Genetic Variants in SNCA and the Risk of Sporadic Parkinson’s Disease and Clinical Outcomes: A Review

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There is increasing evidence of the contribution of genetic susceptibility to the etiology of Parkinson's disease (PD). Genetic variations in the SNCA gene are well established by linkage and genome-wide association studies. Positive associations of single nucleotide polymorphisms (SNPs) in SNCA and increased risk for PD were found. However, the role of SNCA variants in individual traits or phenotypes of PD is unknown. Here, we reviewed the current literature and identified 57 studies, performed in fourteen different countries, that investigated SNCA variants and susceptibility to PD. We discussed the findings based on environmental factors, history of PD, clinical outcomes, and ethnicity. In conclusion, SNPs within the SNCA gene can modify the susceptibility to PD, leading to increased or decreased risk. The risk associations of some SNPs varied among samples. Of notice, no studies in South American or African populations were found. There is little information about the effects of these variants on particular clinical aspects of PD, such as motor and nonmotor symptoms. Similarly, evidence of possible interactions between SNCA SNPs and environmental factors or disease progression is scarce. There is a need to expand the clinical applicability of these data as well as to investigate the role of SNCA SNPs in populations with different ethnic backgrounds.

1. Introduction

Parkinson’s disease (PD) is a neurodegenerative disorder that is characterized by motor dysfunction but also causes nonmotor deficits [1]. Although the etiology of PD remains unclear, the interaction between genetic and environmental factors has been implicated in the emergence of the disease [2, 3]. Genome-wide association studies (GWAS) have identified variants of many candidate genes that contribute to PD susceptibility, such as variations of the SNCA gene [4–6]. Moreover, certain polymorphisms of SNCA are among the major risk factors for sporadic PD [5].

The SNCA gene is located on human chromosome 4 and encodes the protein alpha-synuclein. The physiological function of alpha-synuclein is not completely understood. Studies have shown a key role for alpha-synuclein in the regulation of neurotransmitter release, synaptic function, and plasticity of dopaminergic neurons [7–9]. The involvement in dopaminergic transmission and the predominant presence of alpha-synuclein in Lewy bodies [10–12] denote the relationship of this protein with the etiology of PD. In addition, genetic data support the role of alpha-synuclein in the pathogenic process of the disease. For example, missense mutations in SNCA locus were identified in familial forms of PD (A53T, A30P, E46K, and H50Q) [13–17], as well as in sporadic PD patients (A18T and A29S) [18]. Further, duplications and triplications of the SNCA locus cause familial parkinsonism and correlate with disease severity [19, 20].

Single nucleotide polymorphism (SNP) analyses in case-control studies performed in different populations have shown an association between several SNCA polymorphisms and the risk of PD. For example, the dinucleotide repeat REP1 located in the SNCA promoter (SNCA-REPI) and the 3’ untranslated region (UTR) variants are frequently investigated [21]. Variations in these regions may increase susceptibility to PD by interfering with transcription factor binding sites [22, 23] and creating or destroying microRNAs target sites, which in turn modifies gene expression [24–26].
In spite of the fact that this type of study is frequent, investigations of the association between SNPs and the risk of PD in different populations show conflicting results. Furthermore, the consequences of genetic variability on clinical phenotypes, as well the interaction between genetic and environmental substrates, are poorly elucidated. Ideally, data from SNP studies would improve knowledge of pathophysiological pathways and help to target the best therapeutic program. This review aims to identify and compare the main SNP association studies conducted in different populations. The role of SNCA polymorphisms as a risk factor for PD and their association with clinical outcomes are discussed.

2. Literature Search

We conducted a survey in the relevant databases PubMed/ Medline and Scopus for studies up to July 2016 using combinations of the keywords “polymorphism”, “alpha synuclein”, “SNCA gene”, and “Parkinson’s disease”. We selected articles that met the following inclusion criteria: (a) articles that are written in English; (b) articles that described investigations of SNPs in the SNCA gene; (c) articles that had available data of allele and genotype distributions; (d) studies that were conducted in humans; (e) studies including participants who were diagnosed with Parkinson’s disease. 57 studies were selected to conduct the review. In addition, despite not necessarily meeting the selection criteria, other relevant publications were included throughout the article in order to foster discussion.

The following information was extracted from each study: authors, year of publication, country of the studied population, number of patients and control subjects, risk association with PD, and investigation of environmental factors and clinical outcomes. The association of SNCA polymorphisms and PD susceptibility was often assessed by comparing the frequency of risk allele and risk genotypes in patients and controls. Values of odds ratio (OR) and confidence interval (95% CI) indicated the characteristic and significance of the association (OR values higher than 1 indicated increased risk and values lower than 1 suggested reduced risk).

Table 1 summarizes the main data from the 57 selected studies. The majority of the studies were performed in Caucasian and Asian populations. The studies were carried out in fourteen different countries (Mexico, China, Russia, Germany, Taiwan, USA, Japan, Spain, Italy, Ireland, Netherlands, Norway, Australia, and Greece) assembling patients from twenty countries (Mexico, China, Russia, Germany, Taiwan, USA, Japan, Spain, Italy, Norway, Netherlands, Serbia, Ireland, Australia, France, Greece, Poland, Sweden, Iran, and Australia). Sample sizes varied from 91 to 5302 patients in PD groups. The mean age at onset of PD varied from 45.2 to 68.2 years old.

3. SNPs and the Risk for Parkinson’s Disease

GWAS have identified 28 distinct loci that modify the individual risk to PD [85] and suggest that genetic factors contribute to at least one-fourth of the total variation in liability to PD [86]. The two most consistent genes for susceptibility to sporadic PD are the alpha-synuclein (SNCA) and microtubule-associated protein tau (MAPT) genes, which can exert independent or joint effects on the risk of PD [56, 59, 61, 62, 87]. In addition, variants in other genes previously linked with autosomal forms (LRRK2, PARK16–18, and GBA) have also shown association with PD risk [64, 88–90]. Based on odds ratio and confidence intervals values in the selected studies, thirty-nine different SNPs in the SNCA gene showed a statistically significant effect on PD susceptibility: nine variants in the 5’ end, nine variants near the 3’ end, and 25 intron variants (Table 2). The locations of the six more frequently investigated SNPs within the SNCA gene are illustrated in Figure 1.

Two major linkage disequilibrium blocks in the SNCA gene have been proposed: (1) a 5’ block that extends from the promoter-enhancer region to exon 4 and (2) a 3’ block that includes intron 4, 3’ UTR, and the 3’ end region of the gene [73, 80]. SNPs in the 3’ block presented a more expressive association with PD. The largest number of significant markers in the 3’ block across different populations suggests a major causal effect for variants located in the 3’ end compared with the 5’ end. The 3’ block contains elements with higher conservation across species, which emphasize its biological relevance [25].

The polymorphic microsatellite REP1 (D4S3481) in the promoter region of SNCA is one of the most frequently investigated polymorphisms and was pointed out as a risk factor in thirteen of the articles [47, 50, 60, 64, 65, 68, 71–73, 75, 77, 79, 81]. REP1 region plays a crucial role in the regulation of alpha-synuclein protein expression. Variants in REP1 are the only putative functional polymorphism identified within the SNCA locus. The REP1 SNP is a trilallelic polymorphism with the longest (263 bp) and intermediate length (261 bp) alleles usually associated with an increased risk for PD, as seen in studies with North American [47, 50, 60, 64, 65, 68, 71, 72, 75, 81], German [73], Greek [79], and Dutch [77] samples. In 2006, a meta-analysis including over 5000 subjects provided strong evidence that the 263 bp allele was more frequent in cases and that the 259 bp allele was more frequent in controls (indicating decreased risk of PD) [91]. The other four SNPs in the 5’ region (rs2619362, rs2619363, rs2619364, and rs2583988) contributed to the increase in the risk of PD in North American [49, 65] and European [56, 61, 77] populations.

Twenty-five intronic variants were associated with PD susceptibility, although the precise function of those variants of human SNCA is still unknown. The SNP rs2736990 in intron 4 was the most frequent, with the exception of one study [40]; this SNP was a consistent risk factor for PD [27, 28, 41, 49, 52, 55]. Similarly, the SNPs rs2572324, rs7684318, and rs894278 also increased susceptibility to sporadic PD [49, 60, 64, 65]. In contrast, a significant reduction of PD risk was found for the SNP rs356186 in Italian [56], North American [60], and Irish [61] samples.

Recently, the SNPs located near the 3’ end have also been identified as risk factors for PD. Within the 3’ region, the majority of the studies focused on rs356219, rs1931074, and rs356165. Among them, the SNP rs356219 was the most
Table 1: Characterization of the reviewed studies.

| Studies                        | Study ID | Country of participants       | Sample size | Onset age (mean ± SD) |
|-------------------------------|----------|-------------------------------|-------------|-----------------------|
|                               |          |                               | PD          | Ctr                   |
| Davila-Ortiz de Montellano et al., 2016 | [27]     | Mexico                        | 171         | 171                   | —                      |
| Davis et al., 2016            | [28]     | USA                           | 418         | 150                   | 60.4 ± 11.1            |
| Garcia et al., 2016           | [29]     | Mexico                        | 106         | 135                   | 56.2 ± 14.4            |
| Shahmohammadibeni et al., 2016| [30]     | Iran                          | 489         | 489                   | —                      |
| Wang et al., 2016             | [31]     | China                         | 296         | —                     | —                      |
| Cheng et al., 2016            | [32]     | China                         | 1053        | 1152                  | 52.0 ± 10.4            |
| Guella et al., 2016           | [33]     | Multicentric*                 | 1492        | 971                   | 60.3 ± 10.2            |
| Chen et al., 2015             | [34]     | China                         | 218         | 110                   | 60.6 ± 07.4            |
| Huang et al., 2015            | [35]     | China, Australia              | 402         | —                     | —                      |
| Han et al., 2015              | [36]     | China                         | 91          | 92                    | —                      |
| Chen et al., 2015             | [37]     | China                         | 1276        | 846                   | 56.3 ± 11.5            |
| Gao et al., 2015              | [38]     | USA                           | 507         | 1330                  | 68.3 ± 5.8             |
| Cardo et al., 2014            | [39]     | China                         | 752         | 489                   | —                      |
| Guo et al., 2014              | [40]     | China                         | 1011        | 721                   | 56.6 ± 11.8            |
| Pan et al., 2013              | [41]     | China                         | 515         | 450                   | 45.2 ± 04.6            |
| Mata et al., 2014             | [42]     | USA                           | 1191        | —                     | 59.46 ± 10.6           |
| Markopoulos et al., 2014      | [43]     | USA                           | 1098        | —                     | 62.2                   |
| Emelyanov et al., 2013        | [44]     | Russia                        | 244         | 308                   | —                      |
| Wu-Chou et al., 2013          | [45]     | Taiwan                        | 626         | 473                   | 63.2 ± 07.8            |
| Brockmann et al., 2013        | [46]     | Germany                       | 1396        | —                     | 56.9 ± 01.9            |
| Chung et al., 2013             | [47]     | USA                           | 1098        | 1098                  | 60.4                   |
| Pilhstrom et al., 2013        | [48]     | Norway and Sweden             | 1380        | 1295                  | 59.0                   |
| Heckman et al., 2012          | [49]     | USA                           | 426         | 769                   | 62.0 ± 12.0            |
| Ritz et al., 2012             | [50]     | USA                           | 232         | —                     | —                      |
| Schmitt et al., 2012          | [51]     | Germany                       | 980         | 1005                  | 59.4 ± 12.2            |
| Miyake et al., 2012           | [52]     | Japan                         | 229         | 357                   | 65.7 ± 08.8            |
| Pan et al., 2012              | [53]     | China                         | 403         | 315                   | 57.8 ± 08.6            |
| Cardo et al., 2012            | [54]     | Spain                         | 727         | 480                   | —                      |
| Gao et al., 2012              | [55]     | USA                           | 584         | 1571                  | 68.2 ± 05.7            |
| Trotta et al., 2012           | [56]     | Italy                         | 904         | 891                   | 56.1 ± 11.0            |
| Hu et al., 2012               | [57]     | China                         | 110         | 136                   | 56.7 ± 10.8            |
| Botta-Orfilla et al., 2012    | [58]     | Spain                         | 84          | —                     | —                      |
| Mata et al., 2011             | [59]     | Spain                         | 1445        | 1161                  | 60.0 ± 12.2            |
| Chung et al., 2011            | [60]     | USA                           | 1103        | 1103                  | 62.2                   |
| Elbaz et al., 2011            | [61]     | Multicentric**                | 5302        | 4161                  | —                      |
| Wieder et al., 2011           | [62]     | USA, Ireland, Norway          | 1020        | 1095                  | 58.0 ± 12.0            |
| Botta-Orfilla et al., 2011    | [63]     | Spain                         | 757         | 708                   | —                      |
| Biernacka et al., 2011        | [64]     | USA                           | 1098        | 1098                  | 62.2                   |
| Mata et al., 2010             | [65]     | USA                           | 1956        | 2112                  | 58.7 ± 11.9            |
| Yu et al., 2010               | [66]     | China                         | 332         | 300                   | 54.3 ± 11.1            |
| Hu et al., 2010               | [67]     | China                         | 330         | 300                   | 52.6 ± 11.8            |
| Gatto et al., 2010            | [68]     | USA                           | 333         | 336                   | —                      |
| Rajput et al., 2009           | [69]     | Canada                        | 452         | 245                   | —                      |
| Sutherland et al., 2009       | [70]     | Australia                     | 331         | 296                   | 60.1 ± 10.6            |
| Brighina et al., 2009         | [71]     | USA                           | 893         | 893                   | 62.1                   |
| Kay et al., 2008              | [72]     | USA                           | 1802        | 2192                  | —                      |
| Myhre et al., 2008            | [73]     | Netherlands                   | 236         | 236                   | —                      |
| Verbaan et al., 2008          | [74]     | Netherlands                   | 295         | 150                   | —                      |
| Brighina et al., 2008         | [75]     | USA                           | 833         | 833                   | 61.9                   |
| Ross et al., 2007             | [76]     | Ireland                       | 186         | 186                   | 50.0 ± 11.0            |
| Winkler et al., 2007          | [77]     | Germany, Serbia               | 397         | 270                   | —                      |
investigated, and it stands out as a consistent risk factor for PD in twelve of the studies. Variants in the 3′ region possibly increase SNCA expression because of the misregulation of the posttranscriptional control. In the 3′ untranslated region (UTR), there are target binding sites for two microRNAs (mir-7 and mir-153), and alterations in these regions might affect mRNA stability and translation [92]. Further, mir-7 and mir-153 were associated with SNCA mRNA expression in human studies [23, 24]. The SNP rs356219 showed a robust association as a common susceptibility marker in twelve studies with patients from Russia [44], Germany [46, 80], Spain [58, 59], Japan [52], China [53], USA [28, 65], United Kingdom [78], and Netherlands [73]. Similarly, the SNP rs1931074 showed a significant association with increased PD risk in seven studies, four of which were performed in Chinese samples [32, 34, 39, 40].

The variants rs356221, rs356165, and rs356182 in 3′ UTR also contribute significantly to the increase in the PD risk in Germany [51, 77, 80], USA [28, 50], China [34], Taiwan [45], and Netherlands [73]. These findings reinforce the role of a posttranscriptional mechanism in PD etiology. The variant rs356165 was the most expressive [28, 50, 51, 54, 61, 73, 77, 80].

4. SNCA SNPs and Environmental Factors Interactions

Despite the relevance of environmental data to the understanding of the etiology of PD, the majority of studies contain little or no information on possible associations between SNCA SNPs and environmental factors (Table 3).

Sporadic PD is considered a result of complex interactions between genetic and environmental risk factors. Professional pesticide exposure, rural living, and well-water drinking were reported to increase the risk of PD [93–95]. In contrast, cigarette smoking [96, 97] and caffeine intake [98] have been pointed out as protective factors. Furthermore, though less consistently, reduced PD risk was associated with alcohol drinking [99]. Potential interactions between SNCA SNPs and pesticide exposure, smoking habits, head injury, or coffee and alcohol drinking were investigated in a few of the studies [47, 50, 52, 55, 56]. Overall, data demonstrated some pairwise interactions, but without reaching significant levels after Bonferroni correction. For example, although Miyake et al. [52], Chung et al. [47], and Gao et al. [55] found a significant protective effect of smoking habits against PD, corroborating epidemiological data, only the first study found significant interactions between SNPs rs356219 and rs356220 and smoking.

Meta-analyses [96, 97] have reinforced the inverse association between cigarette smoking and PD risk more consistently than other environmental factors (rural living, well-water consumption, farming, and the use of pesticides). One of the mechanisms suggested to underlie this neuroprotection is the reduction of brain levels of the enzyme monoamine oxidase B (MAO B), an isoform that selectively metabolizes dopamine. This reduction would enhance the levels of dopamine and decrease the production of hydrogen peroxide and oxidative stress rates [100]. An alternative explanation is that smoke induces cytochrome P-450 enzyme activity. This enzyme is responsible for the metabolism of antipsychotic drugs and the detoxification of certain environmental toxins such as MPTP [101]. In this respect, a case-control study carried out in European countries investigated polymorphisms with relevance to brain expression and metabolism.
Table 2: Single nucleotide polymorphisms (SNPs) in SNCA associated with Parkinson’s disease.

| Variant   | Region                  | Alleles       | Studies* with significant association with PD risk |
|-----------|-------------------------|---------------|--------------------------------------------------|
| rs1372519 | Promoter                | A/G           | [49] (†)                                          |
| rs230134  | Promoter                | C/T           | [45, 76] (†)                                      |
| rs230135  | Promoter                | C/G           | [45] (†)                                          |
| rs2619361 | Promoter                | A/C           | [49] (†)                                          |
| rs2619362 | 5’ region               | C/T           | [49] (†)                                          |
| rs2619363 | 5’ region               | G/T           | [49, 77] (†)                                      |
| rs2619364 | 5’ region               | A/G           | [66, 77] (†)                                      |
| rs2583988 | 5' region               | C/T           | [49, 56, 61, 77] (†)                              |
| rs2119787 | Intron                  | A/G           | [65] (†)                                          |
| rs2197120 | Intron                  | A/G           | [56] (†)                                          |
| rs2572324 | Intron                  | C/T           | [49, 60, 64, 65] (†)                              |
| rs2583959 | Intron                  | C/G           | [49, 64] (†)                                      |
| rs2736990 | Intron                  | T/C           | [27, 28, 41, 47, 49, 52, 55, 60] (†) [40] (†)    |
| rs2737020 | Intron                  | C/T           | [76] (†)                                          |
| rs2737029 | Intron                  | C/T           | [56, 65, 80] (†)                                  |
| rs2737033 | Intron                  | A/G           | [46] (†)                                          |
| rs356164  | Intron                  | C/G           | [76] (†)                                          |
| rs356168  | Intron                  | A/G           | [64, 80] (†)                                      |
| rs356186  | Intron                  | A/G           | [56, 60, 76] (†)                                  |
| rs356203  | Intron                  | A/G           | [27, 80] (†)                                      |
| rs356204  | Intron                  | A/G           | [80] (†)                                          |
| rs3822086 | Intron                  | C/T           | [37] (†)                                          |
| rs3857057 | Intron                  | A/G           | [33] (†)                                          |
| rs3857059 | Intron                  | A/G           | [29, 80] (†)                                      |
| rs6848726 | Intron                  | C/T           | [80] (†)                                          |
| rs7684318 | Intron                  | C/T           | [27, 66] (†)                                      |
| rs7689942 | Intron                  | C/T           | [33] (†)                                          |
| rs894278  | Intron                  | G/T           | [35, 36] (†)                                      |
| rs1372520 | Intron                  | C/T           | [47, 49] (†) [60] (†)                             |
| rs10018362| Intron                  | C/T           | [33] (†)                                          |
| rs2737012 | Intron                  | C/T           | [49] (†)                                          |
| rs3756063 | Intron                  | C/G           | [36] (†)                                          |
| rs3775423 | Intron                  | C/T           | [48, 60, 64] (†)                                  |
| rs356221  | 3’ region               | A/T           | [45, 48, 77] (†)                                  |
| rs356165  | 3’ region               | A/G           | [28, 50, 51, 54, 69, 73, 76, 77, 80] (†)          |
| rs356182  | 3’ region               | A/G           | [32] (†)                                          |
| rs356218  | 3’ region               | A/G           | [47, 49, 60] (†)                                  |
| rs356219  | 3’ region               | A/G           | [28, 42, 44, 46, 52, 53, 59, 61–63, 65, 73, 78, 80] (†) |
| rs356220  | 3’ region               | C/T           | [27, 28, 30, 33, 52, 55, 80] (†) [40] (†)        |
| rs356225  | 3’ region               | C/T           | [33] (†)                                          |
| rs181489  | 3’ region               | C/T           | [61, 76, 77] (†)                                  |
| rs1993074 | 3’ region               | G/T           | [30, 31, 34, 39, 55, 57, 61] (†) [37, 45] (†)    |

SNP: single nucleotide polymorphism. *See Table 1. Arrows indicate whether the SNP increased (†) or reduced (¶) PD susceptibility in each study, based on values of odds ratio and confidence intervals.
5. SNCA SNPs and PD Clinical Outcomes Interactions

The influence of polymorphisms on PD phenotypic variability remains unclear. Indeed, few studies specifically investigated their associations with particular aspects of the disease, such as disease history and clinical outcomes (Table 4).

of substances contained in tobacco smoke and confirmed significant interactions of SNPs in cytochrome P-450 enzyme family genes (GSTM1, GSTPI, and NAT2). However, there is no information about the mechanisms that explain the biological interaction between SNCA genotypes and cigarette smoking.

The age at onset is the most frequently investigated and well-established aspect of disease history. Polymorphisms located in the promoter (REPI), introns (rs2736990, rs894278), and 3' region (rs356219 and rs356165) are suggested to be predictors of earlier PD onset in Australian and Chinese [35], Spanish [54], German [46], and UK [61] samples. The identification of genetic features associated with the onset of PD has a relevant potential for therapeutic targeting. In view of the fact that neurodegeneration precedes the appearance of motor symptoms [102], it is critical to predict the risk of developing PD prior to clinical manifestations.

Even though it is expected that SNCA variants would influence individual traits or phenotypes of sporadic PD, this association was poorly explored in the studies. In a

Table 3: Association of environmental factors of PD with SNPs in SNCA.

| Environmental factors | Studies | Results |
|-----------------------|---------|---------|
| Smoking               | [34, 38, 47, 50, 52, 55, 56, 68, 70] | Individuals with GG-rs356219 and TT-rs356220 genotypes [52] and carriers of allele REPI-263 bp [47] who never had smoked had a significantly increased risk of PD. |
| Coffee intake         | [38, 47, 55, 56] | No SNPs were significantly associated with this factor. |
| Pesticide exposure    | [47, 68, 70, 71] | Chung et al. [47] found a suggestive association between C-rs3775423 and pesticide exposure. |
| Alcohol drinking      | [47, 75] | Briggsina et al. [75] found independent effects to alcohol consumption and REPI-SNCA. Alcohol use was associated with a decreased PD risk. |
| Head injury           | [38] | Head injury increases PD risk, especially when it happens before the age of 30; no significant association with SNCA SNPs. |

* See Table 1.

Table 4: Association of clinical aspects of PD and SNPs within SNCA.

| Variables                  | Studies | Results |
|----------------------------|---------|---------|
| Age at onset               | [28, 32, 35, 37, 40, 41, 46, 53, 54, 58, 66, 69, 70, 72, 79] | SNPs were associated with earlier PD onset: REPI-263 bp [35, 69, 79]; C-rs2736990 [41]; G-rs894278 [35]; G-rs356219 [46, 53, 58]; G-rs356215 [54] |
| Motor outcomes a           | [28, 31, 32, 34, 43, 50, 51, 74] | Wang et al. [31] found a protective association between T-rs11931074 allele carriers and motor severity. Ritz et al. [50] found that REPI-263 bp and G-rs356165 alleles increased the risk of faster decline of motor function, whereas Markopoulou et al. [43] demonstrated that REPI-263 bp allele reduced the risk of developing motor impairments |
| Cognition outcomes b       | [31–34, 37, 40, 42, 43, 74, 78] | Markopoulou et al. [43] showed an increased risk of cognitive impairment in carriers of REPI-259 bp allele. Guella et al. [33] found a significant association of C-rs10018362, T-rs7689942, and G-rs1348224 alleles with PD with dementia |
| Anxiety and depression c   | [32, 34, 37, 40, 74] | No SNPs were significantly associated with symptoms |
| Autonomic and sleep disorders d | [34, 74] | No SNPs were significantly associated with symptoms |
| Hyposmia                   | [34, 74] | In Chen et al.’s study [34], TT-rs11931074 genotype increased the risk of hyposmia in PD |

* See Table 1. aQuestionnaires used: Unified Parkinson Disease Rating Scale-III and Hoehn and Yahr. bQuestionnaires used: Mini-Mental State Examination, Frontal Assessment Battery, Montreal Cognitive Assessment, Scales for Outcomes in Parkinson’s Disease Cognition, Hopkins Verbal Learning Test-Revised, Letter-Number Sequencing Test and Trail Making Test, Semantic and Phonemic Verbal Fluency Tests, and Benton Judgment of Line Orientation test. cQuestionnaires used: Hamilton Rating Scale for Depression and Anxiety and Beck Depression Inventory. dQuestionnaires used: REM Sleep Behavior Disorder Questionnaire, and Scales for Outcomes in Parkinson’s Disease Autonomic, Nighttime Sleep, Daytime Sleepiness and Psychiatric Complications.
longitudinal study with a North American sample, Ritz et al. [50] showed that the REPI-263 bp promoter variant and the G-rs356165 allele are risk factors to faster motor progression in Caucasian and non-Caucasian PD patients (OR 1.66; 95% CI: 0.96–2.88). Wang et al. [31] found a protective association between T-rs1931074 allele and motor severity. However, in a larger sample of Caucasian patients, Markopoulou et al. [43] showed that REPI-263 bp allele reduced the risk of developing motor impairments. This divergence can be a result of differences in the methods of motor evaluation. According to Markopoulou et al. [43], the discrepancies may also suggest a dual and time-dependent role of SNCA.

Impairments in the olfactory function are a common early-stage nonmotor feature of PD, and the TT-rs11931074 genotype may increase the risk of hyposmia in PD cases [34]. Few other studies pointed out weak or absent associations with clinical outcomes such as anxiety or depression [32, 34, 37, 40, 74], sleep and autonomic disorders [34, 74], and cognitive impairments [31, 32, 34, 37, 40, 74]. Regarding cognitive features, Markopoulou et al. [43] demonstrated that the REPI-259 pb allele increased the risk of cognitive outcomes. Trotta et al. [56] found significant associations of C-rs10018362, T-rs7689942, and G-rs1348224 alleles with PD with dementia and also identified a specific haplotype in intron 4 of SNCA (C-rs62306323 and T-rs7689942) associated with increased risk of PD with dementia. It is important to mention that limited data of SNP associations with PD phenotype in cross-sectional studies might be related to a single event of clinical assessment, which could mask possible effects. Studies of such associations could provide important clinical applicability of the significant findings of genotyping studies. More studies evaluating specific clinical aspects, especially with longitudinal designs, are necessary to enhance the understanding of how genetic factors contribute to PD.

6. Biological Effects of SNCA SNPs

There is increasing evidence supporting the biological effects of genetic variants in SNCA, possibly by modifying alpha-synuclein expression. Among the studies listed in Table 5, the associations of SNCA-REP1 and 3′ variants (rs356219 and 11931074) and peripheral alpha-synuclein levels were investigated in Chinese [57] and North American [65] populations. Mata et al. [65] found an association of CC-356219 genotype with increased plasma levels of alpha-synuclein. A variation in the REPI region might affect transcriptional activity by increasing the expression of alpha-synuclein and consequent protein accumulation [22, 23]. SNCA duplication and triplication in familial PD have been linked to increased mRNA expression levels [103] and to disease severity [19, 20].

In postmortem brain tissue studies, the 3′ region SNPs rs356219 [84], rs356165 [24], and rs11931074 [39] have been associated with increased gene expression. For rs356219, the heterozygote CT genotype correlated with higher levels of SNCA-mRNA in the substantia nigra of PD patients. However, the TT protective genotype was accompanied by higher expression in the cerebellum, a structure that is more preserved in the course of PD [84]. Similarly, G-rs356219 allele carriers presented higher levels of the SNCA112-mRNA isoform in the frontal cortex [24]. Further, PD patients presented higher levels of the SNCA-112 and SNCA-98 transcripts in the cerebellum and occipital cortex when compared to controls [39].

Linnertz et al. [104] investigated the effects of SNCA SNPs in 5′ and 3′ regions on SNCA expression in postmortem brains from neurologically normal subjects. For REPI, the 256 bp/256 bp genotype correlated with lower SNCA-mRNA levels, corroborating the hypotheses that decreased SNCA levels protect against the disease. Unexpectedly, the protective

| Study            | SNP          | Risk allele | Results                                                                                                                                                                                                 |
|------------------|--------------|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hu et al. [57]   | rs11931074   | T           | The allele was associated with reduced levels of alpha-synuclein in serum                                                                                                                                 |
|                  | REPI         | C           | Different alleles and genotypes did not influence levels of alpha-synuclein in serum                                                                                                                    |
| Mata et al. [65] | rs356219     | C           | CC genotype was correlated with increased levels of alpha-synuclein in plasma                                                                                                                          |
| Fuchs et al. [84] | rs2583988    | T           | No correlation with alpha-synuclein mRNA or protein levels 256 bp/256 bp genotype was associated with lower alpha-synuclein levels assessed in blood samples; no effect in brain samples |
|                  | REPI         | 261 pb      | CT genotype correlated with higher SNCA mRNA levels in the substantia nigra and TT genotype showed higher SNCA mRNA levels in the cerebellum; no effect in blood samples                                         |
|                  | rs356219     | C           |                                                                                                                                                                                                        |
| McCarthy et al. [24] | rs2736990  | G           | In the 3 SNPs, the GG genotype correlated with an increased expression ratio of SNCA112 mRNA in the frontal cortex                                                                                     |
|                  | rs356165     | G           |                                                                                                                                                                                                        |
|                  | rs356165     | G           |                                                                                                                                                                                                        |
| McCarthy et al. [24] | rs3857059  | G           | No correlation between genotypes and the ratio expression levels of SNCA112 mRNA                                                                                                                                 |
|                  | rs17016074   | A           |                                                                                                                                                                                                        |
| Cardo et al. [39] | rs356165    | G           | No significant differences for the SNCA isoform levels between the different genotypes assessed in brain tissues                                                                                         |
|                  | rs11931074   | T           |                                                                                                                                                                                                        |

aPostmortem studies.

Table 5: Interactions between alpha-synuclein levels and SNCA SNPs.
genotypes AA-rs356219 and AA-rs365165 in the 3’ region correlated with higher levels of SNCA-mRNA in the temporal cortex and substantia nigra, which highlights an expanded regulatory effect of this region on total SNCA-mRNA levels.

Regarding in vivo studies, patients with SNP rs2583988 genotypes did not present alterations in alpha-synuclein levels in peripheral blood mononuclear cells, while the protein levels were reduced in the absence of the REPI risk allele [84]. For SNPs in the 3’ region, while carriers of T-rs1931074 allele presented reduced levels of protein in serum [57], a higher level of alpha-synuclein in plasma was observed in carriers of the C-rs356219 allele [65].

7. Genetical Background, Ethnicity, and the Effect of SNCA SNPs

Methodological aspects such as variations in the sample size, control of population stratification, and statistical analyses can explain the discrepancies in the effects of SNPs among the different studies. In addition, it is common to exclude the influence of confounder variables as sex, age, and ethnic background, which can modify the results substantially.

The majority of the studies were carried out in countries of Europe, North America, and Asia, that is, populations with mainly Caucasian and Asian genetic backgrounds. Despite the fact that ethnic differences can preclude the generalization of the results in genetic studies, many of the SNPs showed similar effects in groups with different genetic backgrounds. For example, the SNP rs356219 remained an important risk factor for PD in studies performed within North American [65], Spanish [63], Russian [44], and Chinese [41] populations. Nevertheless, given the significance of results and perspectives of clinical advancement, it seems necessary to extend these investigations to other continents, in order to confirm whether these genetic effects are consistent across different populations and to verify the implications of between-population heterogeneity.

Finally, apart from variants in the SNCA gene, it is necessary to consider the role of interactions between multiple genetic variants in disease risk and clinical profile. For example, investigations of phenotypic diversity in PD have identified an association between SNCA and MAPT. This association contributed to increased cognitive and motor severity in a Chinese sample [31] and influenced the development of cognitive impairment and dementia in a British sample [78]. In addition, polymorphisms in GAB [28] and LRRK2 [58] have been associated with earlier age at the onset in a European-American population and in a Spanish sample, respectively. Also, in North Americans, APOE variants predicted lower cognitive performance in PD patients [42].

8. Conclusions

This review collected the contributions of polymorphisms in the SNCA gene to PD susceptibility and clinical phenotypes. In most of the studies, the influence of polymorphisms in multiple regions of SNCA gene was pointed out, such as the promoter region (REPI-SNCA), 3’ end (e.g., rsI1931074 and rs356219), 3’ untranslated regions (e.g., rs356165), and introns (e.g., rs7684318, rs894278, and rs276990). In addition, we highlight that it is necessary to expand the clinical applicability of these data, as well as investigate the role of SNCA variations in populations with different ethnic backgrounds.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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