



**HAL**  
open science

## Special Issue "Parkinson's Disease: Genetics and Pathogenesis"

Suzanne Lesage, Joanne Trinh

► **To cite this version:**

Suzanne Lesage, Joanne Trinh. Special Issue "Parkinson's Disease: Genetics and Pathogenesis". Special Issue "Parkinson's Disease: Genetics and Pathogenesis", 2023, pp.737. <10.3390/genes14030737>. <hal-04054117>

**HAL Id: hal-04054117**

**<https://hal.sorbonne-universite.fr/hal-04054117v1>**

Submitted on 18 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

1 Editorial

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

3 **Suzanne Lesage** <sup>1,\*</sup> and **Joanne Trinh** <sup>2</sup>

4 <sup>1</sup> Sorbonne Université, Institut du Cerveau—Paris Brain Institute—ICM, INSERM,  
5 CNRS, Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, 75013 Paris,  
6 France; [suzanne.lesage@upmc.fr](mailto:suzanne.lesage@upmc.fr)

7 <sup>2</sup> Institute of Neurogenetics, University of Lübeck, 23562 Lübeck, Germany;  
8 [joanne.trinh@neuro.uni-luebeck.de](mailto:joanne.trinh@neuro.uni-luebeck.de)

9 \* Correspondence: [suzanne.lesage@upmc.fr](mailto:suzanne.lesage@upmc.fr); Tel.: +33 (0) 1 57 27 46 80

10 Received: date; Accepted: date; Published: date

11

12

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  $\alpha$ -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  $\alpha$ -synucleinopathies and 18 healthy controls.  
52 The authors concluded that the  $\alpha$ -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  $\alpha$ -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

130 **Acknowledgments:** We would like to thank Dr Poornima Menon for the manuscript reading.

131 **Funding:** S.L. acknowledges funding from the Fondation pour la Recherche Médicale (FRM,  
132 MND202004011718).

133 **Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design  
134 of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or  
135 in the decision to publish the results.

## 136 References

- 137 1. Jia, F.; Fellner, A.; Kumar, K.R. Monogenic Parkinson's Disease: Genotype, Phenotype,  
138 Pathophysiology, and Genetic Testing. *Genes* **2022**, *13*, 471.  
139 <https://doi.org/10.3390/genes13030471> - 07 Mar 2022.

- 140 2. Elsayed, I.; Martinez-Carrasco, A.; Cornejo-Olivas, M.; Bandres-Ciga, S. Mapping the  
141 Diverse and Inclusive Future of Parkinson's Disease Genetics and Its Widespread Impact.  
142 *Genes* **2021**, *12*, 1681. <https://doi.org/10.3390/genes12111681> - 23 Oct 2021.
- 143 3. Global Parkinson's Genetics Program. GP2: The Global Parkinson's Genetics Program. *Mov.*  
144 *Disord.* **2021**, *36*, 842-851. doi: 10.1002/mds.28494.
- 145 4. Kim, J.; Daadi, E.W.; Oh, T.; Daadi, E.S.; Daadi, M.M. Human Induced Pluripotent Stem  
146 Cell Phenotyping and Preclinical Modeling of Familial Parkinson's Disease. *Genes* **2022**, *13*,  
147 1937. <https://doi.org/10.3390/genes13111937> - 25 Oct 2022.
- 148 5. Mangone, G.; Houot, M.; Gaurav, R.; Boluda, S.; Pyatigorskaya, N.; Chalancon, A.;  
149 Seilhean, D.; Prigent, A.; Lehericy, S.; Arnulf, I.; et al. Relationship between Substantia  
150 Nigra Neuromelanin Imaging and Dual Alpha-Synuclein Labeling of Labial Minor in  
151 Salivary Glands in Isolated Rapid Eye Movement Sleep Behavior Disorder and Parkinson's  
152 Disease. *Genes* **2022**, *13*, 1715. <https://doi.org/10.3390/genes13101715> - 24 Sep 2022.
- 153 6. Usenko, T.; Bezrukova, A.; Basharova, K.; Panteleeva, A.; Nikolaev, M.; Kopytova, A.;  
154 Miliukhina, I.; Emelyanov, A.; Zakharova, E.; Pchelina, S. Comparative Transcriptome  
155 Analysis in Monocyte-Derived Macrophages of Asymptomatic GBA Mutation Carriers and  
156 Patients with GBA-Associated Parkinson's Disease. *Genes* **2021**, *12*, 1545.  
157 <https://doi.org/10.3390/genes12101545> - 29 Sep 2021.
- 158 7. Pantaleo, E.; Monaco, A.; Amoroso, N.; Lombardi, A.; Bellantuono, L.; Urso, D.; Lo  
159 Giudice, C.; Picardi, E.; Tafuri, B.; Nigro, S.; et al. Machine Learning Approach to  
160 Parkinson's Disease Blood Transcriptomics. *Genes* **2022**, *13*, 727.  
161 <https://doi.org/10.3390/genes13050727> - 21 Apr 2022.
- 162 8. Prasuhn, J.; Brüggemann, N. Gene Therapeutic Approaches for the Treatment of  
163 Mitochondrial Dysfunction in Parkinson's Disease. *Genes* **2021**, *12*, 1840.  
164 <https://doi.org/10.3390/genes12111840> - 22 Nov 2021.
- 165 9. Lanore, A.; Lesage, S.; Mariani, L.L.; Menon, P.J.; Ravassard, P.; Cheval, C.; Corti, O.;  
166 Brice, A.; Corvol, J.C. Does the Expression and Epigenetics of Genes Involved in Monogenic  
167 Forms of Parkinson's Disease Influence Sporadic Forms? *Genes* **2022**, *13*, 479.  
168 <https://doi.org/10.3390/genes13030479> - 08 Mar 2022.
- 169 10. Chang, D.; Nalls, M.A.; Hallgrímsson, I.B.; Hunkapiller, J.; van der Brug, M.; Cai, F.;  
170 International Parkinson's Disease Genomics Consortium; 23andMe Research Team;  
171 Kerchner, G.A.; Ayalon, G.; et al. A meta-analysis of genome-wide association studies  
172 identifies 17 new Parkinson's disease risk loci. *Nat. Genet.* **2017**, *49*, 1511-1516. doi:  
173 10.1038/ng.3955.
- 174 11. Jo, S.; Park, K.W.; Hwang, Y.S.; Lee, S.H.; Ryu, H.S.; Chung, S.J. Microarray Genotyping  
175 Identifies New Loci Associated with Dementia in Parkinson's Disease. *Genes* **2021**, *12*, 1975.  
176 <https://doi.org/10.3390/genes12121975> - 10 Dec 2021.
- 177 12. Koch, S.; Laabs, B.H.; Kasten, M.; Vollstedt, E.J.; Becktepe, J.; Brüggemann, N.; Franke,  
178 A.; Krämer, U.M.; Kuhlenbäumer, G.; Lieb, W.; et al. Validity and Prognostic Value of a  
179 Polygenic Risk Score for Parkinson's Disease. *Genes* **2021**, *12*, 1859.  
180 <https://doi.org/10.3390/genes12121859> - 23 Nov 2021.
- 181 13. Nalls, M.A.; Blauwendraat, C.; Vallerga, C.L.; Heilbron, K.; Bandres-Ciga, S.; Chang, D.;  
182 Tan, M.; Kia, D.A.; Noyce, A.J.; Xue, A.; et al. Identification of novel risk loci, causal

- 183 insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide  
184 association studies. *Lancet Neurol.* **2019**, *18*, 1091-1102. doi: 10.1016/S1474-  
185 4422(19)30320-5.
- 186 14. Kobo, H.; Goldstein, O.; Gana-Weisz, M.; Bar-Shira, A.; Gurevich, T.; Thaler, A.; Mirelman,  
187 A.; Giladi, N.; Orr-Urtreger, A. C9orf72-G4C2 Intermediate Repeats and Parkinson's  
188 Disease; A Data-Driven Hypothesis. *Genes* **2021**, *12*, 1210.  
189 <https://doi.org/10.3390/genes12081210> - 05 Aug 2021.
- 190 15. Lüth, T.; Laß, J.; Schaake, S.; Wohlers, I.; Pozojevic, J.; Jamora, R.D.G.; Rosales, R.L.;  
191 Brüggemann, N.; Saranza, G.; Diesta, C.C.E.; et al. Elucidating Hexanucleotide Repeat  
192 Number and Methylation within the X-Linked Dystonia-Parkinsonism (XDP)-Related SVA  
193 Retrotransposon in TAF1 with Nanopore Sequencing. *Genes* **2022**, *13*, 126.  
194 <https://doi.org/10.3390/genes13010126> - 11 Jan 2022.

195  
196



© 2019 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

197