be PD impacted, which is projected to rise to 8.3 million by 2030 (10). A lack of dopamine neurons from substantial nigra pars compacta is the normal neuropathological characteristic of PD (SN). The SN dopaminergic neurons discharge to the striatum releasing dopamine, the critical neurotransmitter for motor control learning and performance (11, 12). Parkinson's disease patients have engine dysfunctions such as bradykinesia, muscle inflexibility, restorative tremor and postural rigidity induced by reduced amounts of dopamine (13, 14). All non-motor symptoms limiting the capacity of the patient to perform include anxiety, stress, diabetes, sleep disturbances, constipation, hyposmia and anosmia (8, 15). While motor features are still the main criteria for diagnosing PD, certain non-motor deficiencies are now used as predictive markers for the disorder because they appear prior to motor symptoms (16, 17). In reality, according to the Braak stage hypothesis, Lewy's body pathology is widely spread not just in the brain but also in other tissues like the stomach.

The progression of Parkinson's disease, according to this definition, is split into six stages. Stages 1-2 are the presymptomatic procedure through which Lewy species appear in the enteric and peripheral autonomous nervous system and range from the olfactory bulb and vagus nerve to the lower brainstem. The symptomatic process starts on stage 3, where the midbrain, including the SN, gets affected. Finally, in phases 4 and 5, the neocortex is influenced by pathological changes, whereas the neocortex is affected by phases 5 and 6 (18). Although this staging approach has been tested by other societies and implemented in several instances, exceptions to the model were observed, there was growing doubt about the general validity of the hypothesis (19, 20).

Parkinson's hereditary

Just 10–15% of Parkinson's disease is family-oriented (21). However, if further genetic studies are done, further findings are likely to be linked to genes currently unidentified (22). Consequently, an increasing number

of genes correlated with the onset of Parkinson's disease (PARK genes). There are presently 20 genes responsible for recessive, dominant or X-linked autosomal ancestry types in the PARK gene family. Moreover, PD genes can involve dot mutation, replication or triplication, which may cause PD both early and late-onset (23, 24).

There were only two PD-associated genes with 500 DNA variants (25). The first mutation correlated with family PD was the alpha-synuclein gene coding (SNCA). Six-point mutations that lead to replacements of amino acids have been linked to autosomal dominant Parkinson's disease models. In addition, doubling and tripling of the SNCA locus are attributed to autosomal dominant parkinson disorder variations (26, 27). While SNCA is a studied gene, it is not understood how the exact function of alpha-synuclein (aSyn) is induced. ASYN is a presynaptic protein that plays a part in both the development of the neurotransmitter and the regulation of the synaptic vesicle pool. Other studies have shown that aSyn binds mitochondria and is present both in mitochondrial membranes and ER interrelationships and in the nucleus (28, 29). The most common cause of autosomal-dominant PD is LRRK2 mutations (30). Any ethnic groups have higher LRRK2 mutation rates (31).

Most patients with LRRK2 mutations are classically clinical with PD, including the presence of LBs; However, the age at which the symptoms are initiated can vary from idiopathic disease, which occurs sooner or later (32). The VPS35 gene encodes the vacuolar protein sorting 35 (VPS35). VPS35 is the main component of the cargo-recognition system retromer which is involved in the trade and recycling of synaptic vesicles and proteins. The p.D620N mutation, with a dominant-negative protein sorting phenotype, became a novel trigger of the late-onset autosomal dominant PD, GBA encodes the glucocerebrosidaselysosomal enzyme (33-35), that is active in the synthesis of the glycolipid. Mutations in this gene are affected by Gaucher disease, one of the lysosome-storage disorders. On the other hand, GBA mutations have been shown to increase the chances of PD developing and are very common in PD patients (36-38). On the other hand, mutations in PARK2, PINK1, and PARK7 can cause early PD recessive autosomal variants. All three genes have identical clinical phenotypes, but LB disease appears to be more nuanced (39). PARK3, PARK10 and PARK12 loci were all linked to the pathology of Parkinson's, but the genes also need to be established. As a result, more studies are important to decide how these loci work in PD pathogenesis (40).

Mechanisms implicated in Parkinson's disease

DNA methylation

Along with histone modifications and pathways involving tiny RNA molecules, DNA methylation is one of the most significant epigenetic processes. Methylation of CpG sequences has been linked to chromatin formation. The transcriptional machinery is unable to reach gene promoter regions due to conformational changes, resulting in changes in gene expression levels. As a consequence, promoter hypermethylation is often related to gene silencing, while promoter demethylation is linked to gene expression; even though specific research differs (41), Folate, other B vitamins (vitamins B6 and B12), and homocysteine (hcy) are all involved in one-carbon metabolism, a complicated process that generates S-adenosylmethionine (SAM), the most powerful intracellular methylating agent. The DNA methylation ability, also known as the ratio between SAM and S-adenosylhomocysteine (SAH) amounts, is crucial for DNA methylation. The main enzymes in DNA methylation are DNA methyltransferases (DNMTs), which catalyze the transfer of a methyl group from SAM to cytosine, resulting in 5-methyl-cytosine. One-carbon metabolism is impaired, DNA methylation ability is altered, and DNA synthesis is limited.

In Alzheimer's disease (AD) cases, altered methylation and expression of multiple genes were found, suggesting that epigenetic modifications play a role in the neurodegenerative mechanism (42). There have been fewer trials of PD patients to date; nevertheless, there are several positive findings. In PD, there is evidence of compromised one-carbon metabolism and altered DNA methylation capacity (43, 44). The SNCA gene can be

subjected to epigenetic control, according to epigenetic studies in PD brains (45, 46). Latest large-scale experiments have also indicated that other PD-related genes could be epigenetically modified in PD brains (47).

α-Synuclein

Several lines of evidence lead to a gene-dosage paradigm, including the discovery of families of SNCA locus replication and triplication and the correlation of promoter and 3UTR polymorphisms with irregular forms. SNCA has a role in the pathogenesis of Parkinson's disease (48). The SNCA promoter was hypermethylated in people with alcoholism (49) and anorexia patients, meaning that the gene is epigenetically controlled. An examination of SNCA alleles in a woman with Parkinson's disease who is heterozygous for the A53T mutation (50).

SNCA demonstrated mono-allelic expression in this patient, with epigenetic silencing of the mutant allele owing to histone modifications but not DNA methylation and upregulation of the wild-type allele resulting in higher expression of the wild-type allele. mRNA amounts were higher in the study community than in the control group (51). Others also discovered that methylating human SNCA intron 1 lowers gene expression while inhibiting DNA methylation enhances SNCA expression. They also discovered that methylation of SNCA intron 1 DNA was decreased in several cases. The substantianigra, putamen, and cortex were epigenetically controlled in intermittent PD patients, leading to an epigenetic modulation of SNCA expression in PD (49).

Another analysis discovered an SNCA CpG island where methylation status shifted in tandem with enhanced SNCA expression. Postmortem brain imaging showed spatial nonspecific methylation variations in this CpG region between controls and PD participants in the anterior cingulate and putamen; however, methylation of this component was dramatically reduced in the substantianigra of PD patients (50). Of them, Previous studies also found elevated SNCA mRNA levels in the substantianigra tissue of people with Parkinson's disease (Figure 1) (52, 53).

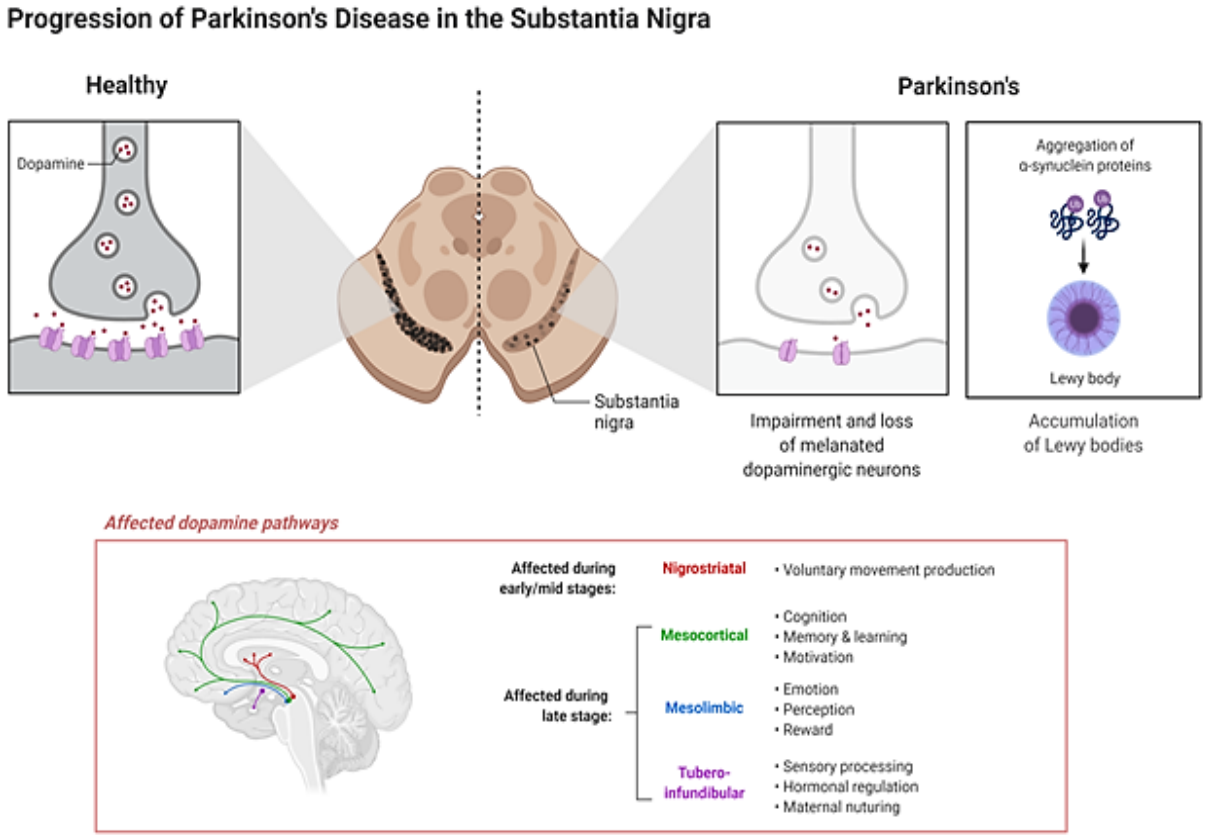

Figure 1. The reduced activity of dopamine (DA) and elevated SNCA mRNA levels in Substantia Nigra observed in Parkinson's disease.

According to a recent report, DNA methyltransferase 1 (DNMT1) is believed to be sequestered by-synuclein in the nucleus. The DNA methylation enzyme DNMT1 is responsible for preserving DNA methylation and is primarily found in the nuclear compartment of the adult brain and is abundantly articulated. Nuclear DNMT1 amounts were shown to be lower in postmortem brain tests from patients with PD and dementia with Lewy bodies (DLBs) and in the brains of healthy individuals; types of-synuclein transgenic mice. Furthermore, the sequestration of DNMT1 in the cytoplasm in inhuman and mouse brains culminated in global DNA hypomethylation, affecting CpG islands upstream of SNCA and other genes. Overexpression of DNMT1 partly restored nuclear DNMT1 values. In neuronal cell cultures and the brains of synuclein transgenic mice, DNMT1 was found. Consequently, the authors hypothesized that the interaction of DNMT1 and synuclein could mediate aberrant subcellular localization of DNMT1, resulting in epigenetic modifications in the brain (54).

Epigenetics Modifications

About 90% of Parkinson's disease patients are idiopathic and manifest as late-onset Parkinsonism. Idiopathic PD has no clear origin, although it is triggered by a mixture of environmental causes and hereditary predisposition. Living in a rural setting, for example, tends to raise the likelihood of Parkinson's disease, likely due to increased sensitivity to chemicals and wood preservatives. Furthermore, lifestyle preferences such as coffee consumption and cigarette smoking are inversely related to the danger of having Parkinson's disease (55). A conclusive role of epigenetic alteration in neurodegeneration in sporadic PD has yet to be identified. Homocysteine cycle dysregulation is evidence for an involvement of DNA methylation in sporadic PD. Plasma homocysteine levels are higher in PD patients, resulting in a rise in SAH and a decline in SAM, resulting in an overall increase in methylation capacity (the ability to methylate) (56), increased SAM/SAH ratios have been linked to improved cognitive performance in Parkinson's disease patients, suggesting a connection between methylation and the disease process (57).

In Japanese PD patients' peripheral leukocytes, proof of less short telomeres with persistent subtelomeric methylation status was detected instead of stable controls. Subtelomeric Hypomethylation is linked to enhanced DNA-binding protein accessibility for suppressing the "telomeric location influence," a process that silences genes near a telomere. The telomeric and subtelomeric regions that are damaged by oxidative stress become hypomethylated, allowing free radicals quick access (58).

Abnormal miRNA profiles are the most significant results relating epigenetic modulation to intermittent PD. MiR-1, miR-22 *, and miR-29 were classified as the most abundant miRNAs in nontreated PD patients' blood samples. When opposed to healthy people, these genes are activated in a particular way. The expression of miR-16-2 *, miR-26a2 *, and miR-30a was found to vary between treated and untreated PD patients. Similarly, miRNA profiling of PD brains showed early downregulation of miR-34b/c, a mitochondrial function modulator. MiR-34b/c was found to be downregulated in particular (59).

These participants did not undergo any PD-related medication during their lives since they were in the premotor phases of the disease (stages 1-3). Downregulation of miR-34b/c was also linked to lower expression of mitochondria-associated and familial PD-based proteins DJ-1 and parkin (60). These results indicate a correlation between mitochondrial dysfunction and genetic pathways of epigenetic control in Parkinson's disease. Pathogenesis is a word used to define the process of an On the issue of environmental pollutants, the unintended exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which caused PD-like symptoms in humans and was later tested in animal models (61, 62), was the first evidence of environmental exposure as a source of PD. Some environmental pollutants, such as pesticides and industrial agents (63, 64), have been linked to elevated risk in addition to MPTP; while a conclusive causal position in the development of PD is still being debated (65), Chronic environmental exposure can change gene expression through epigenetic processes, according to new research, and could be a key risk factor in the pathogenesis of late-onset neurodegenerative diseases. For example, DNA methylation induces allelic skewing in a wide number of genes, causing one allele to be transcribed or expressed at a higher degree than the other depending on the allele's

maternal or paternal origin. This skewing could help researchers figure out how an individual's genotype influences the impact of an environmental factor on the likelihood of having a neurodegenerative disease (66). Histone alteration tends to be the most significant epigenetic shift induced by environmental pollutants, including chemicals, among the numerous epigenetic pathways. Herbicides like paraquat and glyphosate are commonly utilized.Dieldrin, an organochlorine insecticide, is one of the organic chemicals that have been related to PD (59). Due to neurotoxic insults, histone acetylation can be a major epigenetic alteration in dopaminergic neuronal cells. Paraquat treatment of N27 dopaminergic cells resulted in histone H3 acetylation and a reduction in overall HDAC production (67, 68).

Dieldrin triggered histone acetylation in the nigrostriatal system in mouse models. Dieldrin also increased the acetylation of key histones H3 and H4 in a time-dependent manner. Dieldrin induced proteasomal dysfunction was responsible for the hyperacetylation, which resulted in an overabundance of the essential HAT cAMP reaction element-binding protein (CBP). Dieldrin-induced histone acetylation and dieldrin associated apoptosis were greatly reduced by anacardic acid, a HAT inhibitor, independent of its antioxidant effect (69).

Furthermore, MPTP administration has been related to reduce striatal involvement of H3 histone K4 trimethylation in murine and nonhuman primate models, and chronic administration of the DA precursor L-DOPA has been shown to reverse these modifications (70). Exposure to environmental contaminants has also been related to shifts in miRNA profiles. MiR-7 expression was shown to be lower in animal and cell culture models after exposure to MPP + (1-methyl-4-phenylpropionic acid), MPTP's toxic metabolite, phenyl-pyridinium ion), culminating in enhanced-synuclein expression (71). This is an intriguing finding since DA neurodegeneration in Parkinson's disease is linked to synuclein expression levels, implying that miR-7 may be a therapeutic option. The findings reviewed above indicate that prolonged sensitivity to environmental contaminants changes the epigenome, which may clarify the noxious impact of these chemicals on PD pathogenesis.

Conclusion

Clearly, epigenetic mechanisms control convoluted biological processes. However, we should also just understand the role of epigenetic regulation in multifactorial diseases such as Parkinson. in PD pathophysiology and their probable associations between genetic and environmental factors, DNA methylation, histone alteration, and modifications in miRNA profiles are known to occur, Epigenetic medications such as DNMT inhibitors, HDAC inhibitors, or antibiotics that are targeted against histone demethylases may also be used for their targeting (histone methyltransferases or SIRTs), Future study is necessary to analyze, create and correlate epigenetic pathways. In particular, the Human Epigenome Project has launched the cataloging, interpretation and linkage of epigenetic profiles with numerous disease conditions. These molecular signatures were correlated in genome-wide association studies to clinical factors and results of Parkinson's disease. In order to provide a clearer image of the illness, these epigenomic data may ultimately be combined with genomic and phenomic profiles in both the hereditary and sporadic Parkinson disease. In order to best appreciate Parkinson's disease's phenomenal landscape, new and evolving advances will lead to better molecular instruments that enhance the prognosis, diagnosis, and eventually therapeutic intervention.

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