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1 Editorial

2 **Special Issue "Parkinson's Disease: Genetics and Pathogenesis"**

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13 Parkinson's disease (PD) is a common and incurable neurodegenerative disease, affecting 1%
14 of the population over the age of 65. Although the disease remains defined clinically by its
15 cardinal motor manifestations and pathologically by substantia nigra neuronal loss in
16 association with intraneuronal Lewy bodies, the molecular mechanisms that lead to
17 neurodegeneration remains elusive. It is becoming increasingly clear that genetic factors
18 contribute to its complex pathogenesis. More than 23 loci and 13 genes, including *LRRK2*,
19 *SNCA*, *GBA1*, *PRKN*, *PINK1*, and *PARK7/DJ-1* clearly linked to inherited forms of
20 Parkinsonism have been identified to date. The knowledge acquired from their protein
21 products has revealed pathways of neurodegeneration that can be shared by Mendelian and
22 sporadic Parkinsonism, including synaptic, lysosomal, mitochondrial and immune-mediated
23 mechanisms of pathogenesis.

24 This special issue “Parkinson’s Disease: Genetics and Pathogenesis” collects 12 high-quality
25 papers, including seven original research articles, and five reviews, that seeks to deepen the
26 knowledge of multiple aspects related to Parkinsonism.

27 Two reviews by Jia et al. [1] and Elsayed et al. [2] provide a comprehensive overview of the
28 current knowledge of PD genetics in the genotype-phenotype relationship and associated
29 pathophysiology with a focus on genetic testing, its current challenges and limitations. In
30 addition, Jia et al. [1] discuss the role of heterozygous mutations in genes associated with
31 autosomal recessive PD and the impact of digenism (i.e. dual *LRRK2* and *GBA1* mutation
32 carriers) on the clinical outcomes. It is now recognized that important genetic differences exist
33 according to ethnicities and regions. The inclusion of ethnic diversity in PD genetics research,
34 by including under-represented PD populations, is essential to provide novel insights
35 regarding the generalized genetic map of the disease. It will also improve our understanding
36 of the disease biology and pathogenesis and health care of PD patients. In the future, global
37 efforts will play a key role in exploiting the genomic data, to identify rare genetic cause of
38 PD or to replicate important gene discoveries. Furthermore, newer global initiatives such as
39 the Global Parkinson’s disease program (GP2) [3] will offer greater representation of under-
40 represented populations from different ethnic groups and geographical regions. A third
41 review by Kim et al. [4] covers the most common mutations in PD-related genes, such as
42 *LRRK2*, *SNCA*, *GBA1*, *PRKN*, *PINK1*, and *PARK7/DJ-1*, the function of these protein
43 products and the consequences of their mutations on the pathophysiological mechanisms
44 leading to PD. Further consequences of these mutations have been emphasized with the use

45 of induced pluripotent stem cells (iPSCs) for a disease-in-a-dish approach and genetic animal
46 models.

47 To identify potential early predictive biomarkers in PD, Mangone and colleagues [5]
48 investigated the presence of immuno-stained misfolded α -Synuclein in minor salivary gland
49 biopsies in relation with *substantia nigra pars compacta* (SNc) damage measured by
50 magnetic resonance imaging. They included 27 idiopathic PD, 16 with isolated rapid eye
51 movement sleep disorders, a prodromal form of α -synucleinopathies and 18 healthy controls.
52 The authors concluded that the α -Synuclein detection in minor salivary gland biopsies lacks
53 sensitivity and specificity and does not correlate with SNc damage. In a second original
54 paper, Usenko et al. [6] compared the gene expression profile in monocyte-derived
55 macrophages from five PD patients and four asymptomatic relatives carrying either
56 heterozygous *GBA* L444P or N370S mutations and four healthy controls. They found
57 dysregulated genes in *GBA*-PD patients, independent to the nature of *GBA* mutations
58 compared to the other two groups, these genes being involved in neuronal functions,
59 inflammation and zinc metabolism. In particular, altered expression of *DUSP1* encoding the
60 mitogen-activated protein kinase 1 (MKP-1) phosphatase implicated in the regulation of
61 apoptosis, endoplasmic reticulum stress, cell cycle and autophagy can be considered a
62 potential biomarker for *GBA*-related PD. Taking advantages of newer technologies, Pantaleo
63 et al. [7] used whole blood transcriptome data and advanced Machine Learning approaches
64 for future selection and classification of 390 early (drug-naïve) PD patients versus 189 age-
65 matched healthy controls. The authors identified a set of around 500 genes implicated in a
66 certain number of significant functions and pathways, some of which have already been
67 linked to the pathogenesis of PD, such as oxidative stress, inflammation and vesicular
68 dysfunction, as well as associations between PD and diseases such as diabetes mellitus or
69 inflammatory bowel disease. The narrative review by Prasuhn and Brüggemann [8]
70 highlights the importance of one of the known PD-associated pathways, that is mitochondrial
71 dysfunction as a molecular cause in monogenic and idiopathic PD. They focus on gene
72 therapeutic targets and challenges necessary to translate molecular findings into potential
73 clinical applications, highlighting different treatment strategies.

74 Epigenetic modifications are responsible for functional gene regulation during development,
75 adult life and ageing and have also been implicated more recently in neurodegenerative
76 diseases, such as PD. Regulation of genes responsible for monogenic forms of PD may be
77 involved in sporadic PD. Lanoré and colleagues [9] reviewed the epigenetic mechanisms
78 regulating gene expression, including DNA methylation, histone modification and epigenetic
79 changes by non-coding RNAs. An example is *SNCA*, encoding α -Synuclein, with the
80 understanding of its regulation being a longstanding central focus for the community working
81 on PD. The accumulation of this protein in the Lewy bodies or neurites, the identification of
82 mutations in the coding regions of the gene or multiplications (duplications or triplications)
83 of the whole gene in familial PD and the strong association of single nucleotide
84 polymorphisms (SNPs) with sporadic PD indicate the importance of this protein in the
85 pathogenesis of the disease. Interestingly, *SNCA* contains several transcriptionally activated
86 histone modifications and associated potential transcription factor binding sites in the non-
87 coding regions of the gene that strongly suggest alternative regulation pathways. Thus, it has
88 been reported that DNA methylation of *SNCA* may modulate its expression, particularly,
89 hypomethylation in intron 1 of *SNCA* was observed in several brain regions or in peripheral
90 tissues of sporadic PD patients and an increased *SNCA* expression. On the other hand, in post-
91 mortem midbrain samples, an enrichment of three histone modification marks, such as
92 H3K4me3, H3K27ac and H3K27me3, was reported in *SNCA* regulatory regions. Finally,
93 micro-RNAs (miRNAs), such as miR-7 and miR-153, as well as miR-34b/c bind to the 3'-
94 UTR of *SNCA* mRNA, destabilizing the mRNA and reducing its levels.

95 Genome-wide association study (GWAS) have widened our understanding of the genetics of
96 PD and have identified more than 90 genetic loci associated with PD [10]. Jo and colleagues
97 [11] performed a GWAS on dementia in 318 PD patients with dementia, 326 PD patients
98 without dementia and 648 healthy controls, all of Korean origin. The data analysis led to the
99 identification of the new loci of *MUL1* associated with dementia in PD, suggesting an
100 essential role of mitochondrial dysfunction in the development of dementia in patients with
101 PD. Two other loci containing *ZHX2* and *ERP29* were also found to be associated with
102 dementia in PD. In the original research publication, Koch et al. [12] used the development
103 of polygenic risk scores (PRSs) as a means to summarize the effect of the genetic background
104 upon an individual's disease risk in a single number. The authors were able to replicate the
105 performance of the PD-PRS developed by Nalls and colleagues [13] in an independent
106 dataset, suggesting that the PRS may be a meaningful research tool to investigate and adjust
107 for the polygenic component of PD but this tool is not meaningful for individual risk
108 prediction.

109 Emerging studies revealed that expansions or intermediate repeats of simple short DNA
110 sequence can cause or act as risk factors for different neurological diseases, including PD,
111 depending on the number of repeats. In the original paper by Kobo et al [14], stratified
112 analysis in 1106 Ashkenazi PD patients and 600 ethnically matched-controls suggests that
113 intermediate-size hexanucleotide repeats (20-60 repeats) in *c9orf72* are a risk factor for PD
114 in individuals without common Ashkenazi Jewish founder mutations in *LRRK2*, *GBA*, or
115 *SMPD1* compared with those with these mutations. The authors propose a model in which
116 the risk for PD may be driven not only by the number of the repeats, but also by the genotypes
117 of 44 informative single nucleotide variants (SNVs) within the risk-haplotype, affecting the
118 *c9orf72* RNA expression levels. In the second original research paper, Lüth et al. [15]
119 established a straightforward Nanopore long-read deep sequencing workflow to quantify the
120 hexanucleotide repeat number in the *TAF1* SINE-VNTR-Alu (SVA) insertion in patients with
121 X-linked dystonia-Parkinsonism (XDP). In addition, the authors utilized this novel
122 technology to investigate variations within the SVA locus other than the repeat motif and to
123 detect CpG methylation using a Cas9-targeted approach, across a large-22 kb-region
124 containing the *TAF1* SVA.

125 Overall, this special issue highlights the richness of studies bringing recent advances in our
126 knowledge on the genetic architecture contributing to PD. This volume should be an
127 important contribution to the field by improving our understanding of the pathophysiology
128 and thus will help with the efforts to develop targeted therapies and personalized medicine.

129

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