Effect Modification between Genes and Environment and Parkinson's Disease Risk

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Parkinson's disease (PD) is a complex neurodegenerative condition in which genetic and environmental factors interact to contribute to its etiology. Remarkable progress has been made in deciphering disease etiology through genetic approaches, but there is limited data about how environmental and genetic factors interact to modify penetrance, risk, and disease severity. Here, we provide insights into environmental modifiers of PD, discussing precedents from other neurological and non-neurological conditions. Based on these examples, we outline genetic and environmental factors contributing to PD and review potential environmental modifiers of penetrance and clinical variability in monogenic and idiopathic PD. We also highlight the potential challenges and propose how future studies might tackle these important questions.

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Parkinson's disease (PD) is a neurodegenerative disease, characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of α-synuclein aggregates known as Lewy bodies.[1]

Although two broad categories of PD have been described (idiopathic and monogenic), a continuum ranging from rare deleterious and highly penetrant genetic variants responsible for Mendelian forms, to common risk loci increasing susceptibility for idiopathic PD is more likely. In early research on the genetics of PD, several studies identified mutations in genes causing Mendelian forms of PD—*SNCA*, *LRRK2*, *VPS35*, *PINK1*, *PRKN*, and *DJ1*.[2] However, currently, it is heterozygous pathogenic variants in *GBA* that represent the most common genetic risk factor for PD, and there is overlap in some of the genes associated with monogenic and idiopathic PD (eg, *LRRK2* and *SNCA* are implicated in both).[2]

Genetic variation, ranging from high-to-low frequency variants with low-to-high effect size, contributes at least 25% to the overall risk of developing PD.[3] Mutations in some PD-related genes exhibit incomplete penetrance or display variability in expressivity, such as the age

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at onset (AAO) and clinical phenotype. Although penetrance is defined as the probability that a single individual carrying a disease-associated genotype will exhibit a phenotype of the associated disorder, expressivity describes the differences observed in the clinical phenotype between individuals with the same genotype.[4]

Advancing age is the primary determinant of the manifestation of PD, but there is clearly a role for other factors in influencing the penetrance and expressivity of disease-causing mutations, henceforth described as "modifiers." Some progress has been made in this regard by evaluating complex genetic influence on PD; however, this clearly does not represent the entire basis for disease variability.[5] A prominent role for environmental factors (the "exposome") is supported by findings from epidemiological and experimental studies (Fig 1). One way in which genes and the exposome may interact is through epigenetics, which is increasingly thought to play an important role in PD.[6] Evidence for direct epigenetic regulation of familial PD-linked genes is emerging, and the most studied of these is *SNCA*.

In this review, we will focus on existing evidence for environmental modifiers of mutations and genetic risk factors linked to PD to highlight the value of this approach in achieving a greater understanding of the role environmental factors play in PD. To put this into perspective, we discuss precedents from selected examples of monogenic diseases including non-neurological conditions (cystic fibrosis and BRCA-positive breast cancer) and neurological disorders, such as phenylketonuria and *DYT1* dystonia. We highlight genetic factors contributing to PD and review the current knowledge of environmental modifiers of penetrance in PD, placing this in a future-facing context.

Environmental Modifiers Associated with Disease Penetrance

Non-Neurological Monogenic Diseases Influenced by Environmental Modifiers

Knowledge about non-genetic modifiers of monogenic diseases is sparse. Little is known in PD, and understanding in well-defined Mendelian disorders (including diseases such as Huntington's) is generally low. Two diseases that appear to be influenced by exogenous exposures are the autosomal recessive disease cystic fibrosis (CF) and autosomal dominant *BRCA*-positive breast cancer.

Cystic Fibrosis

CF is characterized by abnormal secretions in multiple organ systems and eventual respiratory failure.[7] CF results from mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene; however, the correlation

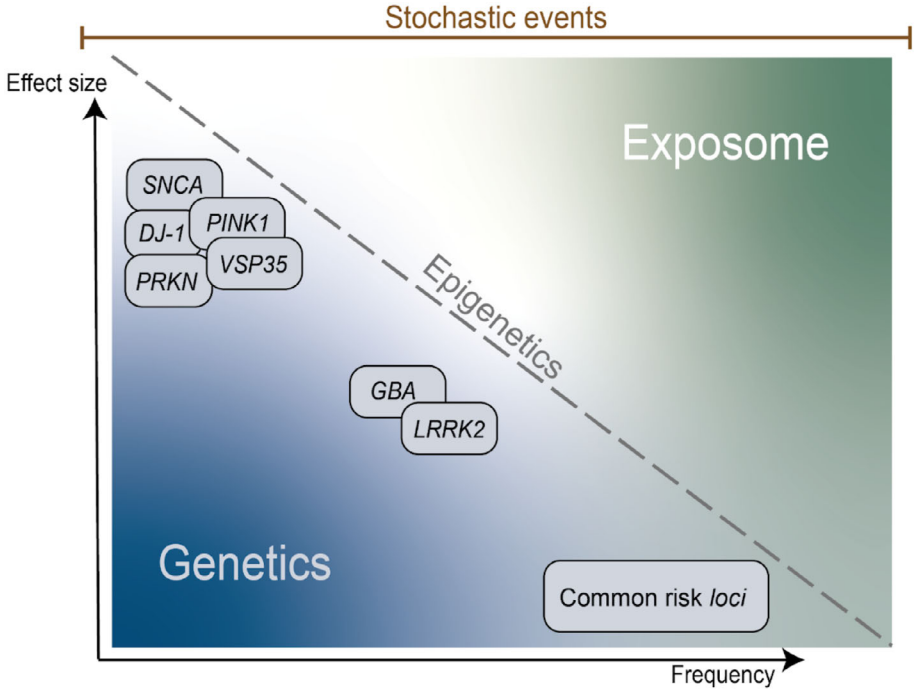

FIGURE 1: A model of the interplay among gene–environment interactions, epigenetic changes, and stochastic events in Parkinson's disease (PD). Interactions between genetic factors and environmental exposures (the "exposome") are thought to be major contributors to the etiology of PD. Emerging evidence has shown that epigenetics may play an important role in the pathophysiology of PD, potentially representing a mechanistic bridge between the gene–environment interactions. However, most of the variation remains unexplained, illustrating the inherently stochastic nature of PD. [Color figure can be viewed at www.annalsofneurology.org]

between genotype and phenotype in CF is imprecise. In particular, the severity of CF cannot be predicted for most *CFTR* genotypes, because both the AAO of pulmonary symptoms and the rate of decline in pulmonary function are variable.[8] In recent years, modifier genes and environmental risk factors have been identified that significantly contribute to the CF phenotype. Non-genetic determinants include environmental exposures, and socioeconomic, cultural, and community influences, which together may account for up to 50% of the clinical variation in CF.[9]

A Danish study found that certain genetic variants in a CF-modifier gene, the mannose-binding lectin (*MBL*) gene, were associated with greater loss of lung function in patients with CF.[10] This effect was limited to patients with chronic *Pseudomonas aeruginosa* infection. Grasemann et al. demonstrated that several polymorphisms in the nitric-oxide synthase 1 (*NOS1*) gene correlated with the variability in the frequency and severity of microbial infections, indicating an interaction between variants of *NOS1* and the environment.[11] Besides, genetic variants in *CFTR*, as well as in the transforming growth factor beta 1 (*TGF-β1*) gene, amplify the negative effects of secondhand smoke exposure.[12] These findings reflect the existence of environmental modifiers of the clinical effect of *CFTR* genotypes and shed light on the impact of environmental factors on disease expressivity and progression.

BRCA -*Positive Breast Cancer*

Germline *BRCA1* or *BRCA2* (*BRCA1/2*) mutations substantially increase the risk of developing breast cancer (BC), accounting for approximately 25 to 30% of familial BC, and about 3% of all BCs.[13] Around 50 common variants, that are also seen in the general population, have been shown to modify BC risk for mutation carriers.[14] Incomplete penetrance of mutations in *BRCA1/2* suggests that additional modifying factors influence BC manifestation among mutation carriers. Breastfeeding and a later age at menarche appear to have protective effects on *BRCA1*-associated BC, but do not appear to influence risk in women with a *BRCA2* mutation. Each year of breastfeeding is associated with a 19% reduction in risk, whereas ≥2 years is associated with an overall 49% reduction in risk.[15] A 15% reduction in *BRCA1*-associated BC risk has been observed for each year of delay in menarche, with a 54% overall reduction in risk for women whose age at menarche was ≥15 years of age versus ≤11 year.[16] Advanced age at first live birth has also been identified as a probable factor modifying the risk of *BRCA1* mutation carriers (risk ratio [RR] = 0.65, 95% confidence interval [CI] = 0.42–0.99 for age ≥30 years vs. <30 years).[17] With respect to exogenous hormones, a significant 40% increased risk of early-onset BC among *BRCA1* mutation carriers was reported with ever versus never oral contraceptive use.[18]

Neurological Monogenic Diseases Influenced by Environmental Modifiers

The role of the exposome in neurological diseases with Mendelian inheritance has been long suspected, with effort devoted to identifying causative agents. In this section, the role of environmental modifiers in selected neurological diseases is discussed.

Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism, characterized by mutations in the phenylalanine hydroxylase (*PAH*) gene. The disease is heterogeneous as it depends on the degree of residual PAH activity and blood phenylalanine (Phe) concentrations.[19] The features, if left untreated, are mostly due to the central nervous system toxicity of Phe, resulting in severe intellectual disability, epilepsy, as well as behavioral, psychiatric, and movement disorders.[20]

Despite a clear genetic basis, the PKU phenotype can be prevented or reduced by dietary manipulation.[21] The mainstay of management of PKU resides in a Phe-free diet to keep Phe plasma levels between 120 and 360 μmol/l.[22] Fulfilment of dietary restriction significantly reduces blood Phe concentration and is the most effective means of achieving normal neurocognitive and psychosocial functioning.[23]

However, dietary modification does not guarantee normal neurological development. Deficits in executive function, motor control, as well as psychiatric symptoms have been reported in patients with early-treated PKU.[24,25] A study by Nardecchia et al. showed that the prevalence of tremor was 32% in early-treated patients with PKU compared with controls who did not show neurological signs.[26] Due to the stringent dietary requirements, nutritional deficits are common in patients with PKU, who are likely to be at risk of deficiencies in cholesterol, choline, and folic acid. Such deficiencies may exacerbate the neurological problems.[27]

DYT-TOR1A Dystonia

Dystonia caused by *TOR1A* gene mutations is the most common cause of early-onset primary generalized dystonia. A 3-base pair (GAG) deletion in the *TOR1A* gene is responsible for most cases, but clinical disease expression occurs in only 30 to 40% of mutation carriers.[28] Individuals with the disease-modifying Asp216His variant in trans configuration with the GAG deletion are largely protected from expression of the disease.[28]

The earliest report of peripheral trauma related to dystonia was made by Gowers in 1888, who observed a patient with cervical dystonia after a local neck injury, as well as a patient with writer's cramp who had previously sprained his thumb.[29] A study by Opal et al., demonstrated a strong intrafamilial variability of the DYT-TOR1A dystonia (*DYT1*) phenotype, from asymptomatic carrier status to focal, segmental, multifocal, and generalized dystonia, including a malignant form culminating in a dystonic storm.[30] This phenotypic variability could potentially imply a role for environmental modifiers altering the function of *TOR1A* to produce such a range of variable expressivity.

Saunders et al. postulated that *DYT1* carriers who experienced childhood illnesses (eg, varicella, mumps, and measles) had a greater prevalence of dystonia. The authors found a greater frequency of early childhood illnesses (occurring at age ≤6 years) in 55 patients with *DYT1* dystonia than in 47 asymptomatic *DYT1* carriers (odds ratio [OR] = 2.71, 95% CI = 1.20–6.20).[31] Separately, a case of a 38 year-old patient who was a *DYT1* mutation carrier was reported developing a dystonic posture of the foot within a few days after twisting the ankle.[32] In 2013, a retrospective study assessed exposure to perinatal adversity, childhood infections, general anesthesia, and physical trauma prior to symptom onset in 39 manifesting and 23 non-manifesting carriers, as well as 48 non-carriers from a series of 28 families with *DYT1*-related dystonia.[33] A positive association between a history of complications of vaginal delivery and manifestation of dystonia was observed (OR = 8.47, 95% CI = 1.45–49.40). The authors concluded that perinatal adversities might modulate the penetrance of *DYT1* dystonia.

Literature Search

This narrative review was undertaken following a literature search on the MEDLINE database using PUBMED to identify articles published from August 1999 to May 2022. The following keywords were used individually or/and in combination with "Parkinson's disease": environment, risk factor, age, gender, sex, smoking, tobacco, exercise, physical activity, education, pesticides, toxins, solvents, metals, air pollutants, comorbidities, body mass index (BMI), infection, head trauma, traumatic brain injury, nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen, dairy, appendectomy, *LRRK2*, *GBA, SNCA*, *PINK1*, *PRKN*, *DJ1*, *VPS35*, penetrance, gene–environment interaction, environmental factors, and modifiers. Articles were assessed for their relevance to the subject matter and we restricted our search to articles written in English.

Non-Genetic Modifiers of Idiopathic PD

For idiopathic PD, a combination of genetic and non-genetic (or environmental) risk factors are believed to modify risk of disease.[3] An important qualifying observation is that many so-called environmental factors are, in part, genetically determined (eg, smoking behavior). Furthermore, because PD is a borderline "rare" outcome, studies of environmental factors in PD are often retrospective case–control studies, rather than prospective cohort studies. Observational studies, in particular case–control studies, are prone to various forms of bias, which makes causal inference challenging. Observed associations could be a consequence of reverse causation or confounding factors, and numerous life-style factors are associated with PD.[34] With these caveats, we will review non-genetic factors associated with PD and evidence for gene–environment interactions.

Age and Sex

The main risk factor for PD is increasing age, such that incidence increases substantially after the age of 60 years.[35] Male sex is a recognized risk factor and, on average, men are at 50% higher risk than women.[36] The difference is likely not explained by common genetic variation on the autosomes because no sex-specific genetic risk factors have been identified.[37] However, two genome-wide significant loci on the X-chromosome have been identified, indicating that the X-chromosome may contribute to PD risk in both sexes.[38]

Lifestyle Factors

Smoking is well-documented as showing an inverse association with subsequent PD.[39] Inverse associations with future PD have also been observed for coffee and alcohol consumption, and the use of NSAIDs.[40] Intake of dairy products and higher education have, on the other hand, been associated with an increased risk of PD.[41,42] An inverse association between PD and moderate to high levels of physical exercise has been reported.[43] Exercise also seems to have a positive impact on several symptoms occurring in PD.[44]

Toxins

Pesticides, such as rotenone and paraquat, along with factors related to pesticide exposure (eg, agricultural occupation and well-water drinking) are associated with an increased PD risk.[45,46] For example, rotenone inhibits mitochondrial function through mitochondrial complex I,[45] whereas paraquat is a structural analogue of MPP+, causing degeneration of dopaminergic neurons.[47]

Exposure to solvents (most notably trichloroethylene) and metals, such as manganese, copper, mercury, lead, iron, zinc, aluminum, and amalgam, have been

associated with an increase in PD risk but the evidence for each of these is inconclusive.[48,49] Exposure to other toxic components, such as air pollutants (nitrogen dioxide [NO_2])[50] and occupational external γ-ray exposure[51] may also be associated with an increased risk of PD.

Comorbidities

Positive associations with PD risk have been observed across other complex diseases, such as bipolar disorder[52] and schizophrenia spectrum disorders.[53] An association among individuals with schizophrenia spectrum disorders could be due to increased vulnerability of the dopamine system or misdiagnosis of drug-induced parkinsonism.[53,54] Inflammatory bowel diseases may be associated with increased PD risk, as well as shared genetic architecture, and there is an emerging association between type 2 diabetes and PD.[55,56]

Associations with other health-related factors, such as serum urate levels, infections, appendectomy, BMI, and head trauma, have been reported frequently. Higher serum urate levels are associated with a decreased PD risk, but the inverse association appears mainly to be seen in men.[40] Certain infections may be a plausible risk factor for PD and a number of viral agents have been suggested, including, for example, influenza and viral hepatitis. There is mounting evidence for a role of bacteria in PD development (especially *Helicobacter pylori* and the gut microbiome). However, higher quality observational, and potentially interventional, studies are needed to further elucidate the potential link between infections and PD risk.[57]

A tendency for lower BMI is commonly observed in patients with PD,[58] but no support for an association between higher BMI and PD risk was observed in a meta-analysis of prospective studies.[59] However, a Mendelian randomization study inferred that liability toward a higher BMI appeared to lower PD risk.[60] Several observational studies have reported associations between head trauma and PD, but, like several examples, could be explained by reverse causation.[61]

Gene–Environment Interactions in Idiopathic PD

Interactions between genetic variants and environmental factors may explain some of the missing risk observed in idiopathic PD. Recent studies aimed at combining non-genetic risk variants and PD polygenic risk scores to identify individuals at higher risk of PD have been published. In one study, an interaction between polygenic risk scores and diabetes was observed, suggesting that diabetes may be a stronger risk factor for PD in individuals with a lower genetic risk of PD.[62]

Gene–environment interactions involved in PD risk have also been seen through synergistic effects between genetic variants and specific environmental factors, such as a higher PD risk among patients with type 2 diabetes that have the common *SNCA* rs356221-AT/TT genotype[63] and a less pronounced inverse association of smoking in carriers of both *RXRA* rs4240705 and *SLC17A6* rs1900586 minor alleles.[64] An earlier PD diagnosis and a higher PD risk following head trauma was observed among carriers of an expanded dinucleotide microsatellite Rep1 in the promoter region of *SNCA*.[65] Several studies have also reported increased PD risk and synergistic effects between pesticide exposure and genetic variants in genes such as *HLA-DRA*,[66] *BCHE*,[67] *PPARGC1α*,[68] among others. General limitations of these studies include relatively small sample sizes and lack of replication.

Environmental Modifiers of Monogenic Forms of PD

LRRK2

LRRK2 mutations are considered a major genetic determinant of PD, with incomplete penetrance. Other genetic or environmental factors likely modulate *LRRK2* expression or its effect on PD pathophysiology (Fig 2, Table S1). The overall PD penetrance in *LRRK2* Gly2019Ser mutation carriers can vary between different populations.[69] The age-specific penetrance of PD among *LRRK2* mutation carriers has been estimated to be 36%, 59%, and 80% at 59, 69, and 79 years of age, respectively.[70] The cumulative incidence of *LRRK2* Arg1441Cys was found to be the least penetrant, with a median AAO of 71 years, whereas *LRRK2* Asn1437His the most highly penetrant, with a median AAO of 46 years.[69] Additional studies found a "sex effect" in the prevalence of *LRRK2*-associated PD,[71–74] whereas others have reported similar PD penetrance in male and female patients carrying *LRRK2* mutations.[75-77]

As for idiopathic PD, the role of NSAIDs has been explored in *LRRK2*-associated PD, because *LRRK2* is expressed in immune cells, such as microglia, and may be involved in inflammatory processes.[78] One study found that the regular use of NSAID medication was associated with reduced odds of PD among *LRRK2* carriers, with similar results for ibuprofen and aspirin.[78] Separately, the role of circulating urate in *LRRK2*-associated PD has been investigated with the rationale that urate acts as an antioxidant and *LRRK2* pathophysiology is thought to involve oxidative stress. In line with this, the results revealed that the odds of developing PD were lower with increasing serum urate levels.[79]

A significant *LRRK2*-caffeine interaction was observed in *LRRK2* Arg1628Pro mutation carriers, with a lower odds ratio for developing PD among the carriers who consumed

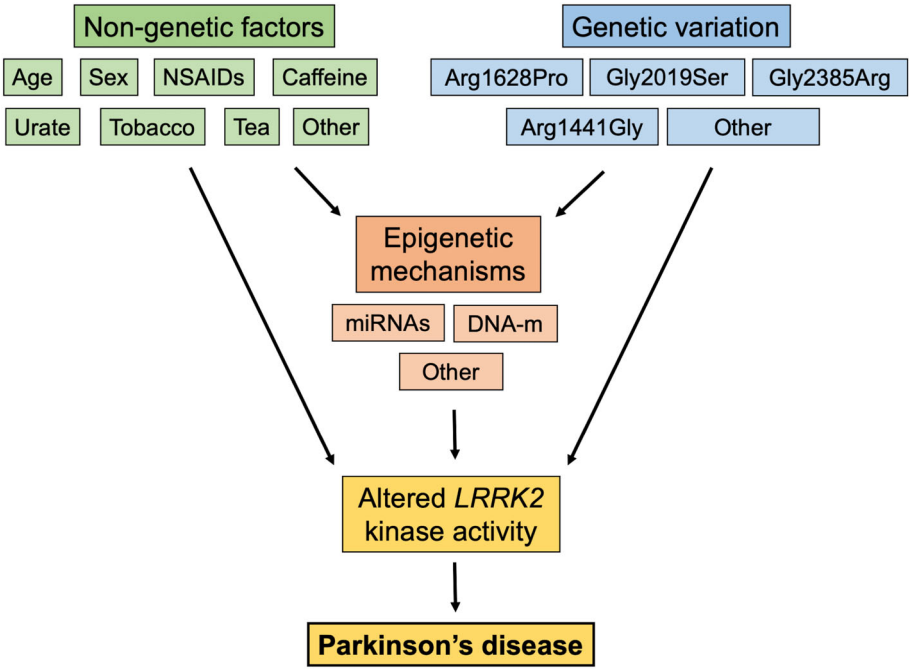

FIGURE 2: Factors regulating the pathogenesis of *LRRK2*-associated Parkinson's disease. Several studies have recognized various risk factors, including genetic variation, non-genetic factors, as well as epigenetic mechanisms that may alter *LRRK2* dynamics. Examples of genetic variants include Arg1628Pro, Gly2019Ser, Gly2385Arg, and Arg1441Gly. Non-genetic factors comprise age, sex, nonsteroidal anti-inflammatory drugs (NSAIDs), caffeine, urate, tobacco, and tea. Examples of epigenetic modifiers include DNA methylation (DNA-m) and microRNAs (miRNAs). [Color figure can be viewed at www.annalsofneurology.org]

caffeine than among carriers who were non-consumers, compared to caffeine consumers without the mutation. In line with these findings, caffeine and trigonelline (an alkaloid contained in coffee) have been associated with lower risk of PD in *LRRK2* carriers.[80] The results of another study showed a significant association between caffeinated soda and black tea drinking with AAO in *LRRK2*-associated PD. Although caffeinated soda drinkers had an earlier AAO than those who did not, *LRRK2* carriers who consumed black tea had a later AAO compared to those who did not.[81] In the same study, tobacco was associated with later AAO in patients carrying the Gly2019Ser mutation.[81] An exploratory analysis further revealed a significant interaction between a combined smoking and caffeine intake exposure and rs2896905 at the *SLC2A13* gene, near *LRRK2*.[82] The mechanisms behind the observed associations between smoking and coffee consumption on the penetrance of *LRRK2* remain unknown. These environmental factors have been reported to contribute to epigenetic modifications,[6] however, no direct link between this and *LRRK2* has been reported to date.

SNCA, VPS35, PRKN, PINK1, and DJ1

The prevalence of disease-causing mutations in PD is low, and the small number of individuals with monogenic PD caused by autosomal dominant mutations in *SNCA*, *VPS35*, or by autosomal recessive mutations in *PINK1*, *PRKN*, or *DJ1*, makes it difficult to conduct well-powered studies of penetrance and potential genetic or non-genetic modifiers. Furthermore, the literature points to many variants of uncertain significance within these genes, raising questions about whether these are non-causative or causative, but with incomplete penetrance.

For the most common pathogenic coding point mutation in *SNCA*, Ala53Thr, it has been suggested that the penetrance is nearly 85%.[83,84] The penetrance of duplications in *SNCA* is lower, with 33% penetrance reported in one family.[85] Furthermore, one study has demonstrated that patients with PD exposed to well water drinking carrying at least one Leu allele at the *PRKN* Val380Leu polymorphism, showed a later AAO compared with those patients without it, suggesting this allele might have a protective effect in the presence of an environmental putative risk factor.[86] However, genetic modifiers of *SNCA*, *PRKN*, and other genes causing monogenic PD, along with non-genetic modifiers and their combinations, are yet to be explored. Several studies have reported epigenetic modifications occurring in PD, including hypomethylation of *SNCA* among patients with PD.[87] Methylation of *SNCA* intron 1 is associated with decreased *SNCA* transcription, whereas reduced methylation has been found in several brain regions, including the substantia nigra of patients with idiopathic PD, and was associated with increased expression of *SNCA*.[88] Interestingly, environmental factors, such as coffee

consumption, have been reported to be associated with CpG methylation sites located near *PRKN*, *PINK1*, and *GBA*.[89]

Environmental Modifiers of *GBA*-Related PD

Mutations in *GBA* cause autosomal recessive Gaucher's disease and can also be a genetic risk factor for PD, where more severe mutations are associated with a higher PD risk and younger AAO compared to milder mutations.[90]

Several studies have estimated the age-specific penetrance of PD among *GBA* mutation carriers, with an estimated 5% to 30% of carriers developing PD at an increasing age (50–80 years).[91–95] With these kinds of studies, penetrance might be overestimated due to selection bias where asymptomatic carriers are missed. A large study on *GBA*-associated PD reported that age-dependent increasing penetrance is paralleled by decreasing relative risk estimates for the *GBA* variants Asn370Ser, Leu444Pro, and Thr369Met. In particular, Leu444Pro showed a peak in relative risk at an age between 35 and 44 years (RR = 7.51, 95% CI = 5.59–9.54), whereas above 75 years of age, the relative risk for this mutation was null.[96] Detailed interactions between *GBA* mutation carriers and potentially modifiable environmental factors, including the mechanisms of their potential interaction, are yet to be evaluated. However, a screening study for *LRRK2* and *GBA* mutations in Ashkenazi Jewish patients with PD revealed a potential interaction between *GBA* Asn370Ser mutation and head trauma. Among *GBA* mutation carriers, a younger AAO was detected in those who experienced head trauma.[97]

Future Directions

Despite progress over 25 years in dissecting genetic and environmental factors that contribute to PD etiology independently, studying the convergence of gene–environment interactions affecting PD is still in its infancy. To improve our understanding of this important topic requires a coordinated approach, and substantial time and financial investment to accelerate investigation and generate insights. Fortunately, this need is recognized by funders and learned societies which, in turn, will help us to create momentum in this field.

To date, progress has been made to identify environmental modifiers of *LRRK2* penetrance, as well as quantifying effects on clinical variability in carriers, but the majority of research studies conducted so far have not implemented unbiased and hypothesis-free approaches. Instead, most analyses undertaken have been directed by knowledge of apparent associations with idiopathic disease. It is plausible that environmental factors influencing risk of idiopathic PD may also influence the penetrance of monogenic PD. However, lessons learned from other monogenic diseases, such as *BRCA*-positive breast cancer, indicate that environmental factors influencing penetrance can differ, implying that we should not narrow our focus in that manner. When weighing the value of pursuing hypothesis-free approaches, caution must also be exercised; research conducted in this area is often affected by lack of statistical power and replication, which will be exacerbated by hypothesis-free designs. In addition, there remains questions to answer about whether other recognized protective factors against idiopathic PD (such as physical activity) also modify penetrance of monogenic PD. Given the heterogeneity of PD, studying carriers of *LRRK2* and *GBA* presents an excellent opportunity to understand more about the interaction between the exposome and genome, which, in turn, may be crucial to developing predictive and preventive approaches.

Data are easier to access than ever, and several large cohort studies (eg, UK Biobank, FinnGen, and Kadoorie) and disease-specific observational studies (eg, Parkinson Progression Markers Initiative [PPMI]) will help support a systematic approach to investigate gene–environment interactions that contribute to PD risk and progression, respectively.[98–101] Initiatives like Genetic Epidemiology of Parkinson's Disease (GEoPD) were set up to investigate genetic epidemiology of PD and have spawned projects like COmprehensive Unbiased Risk factor Assement for Genetics and Environment in Parkinson's Disease (COURAGE-PD), which promise to offer more insight about interactions in the near future.[102] Commercially gathered data, such as that available through research collaboration with organizations like 23andMe, also hold huge potential for examining gene–environment interactions.

However, one concern is how to move beyond identifying associations in observational studies and generate insights into the causal nature of potential interactions. Generating insights about gene–environment interactions ought to integrate information obtained from studying epigenetics, changes in gene expression and post-translational modification in order that observations made in epidemiological data can be related to disease pathways.

Much of what has been published to date gives the impression that the major goal at the outset was DNA sample collection, with little forethought on the importance of parallel data collection and moving beyond our insights from idiopathic PD. A major issue is harmonization of exposure definitions and data collection in which valuable common data elements need to be standardized across studies and sites. Progress can certainly be made with large-scale, collaborative and multicenter research initiatives, and studies like PPMI and its focus on early PD progression are

an exemplar to the field. A comprehensive resource to thoroughly investigate gene–environment interactions for PD may need similar investment and almost certainly requires multidisciplinary input at the design stage from geneticists, epidemiologists, basic scientists, statisticians, data scientists, and clinical experts. In the meantime, we hope that by carefully harmonizing information about environmental risk factors in large-scale initiatives, such as the Global Parkinson's Genetics Program (GP2), will help plug some of the current knowledge gaps and identify where more resources should be directed.[103] Reverse causality, selection bias, and the presence of confounders need to be taken into consideration when designing strategies with a greater focus on exploring causal associations between genes and environment. Needless to say, awareness of the limitations that arise from epidemiological studies are crucial to prediction and prevention strategies in the next generation of PD research.

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Author Contributions

Maria Teresa Periñán, Kajsa Brolin, Sara Bandres-Ciga, and Alastair Noyce contributed to the conception and design of the review. Maria Teresa Periñán, Kajsa Brolin, Sara Bandres-Ciga, and Alastair Noyce contributed to the interpretation of studies included in the review. Maria Teresa Periñán, Kajsa Brolin, Sara Bandres-Ciga, Cornelis Blauwendraat, Christine Klein, Ziv Gan-Or, Andrew Singleton, Pilar Gomez-Garre, Maria Swanberg, Pablo Mir, and Alastair Noyce contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

The authors declared no conflict of interest.

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