2. Panagiotakaki E, Gobbi G, Neville B, Ebinger F, Campistol J, Nevšímalová S, et al. Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults. Brain 2010;133(12):3598–3610.

3. Hunanyan AS, Fainberg NA, Linabarger M, Arehart E, Leonard AS, Adil SM, et al. Knock-in mouse model of alternating hemiplegia of childhood: behavioral and electrophysiologic characterization. Epilepsia 2015;56(1):82–93.

4. Smith SE, Chen X, Brier LM, Bumstead JR, Rensing NR, Ringel AE, et al. Astrocyte deletion of α2-Na/K ATPase triggers episodic motor paralysis in mice via a metabolic pathway. Nat Commun 2020;11(1):6164.

5. Takano T, Tian GF, Peng W, Lou N, Lovatt D, Hansen AJ, et al. Cortical spreading depression causes and coincides with tissue hypoxia. Nat Neurosci 2007;10(6):754–762.

Impact of *APOE* Genotype on Cognition in Idiopathic and Genetic Forms of Parkinson's Disease

The ε4 allele of the apolipoprotein (*APOE*) gene is increasingly recognized to be associated with the development of cognitive decline in idiopathic Parkinson's disease (iPD).[1] The putative role of *APOE* as a genetic modifier of cognitive trajectories in genetic forms of Parkinson's disease (PD) is largely unexplored.[2] We have analyzed two independent PD cohorts. The first cohort (Athens) included 50 iPD patients, 35 patients with the p.A53T α-synuclein (*SNCA*) mutation and 59 patients with glucocerebrosidase (*GBA1*) mutations (13 mild/46 severe). The second cohort (Tübingen) included 292 patients with *GBA1* mutations (170 risk/52 mild/70 severe). All patients were genotyped for *APOE* (Figure S1, Data S1) and underwent cognitive testing using the Montreal Cognitive Assessment test (MoCA) (Table 1). Additionally, patients from the Tübingen cohort have also undergone analysis of cerebrospinal fluid (CSF) biomarkers (Table 1, and expanded cohort in Table S2).

In the iPD and in the p.A53T *SNCA* subgroups of the Athens cohort, carriers of at least one *APOE* ε4 exhibited lower MoCA scores as compared to non-carriers when using age, sex, disease duration, and education as covariates ($P = 0.044$ and $P = 0.039$, respectively) (Figure S2, Table 1). In contrast, in the *GBA1* subgroups from the Athens and Tübingen cohorts, no difference in MoCA score related to *APOE* ε4 status was detected ($P = 0.729$ and $P = 0.585$, respectively) (Figure S3, Table 1). Moreover, there were no associations between *APOE* genotype and Alzheimer's disease (AD)-related biomarker measurement outcomes in CSF in the Tübingen *GBA1* cohort (Table 1, Data S1, Table S2).

Our results are in accordance with literature data regarding the already described impact of *APOE* ε4 on cognitive decline of iPD.[1,3] Notably, the *APOE* ε4 effect on cognitive dysfunction was also present in the p.A53T *SNCA* subgroup, which represents the prototypical genetic synucleinopathy. *APOE* ε4 carriers in this genetic cohort exhibited significantly lower MoCA scores and were more often characterized as demented, based on MOCA cut-offs, compared to non-carriers (Table 1). Therefore, *APOE* appears to act as a genetic modifier of cognitive impairment in this genetic *SNCA* cohort, although this remains to be further demonstrated with larger numbers of subjects. Recent data suggest that *APOE* ε4 may directly exacerbate α-synuclein pathological deposition, beyond its established role in promoting AD co-pathology.[4,5] Previous data from our group, showing marginally low β-amyloid in some *p.A53T SNCA* PD carriers, suggest that at least β-amyloid co-pathology, influenced by *APOE* status, could be a factor in the mediation of cognitive decline.[6]

Regarding the *GBA*1 subgroups, we did not find an effect of *APOE* genotype on cognitive function in two independent cohorts of *GBA1* mutation carriers, who are considered a model of α-synuclein-related cognitive decline.[7] The absence of differences in CSF biomarker profiles between *APOE* ε4 carriers and non-carriers in the *GBA1* cohort further supports that the *APOE* genotype, and hence, probably also AD co-pathology, is irrelevant in this genetic PD form. Specifically, in the *GBA1*_severe subgroup that develops early cognitive impairment, *APOE* ε4 did not play a role, neither clinically nor on biomarker levels (Table 1, Figure S3 and Table S2). This substantiates the hypothesis of a predominant α-synuclein pathology, which is also linked to a pronounced α-synuclein seeding profile. The joint results from our current study and former research suggest differences in factors associated with cognitive decline (genetic, epigenetic, or environmental) between different genetic forms of synucleinopathies, even those that would be expected to be closely related, such as is the case of *GBA1* and *SNCA* mutations. In this respect, carriers of the p.A53T *SNCA* mutation resemble more closely iPD compared to *GBA1* mutation carriers, given the presence of low CSF β-amyloid levels in some cases[6] and the association of cognitive decline with the *APOE* ε4 genotype reported here.

Ethical and Regulatory Aspects

This study was conducted in accordance with the Declaration of Helsinki and the current European Data Protection

Key Words: Parkinson's disease; apolipoprotein E; cognitive decline; α-synuclein gene; glucocerebrosidase gene

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TABLE 1 *Demographic and clinical data of the three Athens cohort subgroups and the Tübingen PD_{GBA1} cohort*

	Idiopathic PD$_{_no\ \varepsilon4}$ n = 44	**Idiopathic PD$_{_at\ least\ one\ \varepsilon4}$ n = 6**	**p.A53T *SNCA*$_{\_no\ \varepsilon4}$ n = 29**	***p.A53T SNCA*$_{\_at\ least\ one\ \varepsilon4}$ *n = 6***	**Athens *GBA1*$_{\_no\ \varepsilon4}$ n = 49**	**Athens *GBA1*$_{\_at\ least\ one\ \varepsilon4}$ n = 10**	***P*-value**
Male sex, % (n)	66 (29)	33 (2)	45 (13)	50 (3)	53 (26)	60 (6)	
Age, years	66.3 ± 1.3	64.7 ± 3.3	50.8 ± 2.1	57 ± 3.3	59.7 ± 1.8	56.6 ± 2.5	
Age at onset, years	59.2 ± 1.5	59.3 ± 3.6	44.7 ± 2.2	50 ± 3.2	51.1 ± 1.6	50 ± 2.9	
Disease duration	7.4 ± 0.9	5.3 ± 0.9	6.1 ± 0.8	7 ± 1.9	8.9 ± 0.8	6.6 ± 1.6	
Education	12.8 ± 0.6	12.6 ± 2.2	13.9 ± 0.8	8.6 ± 1.2	10.9 ± 0.7	13 ± 1.3	
MoCA score	24.7 ± 0.6[b]	22.1 ± 1.9[b]	24.4 ± 1[c]	16.1 ± 3[c]	23.1 ± 0.9[d]	23.2 ± 1.8[d]	0.044[b] 0.039[c] 0.729[d]
Cognitive decline: MoCA cut-off <26/30	22/44 below cut-off[b]	4/6 below cut-off[b]	13/29 below cut-off[c]	6/6 below cut-off[c]	28/49 below cut-off[d]	5/10 below cut-off[d]	0.443[b] 0.014[c] 0.678[d]
	Tübingen *GBA1*$_{risk\_no\ \varepsilon4}$ n = 133	**Tübingen *GBA1*$_{risk\_at\ least\ one\ \varepsilon4}$ n = 37**	**Tübingen *GBA1*$_{mild\_no\ \varepsilon4}$ n = 36**	**Tübingen *GBA1*$_{mild\_at\ least\ one\ \varepsilon4}$ n = 16**	**Tübingen *GBA1*$_{severe\_no\ \varepsilon4}$ n = 51**	**Tübingen *GBA1*$_{severe\_at\ least\ one\ \varepsilon4}$ n = 19**	***P*-value**
Male sex, % (n)	63 (84)	57 (21)	58 (21)	69 (11)	51 (26)	47 (9)	
Age, years	65 ± 10	65 ± 9	65 ± 12	63 ± 11	59 ± 10[e,f]	59 ± 11[e,f]	
Age at onset, years	59 ± 11	61 ± 9	59 ± 11	57 ± 13	53 ± 10[c,e,f]	54 ± 11[f]	
Disease duration	6 ± 5[f]	4 ± 3	6 ± 5	6 ± 5	6 ± 5[f]	5 ± 4	
MoCA score	24 ± 5	24 ± 5	25 ± 5	24 ± 6	25 ± 5	24 ± 5	0.965/0.585[a]
	n = 27	**n = 8**	**n = 7**	**n = 6**	**n = 15**	**n = 4**	
$Abeta_{1-42}$ [pg/mL]	706 ± 283	587 ± 150	706 ± 206	693 ± 266	704 ± 277	567 ± 282	0.814/0.505[a]
t-Tau [pg/mL]	275 ± 204	221 ± 31	263 ± 129	201 ± 63	200 ± 92	174 ± 93	0.548/0.829[a]
p181-Tau [pg/mL]	39 ± 11[g]	36 ± 6[g]	52 ± 27	36 ± 8	38 ± 19[g]	23 ± 1[g]	0.110/0.161[a]
NFL [pg/mL]	804 ± 422	806 ± 474	1106 ± 565	1388 ± 1352	909 ± 788	462 ± 187	0.347/0.291[a]
α-synuclein [pg/mL]	604 ± 239	602 ± 185	668 ± 339	367 ± 116	537 ± 348	536 ± 168	0.422/0.546[a]

Abbreviations: PD, Parkinson's disease, SNCA, α-synuclein gene; GBA1, glucocerebrosidase gene; MoCA, Montreal Cognitive Assessment test; Abeta, β-amyloid; t-Tau, total tau protein; p181-Tau, phosphorylated Tau protein; NFL, neurofilament low molecular weight.

[a]ANCOVA with age and age at onset as covariables.

[b]Idiopathic PD comparisons.

[c]*p.A53T SNCA* comparisons.

[d]Athens *GBA1* PD comparisons.

[e]Compared to $GBA1_{risk\_no\ \varepsilon4}$.

[f]Compared to $GBA1_{risk\_at\ least\ one\ \varepsilon4}$.

[g]Compared to $GBA1_{mild\_no\ \varepsilon4}$ with posthoc LSD test.

Regulation. Written informed consent was obtained from all participants. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors take full responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability Statement

The data supporting the findings of this study are available upon reasonable request from any qualified investigator.

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References

1. Tsuang D et al. APOE ε4 increases risk for dementia in pure synucleinopathies. JAMA Neurol 2013;70:223–228.
2. Koros C, Stefanis L, Scarmeas N. Parkinsonism and dementia. J Neurol Sci 2022;433:120015.
3. Tunold JA et al. APOE and MAPT are associated with dementia in neuropathologically confirmed Parkinson's disease. Front Neurol 2021;12:631145.
4. Zhao N et al. APOE4 exacerbates α-synuclein pathology and related toxicity independent of amyloid. Sci Transl Med 2020;12:eaay1809.
5. Dickson DW et al. APOE epsilon4 is associated with severity of Lewy body pathology independent of Alzheimer pathology. Neurology 2018;91:e1182–e1195.
6. Bougea A et al. Frontotemporal dementia as the presenting phenotype of p.A53T mutation carriers in the alpha-synuclein gene. Parkinsonism Relat Disord 2017;352:82–87.
7. Brockmann K et al. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov Disord 2015;30:407–411.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.