2 Immunogenetics of Parkinson's Disease

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Abstract: Inflammation is a key feature of Parkinson's disease (PD). In postmortem PD brains, microglial activation and enhanced major histocompatibility class II (MHCII) expression are seen concomitant to the accumulation of alpha-synuclein (α-synuclein) and loss of dopaminergic cells in the substantia nigra. Recent findings showed that α-synuclein epitopes can be presented and recognized by T-cells. PD is not a single disorder; rather, it encompasses a range of clinical, epidemiological, and genetic subtypes. Around 10% of the cases have a monogenic origin, and several of the disease-causing mutations are linked to inflammatory processes. The remaining 90% of the cases are complex, where environmental and genetic risk factors synergize to induce PD pathology. To date, 41 genetic loci have been identified in genome-wide association studies as associated with PD risk, and among these, two are within the HLA region, coding for immune genes including MHCII. Thus, genetic and immune findings indicate that the immune system has a role in the etiology of PD. Experimentally, inflammatory stimuli can cause selective nigral cell loss in preclinical models of PD, and MHCII is required to elicit α-synuclein-induced pathology in mice. In this chapter, we focus on immunogenetics, that is, the relation between genetic risk factors and immune processes in PD.

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INTRODUCTION

Parkinson's disease (PD) is an increasingly prevalent and progressively disabling neurodegenerative disease that encompasses a range of clinical, epidemiological, and genetic subtypes (1). The high inter-individual variation in onset, progression, and symptoms is in part due to a complex interplay between genes and environment. According to the latest criteria by the International Parkinson and Movement Disorders Society, PD diagnosis should be based on the presence of general bradykinesia in combination with either rest tremor, rigidity or both (2). Neuropathologically, PD is characterized by loss of nigral dopaminergic neurons that innervate the striatum and pathological accumulation of α-synuclein in Lewy bodies and Lewy neurites (3). In addition to the neurodegenerative phenotype, local neuroinflammation is a hallmark of PD and includes activation of microglia and astrocytes as well as an upregulation of major histocompatibility class II (MHCII) molecules. The inflammatory activation in PD is not only confined to the brain but also involves the peripheral immune system. One example is the increased expression of inflammatory molecules both in the central (4) and peripheral nervous systems (5). At a cellular level, there is an increased infiltration of immune cells into the brain parenchyma and an altered peripheral leukocyte profile in PD (6). The finding that α-synuclein epitopes can be recognized by T-lymphocytes (7) further strengthens the notion that PD is an inflammatory disease, with both innate and adaptive immune responses. Although these findings strongly link inflammation to PD, they do not answer whether inflammation is a cause or consequence of the disease. However, the recent advances in genetic analyses of familial and idiopathic PD strongly support inflammatory processes to play a critical role in disease etiology.

ETIOLOGY OF PARKINSON'S DISEASE

Genetic studies of familial PD have led to the identification of disease-causing mutations in single genes, that is, monogenic forms of PD. Mutations that have been causatively linked to PD are located to the genes encoding α-synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2), vacuolar protein sorting-associated protein 35 (VPS-35), parkin (PARK2), PTEN-induced putative kinase 1 (PINK1), DJ1 (PARK7), and glucocerebrosidase (GBA) (8) (Figure 1). Although mutations in these genes are rare and only account for <10% of all PD cases (9), they have identified key molecular players and processes in PD etiology. This can be illustrated by SNCA, which is both neuropathologically and genetically linked to PD. Lewy bodies and Lewy neurites containing α-synuclein accumulations are present in both familial and idiopathic PD, and in addition to SNCA mutations and copy number variations (CNVs) linked to dominantly inherited monogenic PD (10), common genetic variants in SNCA are associated with increased risk of developing idiopathic PD (11).

In 90% of PD patients, there is no monogenic inheritance pattern, and the disease is determined as idiopathic. Idiopathic PD is sometimes referred to as sporadic but has a multifactorial etiology, where environmental and genetic factors interact, synergize, and together determine an individual's susceptibility to disease. The genetics of idiopathic PD is therefore complex, similar to many other common conditions like Alzheimer's disease, diabetes, and different forms of cancer. In the quest to understand the etiology of idiopathic PD, efforts have been made to identify genetic variants associated with disease risk. These variants include single nucleotide polymorphisms (SNP; the change of a single base pair) and structural variants (microsatellites, minisatellites, insertions, deletions) that, depending on their frequency in the population, are defined as polymorphisms (>1%) or mutations (<1%). Genome-wide association studies (GWAS) are based on the genetic association analysis of SNPs covering the entire genome. Due to the large number of SNPs examined, the analysis is unbiased, but requires large sample sizes. Meta-analyses of several different GWAS have identified 41 PD risk loci (12, 13), each representing common genetic variants conferring an increased risk of developing PD (Figure 1).

In 1983, exposure to the heroin side product 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was identified as the causative agent for severe irreversible parkinsonism in humans and primates (14). MPTP crosses the blood–brain barrier and is converted to MPP+, which accumulates in dopaminergic neurons through dopamine transporters. MPP+ inhibits complex 1 of the electron transport chain, leading to impaired mitochondria and loss of nigral dopaminergic neurons. Although MPTP is not present as an environmental hazard, it pointed out the potential of the molecule to induce parkinsonism and increased interest in environmental risk factors for PD. Exposure to pesticides such as rotenone, paraquat, organophosphates, and pyrethroids has been associated with increased risk of PD in several case-control studies (15). The mechanisms behind the risk increments are not completely understood but, like MPTP, rotenone and paraquat are thought to induce dopaminergic degeneration through oxidative stress and damage. Rotenone acts on complex 1 of the respiratory chain, while paraquat triggers a redox cycle that generates toxic superoxide free radicals.

Environmental and genetic factors are now considered to act in a synergistic manner and modify the risk for idiopathic PD. One such example is genetic variations in glutathione transferase genes which modify the risk conferred by paraquat exposure (16). The risk of PD has also been reported to be increased by head trauma (17) and recurrent CNS infections (18), while moderate amounts of nicotine, caffeine consumption, and the use of non-steroid anti-inflammatory drugs have been reported to reduce the risk for PD (19). Thus, genetic and environmental factors act together to modify PD risk.

IMMUNOGENETICS OF MONOGENIC PD

Advances in the genomics field have generated unprecedented opportunities to define the genetic basis of complex diseases. By applying a genetic strategy,

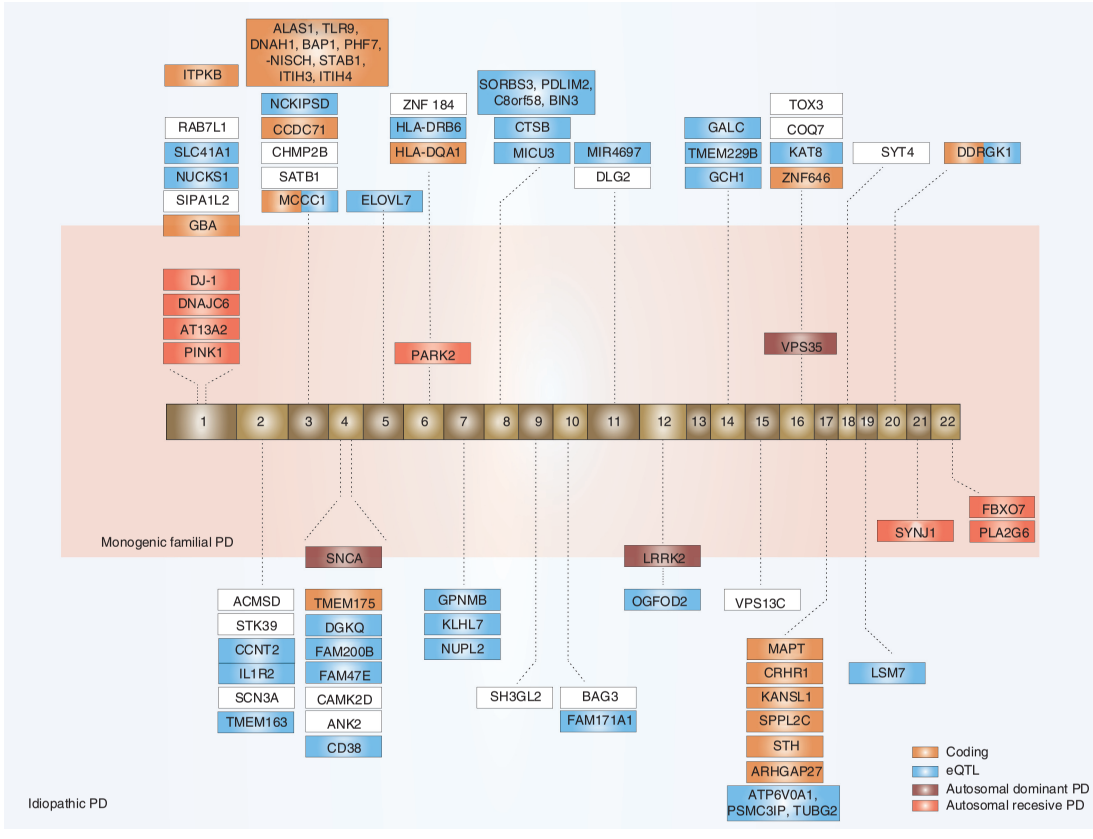

Figure 1 **Insights into the genetics of Parkinson's disease (PD).** The largest meta-analyses until now have identified 41 PD-risk loci (12, 13). Candidate genes are annotated for each region that has been significantly associated with PD. For some of the regions, there is more than one candidate gene.

one can discriminate between causes and consequences of a disease. Furthermore, in situations where a specific gene variant affects the response to therapy, knowledge about an individual's genotype can inform clinical decisions. Immunogenetics specifically studies the relationship between genetics and the immune system, that is, how genetic variants contribute to the inter-individual variation in immune responses.

Autosomal dominant forms

Interestingly, many of the genetic variants linked to monogenic PD also play a critical role in modulating inflammatory responses. Mutations in LRRK2 account for 1–2% of all PD cases (20, 21), but the prevalence varies substantially depending on the population studied. The penetrance is not complete, meaning environmental factors and/or other genes can modulate the disease-causing effect of LRRK2 mutations. LRRK2 encodes a large protein with multiple functions and has a moderate homology to the receptor-interacting protein kinases, a family of kinases with a known role in immunity. Expression of LRRK2 in microglia is induced by pro-inflammatory stimuli and affects microglial activation (22). LRRK2 is also expressed in many other tissues (23), including peripheral immune cells, where its expression is increased by inflammatory mediators such as interferon-γ (IFNγ) and lipopolysaccharide (LPS) (24, 25). Variants at the LRRK2 locus have been reported to confer increased risk of Crohn's disease (26) and leprosy (27). In idiopathic PD patients, the expression of LRRK2 in B-lymphocytes, T-lymphocytes, and monocytes is increased compared to controls and is positively correlated with cytokine expression in T-lymphocytes (28). LRRK2 is thus strongly linked to immune processes in the CNS and periphery and is a promising therapeutic target for both monogenic and idiopathic PD.

Mutations in the SNCA gene and the presence of the encoded protein, α-synuclein, in Lewy bodies were described in 1997 (29, 30), revealing the functional link between α-synuclein and PD. α-synuclein is a nuclear and presynaptic protein, and its overexpression and aggregation within neuron somas and neurites precedes neurodegeneration of dopaminergic cells. Several animal models have been developed that overexpress human α-synuclein in dopaminergic neurons (31), leading to α-synuclein accumulation, dopaminergic neurodegeneration, and microglial activation (32–34). Human macrophages upregulate α-synuclein after LPS stimulation (35), while microglia from mice lacking α-synuclein present a highly activated phenotype in terms of cytokine profile and morphology (36, 37). α-synuclein is a ligand for toll-like receptor 2 (TLR2) on microglia (38), linking α-synuclein to the innate immune system. TLR2 is also present on T-lymphocytes, B-lymphocytes, monocytes, and macrophages, cells that are part of the adaptive immune system. Recently, it was reported that α-synuclein epitopes can be presented on MHC molecules and activate both helper and cytotoxic T-lymphocytes (7). α-synuclein can thus elicit both innate and adaptive immune responses.

Autosomal recessive forms

Parkin, PINK1, and DJ-1 are linked to autosomal juvenile recessive parkinsonism. These three genes are involved in mitochondrial function and oxidative stress

and are also coupled to immune responses. Although loss-of-function mutations in the parkin gene (encoding an E3 ubiquitin ligase) cause early loss of dopaminergic neurons in patients, parkin-deficient mice do not display nigrostriatal pathway degeneration unless they are challenged with low dose of LPS (39). The need of an inflammatory stimulus suggests that the loss of parkin function increases the vulnerability of nigral dopaminergic neurons to inflammation-related degeneration or vice versa. Gene expression profiling in PINK1-deficient mice showed that loss of PINK1 altered the expression of immunomodulatory genes in the striatum (40). In addition, systemic LPS treatment induced higher levels of the pro-inflammatory cytokines interleukin (IL)-1β, IL-12, and tumor necrosis factor α (TNFα) in brain homogenates from PINK1-deficient mice compared to wild-type mice. DJ-1 is implicated in mitochondrial function as a regulator of oxidative stress rather than mitophagy (41). In the human brain, DJ-1 is mostly expressed by astrocytes (42), and astrocytes from DJ-1-deficient mice display an augmented response to LPS and produce more inflammatory cytokines such as IL-6, possibly via increased activation of MAPK p38 and JNK (43). Loss-of-function of parkin, PINK1, and DJ-1 thus seem to increase the sensitivity of dopaminergic neurons to degeneration through oxidative stress and pro-inflammatory immune responses.

IMMUNOGENETICS OF IDIOPATHIC PD

The availability of high-throughput technologies has allowed genotyping of hundreds of thousands to millions of SNPs in the human genome in a cost and time-efficient manner. These technological advancements allow large-scale GWAS, which identify associations between genetic variants and a particular trait or disease. In case-control studies, SNP allele frequencies are compared between patients and controls (44). To date, meta-analyses of GWAS have identified 41 risk loci associated with PD (12, 13). One of the challenges of association studies is the identification of the casual variants, which are most likely genetic variants in linkage disequilibrium (LD) with genotyped SNPs. The consequence of LD, that genetic variants located on the same chromosome have a distance-dependent likelihood of a recombination event during meiosis, is that closely located variants often are inherited together. In addition, associated SNPs can be attributed to different candidate genes and biological function depending on the genetic map used and the availability of gene expression data. Most PD-associated variants confer relatively small risk increments, and the majority are found in non-coding regions regulating gene expression. Such variants are also known as expression quantitative trait loci (eQTLs) and can regulate the expression of multiple genes. Allele-dependent expression of immune-related genes has been reported for eQTLs near or in SNCA, LRRK2, HLA-DQB1, and MAPT (45), with antigen presentation being the most enriched regulated process. Below, we discuss the immune functions of HLA (Figure 2) and other risk loci identified for idiopathic PD (Figure 3) in two GWAS meta-analyses (12, 13).

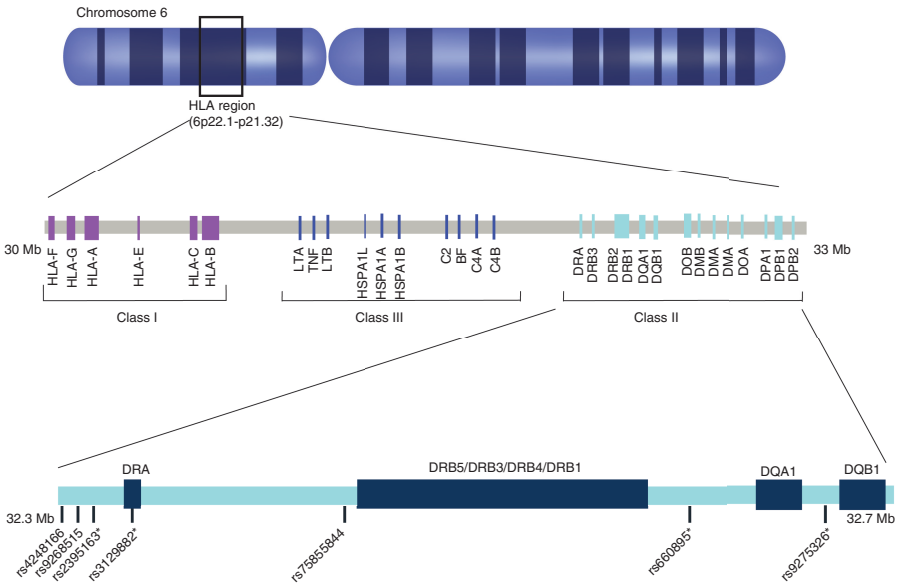

Figure 2 Single nucleotide polymorphisms (SNPs) in the human leukocyte antigen (HLA) locus associated with increased risk for Parkinson's disease (PD). Map of HLA class I, II, and III regions indicating alleles and SNPs associated with PD. An asterisk (*) denotes that the SNP is acting as an expression quantitative trait locus (eQTL). (Adapted from Ref. 85).

Antigen presentation

From the 41 risk loci identified by GWAS, two are within the human leukocyte antigen (HLA) region. HLA is one of the most polymorphic regions in the human genome and presents a complex combination of alleles in high LD (Figure 2). HLA class I and class II genes encode MHCI and MHCII molecules that present antigens to CD8+ and CD4+ T-lymphocytes, respectively, and thereby regulate adaptive immune responses. Different HLA alleles encode MHC molecules with different antigen-binding affinity and are associated with numerous disorders, including autoimmune diabetes and rheumatoid arthritis (46). A combined GWAS of PD with type 1 diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, celiac disease, psoriasis, and multiple sclerosis identified 17 loci shared between PD and these autoimmune disorders (47). Most of the PD risk alleles, including HLA-DQB1, HLA-DRB5, MAPT, and LRRK2, also increased the risk for the autoimmune disorders. Others, including BOLA2, SETD1A, CXCR4, IL12A, and GAK, had opposite effects. The identification of common genetic pathways for PD and autoimmune disorders further strengthens the importance of immunogenetics and immune therapy in PD.

Several studies have found association between SNPs and alleles in the HLA class II region and PD. These are summarized in Tables 1 and 2 and outlined in Figure 2. Using a GWAS approach, Hamza et al. reported a non-coding variant in HLA-DRA (rs3129882) associated with late-onset PD (48). This variant has

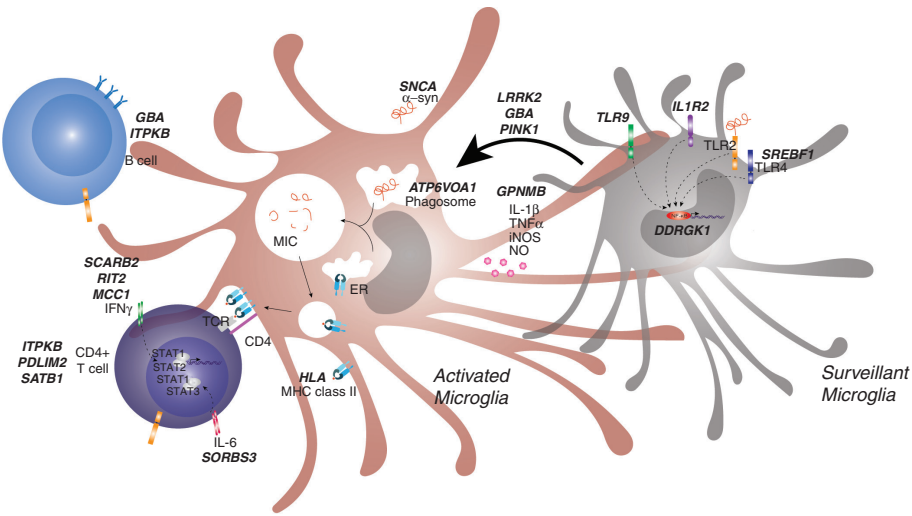

Figure 3 Insights into the immunogenetics of Parkinson's disease (PD). Schematic illustration of the link between genetic risk factors and immune mechanisms underlying PD development. Genes (indicated in bold italics) represent nominated risk genes for idiopathic and/or monogenic PD.

TABLE 1 Key HLA Haplotypes Associated with PD

HLA allele	Association with PD	Meta-analysis *p*-value	Meta-analysis Odds ratio (OR)	Reference
B*07:02	Risk	3×10^{-4}	1.23	(85)
B*40:01	Protective	2×10^{-3}	0.76	(85)
C*03:04	Protective	8×10^{-6}	0.72	(85)
C*07:02	Risk	2×10^{-4}	1.23	(85)
DRB1*04:04	Protective	4×10^{-5}	0.65	(85)
DRB1*15:01	Risk	6×10^{-5}	1.26	(85)
DRB4*01	Protective	4×10^{-5}	0.83	(85)
DRB5*01	Risk	5×10^{-5}	1.25	(85)
DQA1*01:02	Risk	1×10^{-3}	1.17	(85)
DQA1*03:01	Protective	1×10^{-6}	0.77	(85)
DQB1*03:02	Protective	7×10^{-6}	0.74	(85)
DQB1*06:02	Risk	$4 \times 10^{-5*}$	1.26*	(86)

Class I and class II HLA alleles associated with PD together with meta-analysis data for *p*-values and odds ratios. HLA, human leukocyte antigen; PD, Parkinson's disease.

been reported to be a *cis*-acting eQTL that correlates significantly with expression levels of HLA-DRA, DRB5, and DQA2 (49, 50). Studies following the GWAS approach, conducted in a Dutch population by the International Parkinson Disease Genomics Consortium, confirmed the association of the HLA class II region (rs4248166 and chr6:32588205, respectively) with PD (51, 52). Another study reported the presence of three HLA class II variants (not in LD) to be significantly associated with PD risk (53). Taken together, several studies confirm the association of the HLA class II region with PD risk and suggest associated variants

TABLE 2 SNPs in the HLA Region Associated with PD

SNP	Allele/ gene	Tissue	*p*-value	Effect size	Data base/ original article
rs3129882	DRA4		9×10^{-11}	1.30*	(48)
	DRB6	Brain	[6.4×10^{-7}; 2.4×10^{-7}]	[0.52; 0.58]	Gtex
		Whole blood	2.7×10^{-17}	0.45	Gtex
	DRB5	Hypothalamus	1.6×10^{-5}	–0.44	Gtex
		Whole blood	6.6×10^{-9}	–0.25	Gtex
	DQA2	Whole blood	3.3×10^{-5}	0.27	Gtex
	C4A	Whole blood	3.7×10^{-5}	–0.24	Gtex
	DQB1-AS1	Whole blood	4.4×10^{-5}	–0.16	Gtex
	DRB9	Whole blood	1.5×10^{-5}	0.22	Gtex
rs660895	DRB1-DQA1		8×10^{-7}	0.80*	(87)
	DQA1	Whole blood	1.3×10^{-6}	–0.18	Gtex
	DQA2	Brain	[6.0×10^{-17}; 1.6×10^{-9}]	[0.83; 1.1]	Gtex
		Substantia nigra	6.2×10^{-9}	0.95	Gtex
	DQB1	Brain	[6.8×10^{-6}; 9.7×10^{-6}]	[–0.55; –0.65]	Gtex
		Whole blood	3.3×10^{-12}	–0.41	Gtex
	DQB1-AS1	Whole blood	2.2×10^{-6}	–0.24	Gtex
	DQB2	Whole blood	7.9×10^{-13}	0.52	Gtex
	DRB1	Cortex	5.5×10^{-6}	0.58	Gtex
		Whole blood	5.3×10^{-14}	–0.21	Gtex
	DRB6	Brain	[7.8×10^{-7}; 5.4×10^{-6}]	[0.59; 0.58]	Gtex
		Whole blood	5.3×10^{-14}	–0.21	Gtex
	LY6G5B	Whole blood	1.4×10^{-5}	–0.12	Gtex

Table continued on following page

TABLE 2 SNPs in the HLA Region Associated with PD (Continued)

SNP	Allele/ gene	Tissue	*p*-value	Effect size	Data base/ original article
rs2395163	DRA/ BTNL2		3×10^{-11}	0.81*	(88)
	DAQ1	Whole blood	7.8×10^{-6}	–.017	Gtex
	DQA2	Brain	$[1.2 \times 10^{-9}; 1.2 \times 10^{-6}]$	[0.73; 0.83]	Gtex
		Whole blood	8.4×10^{-31}	0.89	Gtex
	DQB1	Whole blood	7.5×10^{-7}	–0.30	Gtex
	DQB2	Whole blood	1.0×10^{-8}	0.43	Gtex
	DRB1	Brain	$[5.4 \times 10^{-7}; 3.8 \times 10^{-5}]$	[–0.45; –0.46]	Gtex
		Whole blood	1.7×10^{-16}	–0.23	Gtex
	DRB6	Brain	$[3.6 \times 10^{-5}; 5.9 \times 10^{-6}]$	[0.55; 0.57]	Gtex
		Whole blood	1.2×10^{-10}	0.46	Gtex
rs9275326	DQB1		1.19×10^{-12}	0.826*	(13)
	DQA1	Whole blood	3.9×10^{-5}	–0.20	Gtex
	DQB1	Whole blood	1.4×10^{-7}	–0.41	Gtex
	DQA2	Brain	$[2.5 \times 10^{-9}; 4.1 \times 10^{-7}]$	[1.0; 1.1]	Gtex
		Whole blood	1.9×10^{-20}	0.96	Gtex
	DRB1	Whole blood	6.1×10^{-8}	–0.20	Gtex
	DRB6	Brain	$[1.1 \times 10^{-7}; 2.1 \times 10^{-5}]$	[0.79; –0.94]	Gtex
		Whole blood	1.4×10^{-6}	0.45	Gtex
	TAP2	Whole blood	67×10^{-8}	–0.28	Gtex
rs9268515			4×10^{-4}	1.25*	(53)
rs4248166	DRA/ BTNL2		0.07	1.08*	(51)
rs75855844	DRAB5		4×10^{-4}	1.25*	(13)

Summarized eQTL data from publically available databases (Gtex) for whole blood and brain regions. An asterisk (*) denotes values from meta-analyses. p-values were generated for each variant-gene pair by testing the alternative hypothesis that the slope of a linear regression model between genotype and expression deviates from 0. The effect size of the eQTLs is defined as the slope of the linear regression and is computed as the effect of the alternative allele relative to the reference allele in the human genome reference GRCh37/hg19 (i.e., the eQTL effect allele is the alternative allele). HLA, human leukocyte antigen; PD, Parkinson's disease; SNP, single nucleotide polymorphism.

to be eQTLs, that is, regulating gene transcription. This could provide a functional link to the increased expression of MHCII molecules observed in PD brains and affect the interaction between antigen-presenting cells and lymphocytes.

T- and B-lymphocyte development

From the 41 PD-risk loci identified by GWAS (Figure 1), ITPKB, PDLMI2, SATB1, and BST1 are involved in T- or B-lymphocyte development. Inositol 1,4,5-trisphosphate 3-kinase B (ITPKB) controls positive selection of T-lymphocytes and modulates Erk activity, an important kinase that regulates extracellular signal response and plays a crucial role in the production of pro-inflammatory cytokines and chemokines. Studies in mice have shown that nonsense mutations in ITPKB attenuate Erk signaling in T-lymphocytes (54) and that ITPKB-deficiency leads to defects in B-lymphocyte survival, developmental alterations of B-lymphocytes, and antigen unresponsiveness *in vivo* (55). PDLIM2 has been reported to inhibit T-helper 17 (TH17) cell development through signal transducer and activator of transcription 3 (STAT3). PDLIM2 deficiency in mice resulted in the accumulation of STAT3 in the nucleus and enhanced the extent of TH17 cell differentiation, known to have a pathogenic role in inflammatory diseases (56). SATB1 encodes for special AT-rich binding protein 1, a T-lymphocyte-enriched transcription factor and chromatin organizer essential for controlling a large number of genes participating in T-lymphocyte development and activation (57). Moreover, it has been observed that mouse SATB1 coordinates the expression of Th2 cytokine genes (58). BST1 encodes for the leukocyte surface protein CD157 that is upregulated in bone marrow cells from patients diagnosed with rheumatoid arthritis (59) and may facilitate pre-B-lymphocyte growth.

NF-κB and IFNγ-signaling

Four loci reported to be associated with PD relate to the transcription factor NF-κB that regulates a number of immune genes in response to different stimuli. These loci include MCCC1 and DDRGK1 (12) (Figure 1) as well as RIT2 and SCARB2 reported in an earlier GWAS meta-analysis (13). MCCC1 knockdown strongly inhibits induction of IFNs and inflammatory cytokines in response to viral infection (60). It has also been observed that expression patterns of RIT2 and IFNγ are positively correlated in PD brains, indicating that RIT2 may modulate IFNγ signaling (61). Depletion of DDRGK1 dramatically inhibits the expression of NF-κB target genes, suggesting that DDRGK1 plays an important role in regulating the NF-κB signaling pathway through interaction with IκBα (62). SCARB2 is a known receptor for GBA and for enterovirus 71 (EV1) and is highly expressed in human plasmacytoid dendritic cells where it has been reported to regulate the production of type I IFN through TLR9 and IFN regulatory factor 7 (63).

Regulation of inflammation through metabolic pathways

Biallelic mutations in GBA cause Gaucher's disease, and carriage of one mutated GBA allele substantially increases the risk for PD (64). Although GBA mutations are the single largest risk factor for idiopathic PD, the mechanisms behind

the risk increment are not fully understood. There are several immune-related effects of GBA deficiency, including multisystem inflammation, B-lymphocyte hyperproliferation (65), increased levels of pro-inflammatory cytokines (66), microglial activation and astrogliosis (67). Less is known about the role of GPNMB, SREBF1, and ACMSD in conferring increased risk for PD. GPNMB encodes for glycoprotein nonmetastatic melanoma B and is highly expressed in microglia after LPS treatment. Inhibition by GPNMB siRNA dramatically suppressed the expressions of TNF-α, IL-1β, and inducible nitric oxide synthase (iNOS) in activated mouse BV2 cells, indicating a role in microglial activation and pro-inflammatory cytokine release (68). SREBF1 may regulate innate immune responses through its actions on lipid metabolism since it contributes to resolution of pro-inflammatory TLR4 signaling by reprogramming fatty acid metabolism (69). ACMSD has a well-described biological function in the kynurenine pathway, where it regulates and limits the formation of quinolinic acid. Quinolinic acid is an NMDA receptor agonist with excitotoxic properties that can also modulate inflammatory responses. ACMSD could therefore reduce inflammation-induced neurodegeneration (70).

Innate immune response

PD risk-loci linked to innate immune responses include TLR9, IL1R2, and ATP6V0A1. TLR9 is part of the toll-like receptor family and can recognize mitochondrial DNA as an endogenous danger-associated molecular pattern (DAMP) and activate an inflammatory cascade (71). IL-1 receptor type 2 (IL1R2) acts as a decoy receptor for IL1 by competing with IL1R1 for ligands and co-receptors. IL1R2 has been implicated in arthritis, endometriosis, organ transplantation, and Alzheimer's disease (72). *In vitro*, the expression of IL-1R2 is suppressed by pro-inflammatory agents like LPS and IFN-γ (73). The ATP6V0A1 gene is expressed in microglia and their precursors and is involved in the acidification of intracellular compartments and the phagosomal fusion, a process that is crucial for phagocytosis (74). In addition to these, many gene variants conferring increased risk for PD act, in some way, on the complement system. These include *SNCA*, *MAPT*, *GBA*, *STK39*, *LRRK2*, *HLA*, *GPNM8*, *GCH1*, *DDRGK1*, *SCARB2*, *FGF20,* and *SREBF1* (75).

ENVIRONMENTAL FACTORS AFFECTING IMMUNOGENETICS IN PARKINSON'S DISEASE

As mentioned above, the incomplete penetrance of monogenic forms of PD and the complex genetic structure of idiopathic PD suggest the presence of environmental components that modify disease risk. The link between inflammation and PD genetic risk factors described above is strong, but how immunogenetics interacts with environmental factors is a research field still in development. For example, a SNP (rs*3129882*) in *HLA-DRA* associated with increased MHCII molecule expression has been reported to significantly increase the risk of PD in synergy with environmental exposure to pyrethroid (76). The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been suggested to be neuroprotective,

with ibuprofen being significantly associated with a reduced risk for PD (77, 78). Any interaction between the effect of NSAIDs and genetic risk factors for PD is, however, not known.

The gastrointestinal tract has an extensive immune and neuronal network and is in direct contact with the external environment. According to the Braak observations (79), the enteric nervous system is affected by α-synuclein pathology before the substantia nigra. It has been proposed that PD pathology actually starts in the gut and propagates through the vagus nerve to reach the substantia nigra; however, this hypothesis remains under debate (80). Several of the genes linked to familial PD or associated with idiopathic PD are also linked to the gastrointestinal tract. As mentioned above, GWAS have identified variants at the LRRK2 locus which are also known to be associated with Crohn's disease (26), and FGF20 has been associated with colitis and has demonstrated therapeutic activity in experimental models of intestinal inflammation (81). The overlapping susceptibility between inflammatory bowel disease and PD suggests that inflammatory processes in the intestines may promote PD pathology. Patients with PD have also been shown to have an altered gut microbiota pattern compared with controls (82, 83), and there is emerging evidence that the microbiota can influence the development of PD. In α-synuclein-overexpressing mice, microbiota were required for α-synuclein pathology, microglial activation, and motor deficits to occur (84). In addition, transplantation with microbiota from PD patients, but not from control subjects, worsened the physical impairment in the α-synuclein-overexpressing mice. These findings suggest the microbiome not only as a risk factor for PD but also as a potential therapeutic target. How genetic factors contribute to the microbiome and its impact on PD risk remains to be determined.

CONCLUSION

Many of the identified gene mutations linked to monogenic PD and common variants associated with idiopathic PD are involved in immune pathways. There is thus increasing evidence that inflammation has a causative role rather than being a consequence of neurodegeneration in PD. The involved pathways include both innate and adaptive immune responses in the CNS and in the periphery. If the risk for PD is, in part, mediated through immune mechanisms, these are obvious targets for therapeutic intervention. The field of immunogenetics in PD is therefore likely to unravel more of the etiology underlying PD, as well as identifying potential targets for novel treatments.

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