Journal of Neural Transmission (2024) 131:773–779
https://doi.org/10.1007/s00702-024-02759-1

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

NFKB1 variants were associated with the risk of Parkinson´s disease in male

Sergio Perez-Oliveira[1,2] · Daniel Vazquez-Coto[1,2] · Sara Pardo[1] · Marta Blázquez-Estrada[2,3] · Manuel Menéndez-González[2,3] · Pablo Siso[2,3] · Esther Suárez[2,3] · Ciara García-Fernández[2,3] · Beatriz de la Casa Fages[4] · Eliecer Coto[1,2] · Victoria Álvarez[1,2]

Received: 24 December 2023 / Accepted: 22 February 2024 / Published online: 28 February 2024
© The Author(s), under exclusive licence to Springer-Verlag GmbH Austria, part of Springer Nature 2024

Abstract

The NF-κB pathway is involved in the pathogenesis of neurological disorders that have inflammation as a hallmark, including Parkinson's disease (PD). Our objective was to determine whether common functional variants in the *NFKB1, NFKBIA* and *NFKBIZ* genes were associated with the risk of PD. A total of 532 Spanish PD cases (61% male; 38% early-onset, ≤55 years) and 300 population controls (50% ≤55 years) were genotyped for the *NFKB1* rs28362491 and rs7667496, *NFKBIA* rs696, and *NFKBIZ* rs1398608 polymorphisms. We compared allele and genotype frequencies between early and late-onset, male and female, and patient's vs. controls. We found that the two *NFKB1* alleles were significantly associated with PD in our population ($p=0.01$; total patients vs. controls), without difference between Early and Late onset patients. The frequencies of the *NFKB1* variants significantly differ between male and female patients. Compared to controls, male patients showed a significantly higher frequency of rs28362491 II ($p=0.02$, OR = 1.52, 95%CI = 1.10–2.08) and rs28362491 C ($p=0.003$, OR = 1.62, 95%CI = 1.18–2.22). The two *NFKB1* variants were in strong linkage disequilibrium and the I-C haplotype was significantly associated with the risk of PD among male ($p=0.002$). In conclusion, common variants in the NF-kB genes were associated with the risk of developing PD in our population, with significant differences between male and female. These results encourage further studies to determine the involvement of the NF-kB components in the pathogenesis of Parkinson´s disease.

Keywords Parkinson´s disease · Genetic susceptibilty · Gene polymorphisms · Nuclear-factor kappa-b

Introduction

The nuclear factor kappa light chain enhancer of activated B cells (NF-κB) comprises a family of transcription factors that drive the expression of many genes which regulate pro-inflammatory responses (Lawrence 2009; Liu et al. 2017). The functional NF-κB transcription factor is a complex of at least one Rel protein (RelA, RelB, or RelC) and the p50 or p52 proteins. The p50 protein is encoded by the *NFKB1* gene and as homo or heterodimer with p52 (encoded by *NFKB2*) acts as repressor of transcription, while as heterodimers with Rel proteins enhances the transcription of many genes by binding to their κB promoter consensus site (5′-GGGRNYY YCC-3). The NF-κB pathway is regulated through the binding of several inhibitors in the cytoplasm (IκBα, IκBβ, IκBε, and Bcl-3) that prevent the translocation of the Rel/p50/p52 complexes to the nucleus. Several stimuli mediate the phosphorylation of these IκBs and their

Sergio Perez-Oliveira and Daniel Vazquez-Coto contributed equally to this work.

✉ Victoria Álvarez
victoria.alvarez@sespa.es

1 Laboratorio de Genética, Hospital Universitario Central de Asturias, Avd de Roma s/n, Oviedo 33011, Spain

2 Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain

3 Servicio de Neurología, Hospital Universitario Central de Asturias, Oviedo 33011, Spain

4 Servicio de Neurología, Hospital Universitario Gregorio Marañon, Madrid, Spain

dissociation from the complex, that are then translocated into the nucleus. In the nucleus, the NF-κB is also regulated by atypical proteins, such as NFKBIZ/IκBζ (Feng et al. 2023). The NF-kB components are highly expressed in immune cells but are also present in most tissues and cell types. The inappropriate activation of NF-κB pathway has been associated with inflammatory diseases, while its persistent inhibition would result in a lack of immune response to infection or delayed cell growth (Park and Hong 2016).

The NF-κB pathway plays a role in the pathogenesis of neurological disorders that have inflammation as a pathological hallmark (Ju Hwang et al. 2017; Kaltschmidt et al. 2022; Singh and Singh 2020). NF-κB has been implicated in processes of synaptic plasticity and memory, and in the development of Parkinson's disease (PD) (Bellucci et al. 2020; Dolatshahi et al. 2021; Kaltschmidt et al. 2022; Kaltschmidt and Kaltschmidt 2015; Mattson & Meffert 2006). The selective inhibition of NF-κB activation prevented dopaminergic neuronal loss in a mouse model of Parkinson's disease (Ghosh et al. 2007). Mice deficient for the c-Rel peptide developed a PD-like phenotype (Baiguera et al. 2012; Parrella et al. 2019). The expression of Parkin (a gene mutated in early-onset recessive PD) could enhance the activation of NF-κB by promoting the phosphorylation of IκBs and subsequent nuclear translocation of p65 (Wang et al. 2018). In iPSC-derived neurons the silencing of *LRRK2* (a gene mutated in familial PD with dominant inheritance) decreased α-syn protein levels in mutated neurons and modified NF-κB transcriptional targets (López de Maturana et al., 2016). The NF-κB dysregulation in *LRRK2* mutated neurons was also demostrated by a protracted recovery of IκBα and a marked impairment in p65 nuclear translocation (Russo 2019). Microglia from Lrrk2-null mice showed increased inhibition of nuclear p50 homodimer and attenuated inflammatory response, with markedly reduction of the nuclear inhibitor *NFKBIZ* (Bellucci et al. 2020). The NF-kB pathway also mediated the protective effect of NME1 in LRRK2 models of PD (Anantha et al. 2022). The above referred studies strengthened the interplay between PD and NF-κB inflammatory pathways. Likewise, pharmacological targeting of the NF-κB pathway may prevent PD progression (Flood et al. 2011).

The association of nucleotide variants in the NF-kB genes has been widely investigated in cancer and several immune-mediated diseases (Baltus et al. 2021; Camblor et al. 2022; Coto et al. 2019; Coto-Segura et al. 2017; Gao et al. 2007, 2012; Lin et al. 2012; López-Mejías et al. 2012; MohdSuzairi et al. 2013; Vogel et al. 2011). The best characterised variant is rs28362491, a biallelic 4-nucleotides indel in the *NFKB1* promoter (-94 delATTG) that has been linked to differences in gene expression. Variants in the *NFKBIA* and *NFKBIZ* genes have been associated with different transcript expression between the genotypes and the risk for immune mediated diseases (Song et al. 2011; Coto-Segura et al. 2017).

Based on the evidences described above, we hypothesised that gene variants in the genes that encode NF-κB components might be involved in the susceptibility of developing PD or act as modifiers of the age at disease onset.

Patients and methods

Study subjects

This study was approved by the Asturias Ethical Committee for Medical Research, and all the participants gave their informed consent. All the patients ($N=532$) and controls ($N=300$) were of European ancestry and from the region of Asturias (Northern Spain, total population approx. 1 million). PD was diagnosed by Neurologists from the Hospital Universitario Central Asturias (HUCA) and Hospital Cabueñes-Gijón according to the UK Parkinson's Disease Society Brain Bank clinical criteria. Patients with disease symptoms at an age ≤ 55 years ($N=201$, 38%) or > 55 years ($N=331$, 62%) were classified as early-onset (EO) and late-onset (LO), respectively (Camerucci et al. 2021).

Controls were a total of 300 individuals randomly selected from the general population of Asturias, without other inclusion or exclusion criteria. They were studied with the only purpose of determining allele and genotype frequencies of theNF-Kb in the general population in the context of a case-control study.

NF-κB variants genotyping

The DNA of all the participants was obtained from blood leukocytes. We studied the *NFKB1* rs28362491, *NFKB1* rs7667496, *NFKBIA* rs696 and *NFKBIZ* rs1398608 variants. The four polymorphisms were selected based on their reported functional effects on the NF-κB expression and signaling, their previous association to immune-mediated and inflammatory diseases, or the significant effect on gene expression according to the GTEX Portal (https://gtexportal.org/) (suppl. Figure 1).

The *NFKB1* rs28362491 and *NFKBIA* rs696 were genotyped with TaqMan probes (assays id. C_61632788_30 for rs28362491 and id. C_145669_30 for rs696). DNAs were amplified in 96 well qPCRs plates with a 7500 Fast Real-Time PCR System and following the manufacturer protocol (Thermo Fisher Scientific).

The *NFKB1* rs28362491 and *NFKBIZ* rs1398608 were genotyped by digestion of PCR fragments with the

restriction enzymes MspI or TaqI, as previously reported (Coto et al. 2018) (suppl. Figure 2).

LRRK2 mutation analysis

Pathogenic mutations in the leucine-rich repeat kinase 2 gene (*LRRK2*; PARK8) have been implicated in autosomal dominant parkinsonism. Two *LRRK2* pathogenic variants are the most common cause of familial PD among Europeans: p.R1441G (c.4321 C > G, SNP rs33939927) and p.G2019S (c.6055G > A, SNP rs34637584). (Mata et al. 2006) All the patients were genotyped for the two variants by real-time PCR with Taqman probes (assays C_63497391_10 and C_63498123_10; ThermoFisher Scientific).

Statistical analysis

All the values were collected in an Excel file (available as reasonable request to the corresponding author). The statistical analyses were performed in R (www.r-project.org). Chi-squared tests were done to compare genotype and allele frequencies between groups. Odds Ratio (OR) values and their 95% confidence intervals (95% CI) were determined by logistic regression (generalized linear model). A $p < 0.05$ was taken as the cutoff for significance.

Haplotype frequencies were calculated online with CubeX program (http://apps.biocompute.org.uk/cubex/) (Gaunt et al. 2007).

Results

The main values in our PD patients and their age-matched controls are summarised in Table 1. There were no difference in sex frequencies between early and late onset cases. A total of 10% of the patients were carriers of one of the *LRRK2* pathogenic variants, 13% of the EO-PD and 8% of the LO-PD.

The genotype frequencies for three *NFKBIA* and *NFKB1* polymorphisms did not deviate from the Hardy-Weinberg equilibrium in the total patients and controls. For the controls the observed frequencies were close to the reported among Europeans (**suppl. Figure 2**). We did not find significant differences between population controls aged ≤ 55 and > 55 years for the four gene variants, or between patients with early and late-onset PD (Table 1). We compared the allele frequencies between total patients and controls. The *NFKB1* rs28362491 Insertion (I) and rs28362491 C alleles were significantly more frequent in the patients ($p = 0.018$ and $p = 0.013$, respectively). In reference to the genotypes, in our population the *NFKB1* rs28362491 II genotype and

Table 1 Main values in the early and late-onset PD and the age matched controls. *LRRK2*+: carriers of pathogenic variants, p.Arg1441Gly or p.Gly2019Ser. MAF: minor allele frequency

	PD ≤ 55 *N* = 201	PD > 55 *N* = 331	TOTAL Patients *N* = 532	Controls ≤ 55 *N* = 150	Controls > 55 *N* = 150	TOTAL controls *N* = 300
FEMALE	79 (39%)	128 (39%)	207 (39%)	69 (46%)	68 (45%)	137 (46%)
MALE	122 (61%)	203 (61%)	325 (61%)	81 (54%)	82 (55%)	163 (54%)
ONSET AGE RANGE years	20–55	56–88	20–88	18–55	56–85	18–85
ONSET AGE MEDIAN years	48	66	62	49	63	60
LRRK2+	26 (13%)	28 (8%)	54 (10%)	-	-	-
LRRK2 R1441G	10 (5%)	14 (4%)	24 (5%)	-	-	-
LRRK2 G2019S	16 (8%)	14 (4%)	30 (6%)	-	-	-
NFKBIA rs696 **MAF T**	0.43	0.39	0.39	0.38	0.36	0.37
NFKB1 rs28362491 MAF**D**	0.33	0.32	0.32	0.38	0.39	0.38
NFKB1 rs7667496 MAF**T**	0.30	0.29	0.30	0.36	0.35	**0.38**
NFKBIZ rs1398608 MAF G	0.25	0.27	0.27	0.23	0.24	0.24

Total patients vs. total controls

NFKBIA rs696 C vs. T:p = 0.44

NFKB1 rs28362491 I vs. D:p = 0.018, OR = 1.29,95%CI = 1.04–1.59

NFKB1 rs7667496 C vs. T:p = 0.013, OR = 1.31, 95%CI = 1.06–1.62

the rs28362491 CC were non significantly increased among the patients (suppl Table 1). The *NFKBIA* and *NFKBIZ* allele and genotype frequencies did not differ between patients and controls.

There were significant differences between total male and female patients for the two *NFKB1* polymorphisms (Table 2). The rs28362491 II and rs28362491 CC genotypes were significantly more frequent in the male patients ($p = 0.002$ and $p = 0.005$, respectively). The difference was significant after applying the Bonferroni´s correction for multiple testing ($p < 0.01$). Moreover, for $p < 0.05$ and the frequencies found of the risk genotypes, the post hoc statistical power of the sample size (male vs. female) wa 84%, above the recommended 80%.

Compared to controls, male patients showed a significantly higher frequency of rs28362491 II ($p = 0.02$, OR = 1.52, 95%CI = 1.10–2.08) and rs28362491 C ($p = 0.003$, OR = 1.62, 95%CI = 1.18–2.22). There were no differences between female patients and controls. The *NFKBIA* rs696 and *NFKBIZ* rs1398608 allele and genotype frequencies did not differ between the patients groups.

The two *NFKB1* polymorphisms were in strong linkage disequilibrium in our population (D´=0.98, $r^2 = 0.85$) (suppl. Tables 2 and 3). Haplotype rs28362491 I - rs28362491 C was significantly more frequent among male patients compared to female, and compared to total controls ($p = 0.002$, OR = 1.56, 95%CI = 1.17–2.07) (Fig. 1).

In reference to the *LRRK2* variants, 13% of the patients ≤ 55 years and 8% of the patients > 55 years were carriers of p.R1441G or p.G2019S. We compared the *NFKB1*, *NFKBIA* and *NFKBIZ* frequencies between carriers and non-carriers of the *LRRK2* variants. No significant difference was observed between the groups (suppl. Table 4).

Discussion

The main finding of our study was a significant association between common functional variants in the *NFKB1* gene and the risk of developing PD. This agreed with studies that reported a functional effect of the NF-Kb pathway in dopaminergic neurons of patients with PD (Hunot et al. 1997). We also found that the association was mainly due to a significant difference between male and female patients. Several studies showed that the NF-κB components might be differentially activated in male and female patients with Parkinson´s disease. A transcriptome meta-analysis in brain

Table 2 Allele and genotype frequencies in early and late onset male and female patients

	EO-Male $N = 122$	LO-Male $N = 203$	EO-Female $N = 79$	LO-Female $N = 128$	TOTAL MALE $N = 325$	TOTAL FEMALE $N = 207$
NFKBIA rs696						
CC	**45 (37%)**	**80 (39%)**	**22 (28%)**	**45 (35%)**	125 (38%)	**67 (32%)**
CT	**53 (43%)**	**95 (47%)**	**41 (52%)**	**62 (48%)**	148 (46%)	**103 (41%)**
TT	**24 (20%)**	**28 (14%)**	**16 (20%)**	**21 (17%)**	52 (16%)	**37 (18%)**
T	**0.41**	**0.37**	**0.46**	**0.41**	0.39	**0.44**
					C vs. T: *p = 0.19*	
NFKB1 rs28362491						
II	**62 (51%)**	**98 (48%)**	**27 (34%)**	**47 (37%)**	160 (49%)	**74 (36%)**
ID	**51 (42%)**	**94 (46%)**	**41 (52%)**	**65 (51%)**	145 (45%)	**106 (51%)**
DD	**9 (7%)**	**11 (6%)**	**11 (14%)**	**16 (13%)**	20 (6%)	**27 (13%)**
D	**0.28**	**0.29**	**0.40**	**0.37**	0.29	**0.34**
					I vs. D: *p = 0.001*	
					II vs. ID + DD, *p = 0.002*	
NFKB1 rs7667496						
CC	**64 (52%)**	**108 (53%)**	**31 (39%)**	**53 (41%)**	172 (53%)	**84 (41%)**
CT	**52 (43%)**	**85 (42%)**	**40 (51%)**	**60 (47%)**	137 (42%)	**100 (48%)**
TT	**6 (5%)**	**10 (5%)**	**8 (10%)**	**15 (12%)**	16 (5%)	**23 (11%)**
T	**0.26**	**0.26**	**0.35**	**0.33**	0.26	**0.34**
					C vs. T: *p = 0.001*	
					CC cs CT + TT, *p = 0.005*	
***NFKBIZ*rs1398608**						
AA	**66 (54%)**	**112 (55%)**	**43 (55%)**	**67 (52%)**	178 (55%)	**110 (53%)**
AG	**51 (42%)**	**75 (37%)**	**33 (42%)**	**47 (37%)**	126 (39%)	**80 (39%)**
GG	**5 (4%)**	**16 (8%)**	**3 (3%)**	**14 (8%)**	21 (6%)	**22 (11%)**
G	**0.25**	**0.26**	**0.25**	**0.29**	0.26	**0.29**

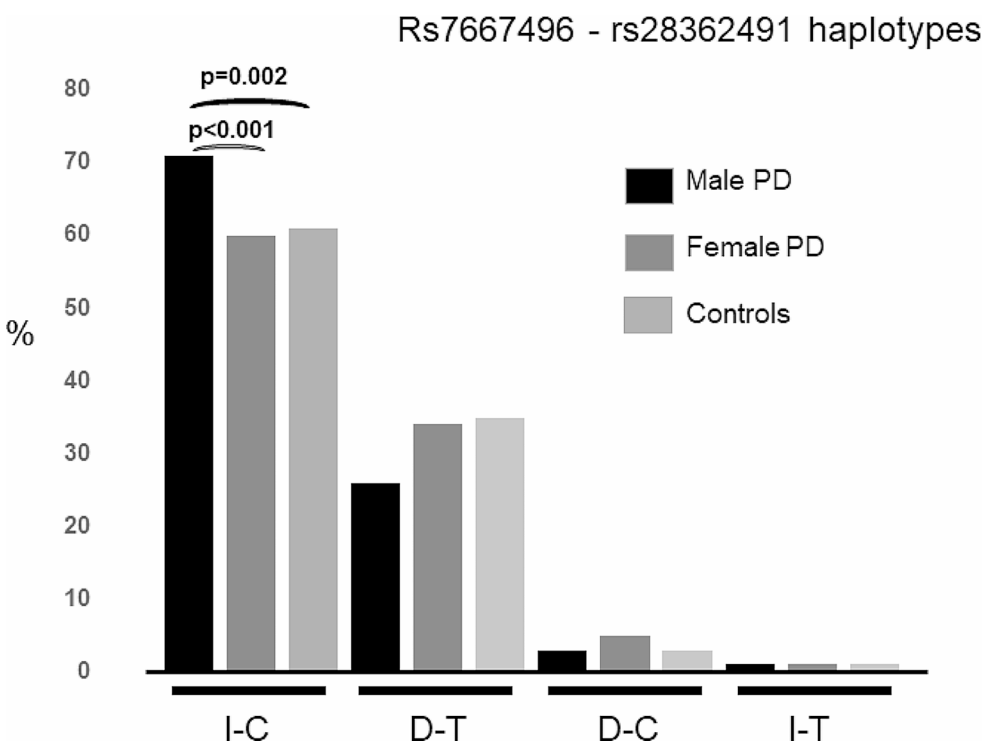

Fig. 1 Frequency of the NFKB1 haplotypes, rs76675496 ID – rs28362491 CT. Haplotype I-C was significantly more frequent in male patients vs. female ($p < 0.001$) and male patients vs. controls ($p = 0.002$). Haplotype frequencies were calculated with CubeX (http://apps.biocompute.org.uk/cubeX/) from the genotype combinations (**suppl table**)

found significant disease-associated sex differences in several pathways, including NF-Kb genes (Tranchevent et al. 2023). In particular, *NFKB1* was among the top enriched transcription factors.

The *NFKB1* rs28362491 insertion allele that was significantly more frequent in the male patients has been associated with a decreased basal expression of NFKB1/p50. The increased risk among *NFKB1* II was in agreement with the reported decreased levels of *NFKB1*/p50 in the pars compacta of the substantia nigra of cases with dementia with Lewy bodies (DLB) compared to controls (Saldaña et al. 2007). The decreased basal expression of the p50 subunit in the substantia nigra could increase the vulnerability of the dopaminergic neurons to a possible neurotoxic effect of the p65 subunit. In this way, the lower expression of *NFKB1* (p50 subunit) among rs28362491-II and rs28362491-CC carriers could increase the risk of a toxic effect of p65 in neurons.

The reduction of NF-κB/p50 function in mice would results in augmented peripheral/microglial pro-inflammatory responses and neuroinflammation signalling mechanisms (Taetzsch et al. 2019). Mice lacking p50 treated with LPS showed different degree of neuroinflammation and microglia morphology compared to normal mice, and the loss of p50 function could thus results in increased microglial pro-inflammatory responses.

Recent studies gave some clues about the involvement of *NFKBIZ* in neurodegeneration. In human induced pluripotent stem cell-derived microglia *NFKBIZ* and *NFKBIA* regulated the iron-induced neurotoxicity and iron overload, with a marked shift in the microglial transcriptional profile that overlapped with the transcriptomic signature found in microglia from PD postmortem brain (Ryan et al., 2023). Other study reported that microglia from PD brains were enriched for *NFKBIZ* (Zhu et al., 2022). The two *NFKBIA* and *NFKBIZ* in our study have been described as eQTLs associated with significantly different gene expression in several tissues (suppl. Figure 1). Moreover, *NFKBIA* rs696 is in the 3´non translated region of the mRNA and the reduction of expression among carriers of the G-allele could be explained by an increased affinity for micro-RNAs that bind to this mRNA sequence. Thus, the G allele would result in reduced basal levels of the NFKBIA protein (Song et al. 2011). In our study we did not find significant difference for the two *NFKBIZ* and *NFKBIA* frequencies between the groups.

Several studies have reported a significant interaction between LRRK2 and the NF-κB pathway. Among others, the downregulation of LRRK2 could result in inhibition of p50 dimerization and reduced expression of NFKBIZ (Bellucci et al. 2020). We did not find significant *NFKB1*, *NFKBIZ* and *NFKBIA* allele and genotype frequencies between patients with and without one of the two LRRK2 variants. However, the comparison was based on only 54 *LRRK2*-positive patients and thus underpowered for this comparison.

Our study has several limitations that could condition the conclusions. First, it was based on a limited number of PD patients. Second, it was based on a single population and

would thus require replication in different cohorts. Third, although the association of the studied variants with PD is plausible, functional studies to determine the different effect of the variants on gene expression from brains of PD patients are also necessary.

In conclusion, we report a significant association between common *NFKB1* variants and PD. We also found a different degree of association of the *NFKB1* variants in male and female. In particular, variants associated with decreased basal expression of *p50/NFKB1* could increase the risk of developing PD. These results encourage further studies to determine the involvement of the NF-kB components in the pathogenesis of PD.

Acknowledgements This study has been funded by Instituto de Salud Carlos III (ISCIII) through the project P21/0467 and co-funded by the European Union. S.P.O. is supported by a predoctoral grant from FINBA. D.V.C. is supported by Fundación Parkinson Asturias-Obra Social Cajastur.

Author contributions All the authors contributed to this work by recruiting the patients and controls (MBE, MMG, PS, ES, CGF, BCF), performing the genetic study (SPO, DVC, SP, EC, VA), and/or the statistical analysis (EC, VA). E.C. and V.A. wrote the ms. All the authors have revised the text and approved the submission.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request. An Excel file with the raw data would be available for meta-analysis research.

Declarations

Ethics and consent to participate This study was approved by the clinical research ethics committee of Hospital Universitario Central Asturias (HUCA). All the participants gave written or verbal consent. Data were handled in observance of Spanish legislation on data protection. The study complies with the principles of the Declaration of Helsinki ("Recommendations guiding doctors in biomedical research involving human subjects").

Competing interests None of the authors have competing interests related to this work.

References

Anantha J, Goulding SR, Tuboly E, O'Mahony AG, Moloney GM, Lomansey G, McCarthy CM, Collins LM, Sullivan AM, O'Keeffe GW (2022) NME1 protects against Neurotoxin-, α-Synuclein- and LRRK2-Induced Neurite Degeneration in Cell models of Parkinson's Disease. Mol Neurobiol 59(1). https://doi.org/10.1007/s12035-021-02569-6

Baiguera C, Alghisi M, Pinna A, Bellucci A, De Luca MA, Frau L, Morelli M, Ingrassia R, Benarese M, Porrini V, Pellitteri M, Bertini G, Fabene PF, Sigala S, Spillantini MG, Liou HC, Spano PF, Pizzi M (2012) Late-onset parkinsonism in NFκB/c-Rel-deficient mice. Brain 135(9). https://doi.org/10.1093/brain/aws193

Baltus THL, Morelli NR, de Farias CC, Trugilo KP, Okuyama NCM, de Oliveira KB, de Melo LB, Smaili SM, Barbosa DS (2021) Association of -94 ATTG insertion/deletion NFkB1 and c.*126G>A NFkBIA genetic polymorphisms with oxidative and nitrosative stress biomarkers in Brazilian subjects with Parkinson's Disease. *Neuroscience Letters*, *740*. https://doi.org/10.1016/j.neulet.2020.135487

Bellucci A, Bubacco L, Longhena F, Parrella E, Faustini G, Porrini V, Bono F, Missale C, Pizzi M (2020) Nuclear Factor-κB dysregulation and α-Synuclein Pathology: critical interplay in the pathogenesis of Parkinson's Disease. Front Aging Neurosci 12. https://doi.org/10.3389/fnagi.2020.00068

Camblor DG, Miranda D, Albaiceta GM, Amado-Rodríguez L, Cuesta-Llavona E, Vázquez-Coto D, Gómez de Oña J, García-Lago C, Gómez J, Coto E (2022) Genetic variants in the NF-κBsignaling pathway (NFKB1, NFKBIA, NFKBIZ) and risk of critical outcome among COVID-19 patients. Hum Immunol 83:8–9. https://doi.org/10.1016/j.humimm.2022.06.002

Camerucci E, Stang CD, Hajeb M, Turcano P, Mullan AF, Martin P, Ross OA, Bower JH, Mielke MM, Savica R (2021) Early-Onset Parkinsonism and Early-Onset Parkinson's Disease: A Population-Based Study (2010–2015). In *Journal of Parkinson's Disease* (Vol. 11, Issue 3). https://doi.org/10.3233/JPD-202464

Coto E, Díaz-Corte C, Tranche S, Gómez J, Alonso B, Iglesias S, Reguero JR, López-Larrea C, Coto-Segura P (2018) Gene variants in the NF-KB pathway (NFKB1, NFKBIA, NFKBIZ) and their association with type 2 diabetes and impaired renal function. Hum Immunol 79(6):494–498 Epub 2018 Mar 27.PMID: 29601852

Coto E, Reguero JR, Avanzas P, Pascual I, Martín M, Hevia S, Morís C, Díaz-Molina B, Lambert JL, Alonso B, Cuesta-LLavona E, Díaz-Corte C, Gómez J (2019) Gene variants in the NF-KB pathway (NFKB1, NFKBIA, NFKBIZ) and risk for early-onset coronary artery disease. ImmunologyLetters 208. https://doi.org/10.1016/j.imlet.2019.02.007

Coto-Segura P, Gonzalez-Lara L, Gómez J, Eiris N, Batalla A, Gómez C, Requena S, Queiro R, Alonso B, Iglesias S, Coto E (2017) NFKBIZ in Psoriasis: assessing the association with gene polymorphisms and report of a new transcript variant. Hum Immunol 78:5–6. https://doi.org/10.1016/j.humimm.2017.02.008

de López R, Lang V, Zubiarrain A, Sousa A, Vázquez N, Gorostidi A, Águila J, de López A, Rodríguez M, Sánchez-Pernaute R (2016) Mutations in LRRK2 impair NF-KB pathway in iPSC-derived neurons. J Neuroinflamm 13(1). https://doi.org/10.1186/s12974-016-0761-x

Dolatshahi M, RanjbarHameghavandi MH, Sabahi M, Rostamkhani S (2021) Nuclear factor-kappa B (NF-κB) in pathophysiology of Parkinson disease: diverse patterns and mechanisms contributing to neurodegeneration. Eur J Neurosci (Vol 54(1). https://doi.org/10.1111/ejn.15242

Feng Y, Chen Z, Xu Y, Han Y, Jia X, Wang Z, Zhang N, Lv W (2023) The central inflammatory regulator IκBζ: induction, regulation and physiological functions. In *Frontiers in Immunology* (Vol. 14). https://doi.org/10.3389/fimmu.2023.1188253

Flood PM, Qian L, Peterson LJ, Zhang F, Shi JS, Gao HM, Hong JS (2011) Transcriptional factor NF-κb as a target for therapy in Parkinson's disease. In *Parkinson's Disease*. https://doi.org/10.4061/2011/216298

Gao J, Pfeifer D, He LJ, Qiao F, Zhang Z, Arbman G, Wang ZL, Jia CR, Carstensen J, Sun XF (2007) Association of NFKBIA polymorphism with colorectal cancer risk and prognosis in Swedish and Chinese populations. Scand J Gastroenterol 42(3). https://doi.org/10.1080/00365520600880856

Gao M, Wang CH, Sima X, Han XM (2012) NFKB1-94 insertion/deletion ATTG polymorphism contributes to risk of systemic lupus erythematosus. DNA Cell Biol 31(4). https://doi.org/10.1089/dna.2011.1389

Gaunt TR, Rodríguez S, Day IN (2007) Cubic exact solutions for the estimation of pairwise haplotype frequencies: implications for linkage disequilibrium analyses and a web tool 'CubeX'. BMC Bioinformatics 8:428. https://doi.org/10.1186/1471-2105-8-428

Ghosh A, Roy A, Liu X, Kordower JH, Mufson EJ, Hartley DM, Ghosh S, Mosley RL, Gendelman HE, Pahan K (2007) Selective inhibition of NF-κB activation prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease. Proc Natl Acad Sci USA 104(47). https://doi.org/10.1073/pnas.0704908104

Hunot S, Brugg B, Ricard D, Michel PP, Muriel MP, Ruberg M, Faucheux BA, Agid Y, Hirsch EC (1997) Nuclear translocation of NF-κb is increased in dopaminergic neurons of patients with Parkinson disease. Proc Natl Acad Sci USA 94(14). https://doi.org/10.1073/pnas.94.14.7531

Ju Hwang C, Choi D-Y, Park MH, Hong JT (2017) NF-κB as a key mediator of brain inflammation in Alzheimer's Disease. CNS Neurol Disorders - Drug Targets 18(1). https://doi.org/10.2174/1871527316666170807130011

Kaltschmidt B, Kaltschmidt C (2015) NF-KappaB in long-term memory and structural plasticity in the adult mammalian brain. In *Frontiers in Molecular Neuroscience* (Vol. 8, Issue November). https://doi.org/10.3389/fnmol.2015.00069

Kaltschmidt B, Helweg LP, Greiner JFW, Kaltschmidt C (2022) NF-κB in neurodegenerative diseases: Recent evidence from human genetics. In *Frontiers in Molecular Neuroscience* (Vol. 15). https://doi.org/10.3389/fnmol.2022.954541

Lawrence T (2009) The nuclear factor NF-kappaB pathway in inflammation. In *Cold Spring Harbor perspectives in biology* (Vol. 1, Issue 6). https://doi.org/10.1101/cshperspect.a001651

Lin CW, Hsieh YS, Hsin CH, Su CW, Lin CH, Wei LH, Yang SF, Chien MH (2012) Effects of NFKB1 and NFKBIA gene polymorphisms on susceptibility to environmental factors and the clinicopathologic development of oral cancer. PLoS ONE 7(4). https://doi.org/10.1371/journal.pone.0035078

Liu T, Zhang L, Joo D, Sun SC (2017) NF-κBsignaling in inflammation. In *Signal Transduction and Targeted Therapy* (Vol. 2). https://doi.org/10.1038/sigtrans.2017.23

López-Mejías R, García-Bermúdez M, González-Juanatey C, Castañeda S, Miranda-Filloy JA, Gómez-Vaquero C, Fernández-Gutiérrez B, Balsa A, Pascual-Salcedo D, Blanco R, González-Álvaro I, Llorca J, Martín J, González-Gay MA (2012) NFKB1-94ATTG ins/del polymorphism (rs28362491) is associated with cardiovascular disease in patients with rheumatoid arthritis. Atherosclerosis 224(2). https://doi.org/10.1016/j.atherosclerosis.2012.06.008

Mata IF, Ross OA, Kachergus J, Huerta C, Ribacoba R, Moris G, Blazquez M, Guisasola LM, Salvador C, Martinez C, Farrer M, Alvarez V (2006) LRRK2 mutations are a common cause of Parkinson's disease in Spain. Eur J Neurol 13(4). https://doi.org/10.1111/j.1468-1331.2006.01256.x

Mattson MP, &Meffert MK (2006) Roles for NF-κB in nerve cell survival, plasticity, and disease. In *Cell Death and Differentiation* (Vol. 13, Issue 5). https://doi.org/10.1038/sj.cdd.4401837Park

MohdSuzairi MSi, Tan SC, Ahmad Aizat AA, MohdAminudin M, SitiNurfatimah MS, Andee ZD, Ankathil R (2013) The functional −94 insertion/deletion ATTG polymorphism in the promoter region of NFKB1 gene increases the risk of sporadic colorectal cancer. Cancer Epidemiol 37(5). https://doi.org/10.1016/j.canep.2013.05.007

Park MH, Hong JT (2016) Roles of NF-κB in cancer and inflammatory diseases and their therapeutic approaches. In *Cells* (Vol. 5, Issue 2). https://doi.org/10.3390/cells5020015

Parrella E, Bellucci A, Porrini V, Benarese M, Lanzillotta A, Faustini G, Longhena F, Abate G, Uberti D, Pizzi M (2019) NF-κB/c-Rel deficiency causes Parkinson's disease-like prodromal symptoms and progressive pathology in mice. Translational Neurodegeneration 8(1). https://doi.org/10.1186/s40035-019-0154-z

Russo I (2019) The role of LRRK2 on PKA-NFκB pathway in microglia cells: implications for Parkinson's disease. In *Neural Regeneration Research* (Vol. 14, Issue 10). https://doi.org/10.4103/1673-5374.257523

Ryan SK, Zelic M, Han Y, Teeple E, Chen L, Sadeghi M, Shankara S, Guo L, Li C, Pontarelli F, Jensen EH, Comer AL, Kumar D, Zhang M, Gans J, Zhang B, Proto JD, Saleh J, Dodge JC, Savova V, Rajpal D, Ofengeim D (2023) Hammond TR.Microgliaferroptosis is regulated by SEC24B and contributes to neurodegeneration. NatNeurosci. 26(1):12–26. https://doi.org/10.1038/s41593-022-01221-3. Epub 2022 Dec 19.PMID: 36536241

Saldaña M, Mullol J, Aguilar E, Bonastre M, Marin C (2007) Nuclear factor kappa-B p50 and p65 subunits expression in dementia with Lewy bodies. Neuropathol Appl Neurobiol 33(3). https://doi.org/10.1111/j.1365-2990.2007.00806.x

Singh S, Singh TG (2020) Role of nuclear factor Kappa B (NF-κB) signalling in neurodegenerative diseases: an mechanistic Approach. Curr Neuropharmacol 18(10). https://doi.org/10.2174/1570159x18666200207120949

Song S, Chen D, Lu J, Liao J, Luo Y, Yang Z et al (2011) NFκB1 and NFκBIA polymorphisms are associated with increased risk for sporadic colorectal cancer in a southern Chinese population. PLoS ONE 6:e21726

Taetzsch T, Benusa S, Levesque S, Mumaw CL, Block ML (2019) Loss of NF-κB p50 function synergistically augments microglial priming in the middle-aged brain. J Neuroinflamm 16(1). https://doi.org/10.1186/s12974-019-1446-z

Tranchevent LC, Halder R, Glaab E (2023) Systems level analysis of sex-dependent gene expression changes in Parkinson's disease. Npj Parkinson's Disease 9(1). https://doi.org/10.1038/s41531-023-00446-8

Vogel U, Jensen MK, Due KM, Rimm EB, Wallin H, Nielsen MRS, Pedersen APT, Tjønneland A, Overvad K (2011) The NFKB1 ATTG ins/del polymorphism and risk of coronary heart disease in three independent populations. Atherosclerosis 219(1). https://doi.org/10.1016/j.atherosclerosis.2011.06.018

Wang Y, Shan B, Liang Y, Wei H, Yuan J (2018) Parkin regulates NF-κB by mediating site-specific ubiquitination of RIPK1. Cell Death Dis 9(7). https://doi.org/10.1038/s41419-018-0770-z

Zhu B, Park JM, Coffey S, Hsu IU et al Single-cell transcriptomic and proteomic analysis of Parkinson's disease brains. bioRxiv (2022) 2022-02. https://doi.org/10.1101/2022.02.14.480397

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.