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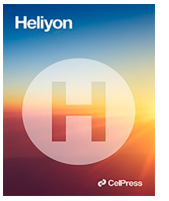

Research article

Genetic variability of incretin receptors affects the occurrence of neurodegenerative diseases and their characteristics

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ABSTRACT

Background: Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative diseases. Their treatment options are rather limited, and no neuroprotective or disease-modifying treatments are available. Anti-diabetic drugs, such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) agonists, have been suggested as a potential therapeutic option.

Aims: Assess *GLP1R* and *GIPR* genetic variability in relation to AD- and PD-related phenotypes.

Methods: AD, PD patients and healthy control subjects were included in the study. Cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease were measured in AD patients, while cognitive impairment was evaluated in PD. All participants were genotyped for three SNPs: *GLP1R* rs10305420, *GLP1R* rs6923761 and *GIPR* rs1800437.

Results: *GLP1R* rs10305420 genotypes were associated with increased odds for AD and PD development. *GLP1R* rs10305420 and *GLP1R* rs6923761 genotypes were significantly associated with $A\beta_{42/40}$ ratio ($p = 0.041$ and $p = 0.050$), while *GLP1R* rs6923761 was also associated with p-tau levels ($p = 0.022$). Finally, *GIPR* rs1800437 heterozygotes as well as carriers of at least one *GIPR* rs1800437 C allele presented with increased odds for the development of dementia in PD (OR = 1.92; 95 % CI = 1.05–3.51; $p = 0.034$ and OR = 1.95; 95 % CI = 1.08–3.52; $p = 0.027$, respectively).

Conclusion: *GLP1R* and *GIPR* genetic variability may affect the occurrence of AD and PD and is also associated with AD CSF biomarkers for Alzheimer's disease and dementia in PD. The data on *GLP1R* and *GIPR* genetic variability may support the function of incretin receptors in neurodegeneration.

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1. Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) stand out as the two most common neurodegenerative diseases. AD is primarily recognized as the leading cause of dementia [1], whereas PD initially displays motor signs and symptoms, such as bradykinesia, resting tremor and muscular rigidity [2]. PD patients develop also various non-motor symptoms, among which cognitive impairment and dementia are very common. There is no disease-modifying or neuroprotective treatment available for these diseases [3]. AD and PD share several risk factors, including older age, high blood pressure, head injury, elevated blood cholesterol levels, and also pre-existing type 2 diabetes [1–4].

Desensitization of the insulin signalling has been detected in the brain of both AD and PD patients, sometimes even without diabetes diagnosis [3–5]. Insulin desensitization is most likely driven by the chronic neuroinflammation in individuals with AD and PD [4,6]. Two important incretin hormones are affecting insulin secretion, namely glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Endogenous GLP-1 is primarily produced in the intestinal enteroendocrine L-cells in response to the meal intake. Its binding to the glucagon-like peptide 1 receptor (GLP-1R) on the pancreatic islet β-cells leads to enhanced glucose-stimulated insulin secretion [7]. Moreover, in the upper enteroendocrine K-cells, the synthesis and maturation of GIP, the GLP-1 synergistic hormone GIP is initiated [3]. Both GLP-1 and GIP contribute to the transmission of insulin-signalling in the central nervous system. Blood-borne GLP-1 activates the GLP-1R on hepatic branch of vagal sensory neurons glucose sensor, guiding further communication with brainstem neurons and extending GLP-1 effect to multiple brain regions [8]. Concomitantly, GLP-1R is broadly expressed in the brain tissue by various types of cells, such as neurons, astrocytes, and microglia [3]. GLP-1 influences various neuronal processes, including neurogenesis and neurodegeneration [8]. Similarly, GIP and GIP receptors (GIPR) are widely distributed in the brain tissue, but unlike GLP-1 and GLP-1R, they are not expressed on the glial cells [3].

Normalizing the insulin signalling was proposed as a viable strategy to treat AD and PD, as anti-diabetic drugs could have a potentially protective effect against neurodegeneration. Indeed, anti-neurodegenerative or neuroprotective potential was reported in some of the novel anti-diabetic drugs, such as incretin analogues, GLP-1 and GIP agonists in particular [9,10]. The GLP-1 and GIP analogues do not activate the insulin receptors and thus do not affect insulin desensitization. However, they do resensitize insulin signalling without influencing glucose levels in normoglycemic people, making them suitable for AD and PD patients without diabetes. Importantly, these analogues also cross the blood brain barrier, reducing the need for special dosage forms [4]. GLP-1 mimetics, GIP analogues and dual GLP-1/GIP receptor agonists have all shown to be neuroprotective in AD and PD animal models [4]. Recent findings highlight the protective effect of GLP-1 receptor agonists and mimetics on the pathological accumulation of amyloid β (Aβ) and tau phosphorylation, two key pathological events in AD [3]. GLP-1 agonists exendin-4 and liraglutide have been tested in clinical trials in PD and AD patients, respectively. Treatment with exendin-4 led to a mild improvement in motor symptoms measured by the MDS-UPDRS III of PD patients [11], while liraglutide maintained neuronal activity and the decrease of glucose metabolism in the AD brain [12]. Studies in *in vivo* animal models indicated superior effects of dual GLP-1/GIP receptor agonists compared to individual GLP-1 and GIP agonists, emphasizing the synergistic action of incretins [4].

Incretin receptors *GLP1R* and *GIPR* are encoded by polymorphic genes *GLP1R* and *GIPR*. The genetic variability within these genes may influence patients' response to the above-mentioned drugs. Several functional non-synonymous single nucleotide polymorphisms (SNPs), such as *GLP1R* rs10305420, *GLP1R* rs6923761, and *GIPR* rs1800437, have been linked to diverse pathologies, primarily to metabolic disorders such as type 2 diabetes [13–15], polycystic ovary syndrome [16], obesity [17–21], but also psychiatric diseases [22–25]. Additionally, genetic variability in *GLP1R* was previously associated with decreased AD risk [26]. Conversely, another polymorphism in *GLP1R* (rs3765467) was associated with increased PD risk, while no such associations were observed for *GLP1R* rs6923761 [27].

This study aimed to investigate whether common functional *GLP1R* and *GIPR* SNPs influence the occurrence of AD and PD. We also aimed to assess the associations of these SNPs with the CSF biochemical markers of AD and with the risk to develop dementia in PD patients.

2. Materials and methods

2.1. Participants and clinical data

The first study group included patients, diagnosed with AD at the Department of Neurology, University Medical Centre Ljubljana, Slovenia, between June 2019 and March 2022. All patients were invited to participate in the study at their clinical evaluation and lumbar puncture appointment.

The inclusion criteria were age above 55 years and confirmed diagnosis of AD dementia, established through a consensus meeting with clinicians and neuropsychologists as previously described [28–31]. We excluded patients with non-AD-related cognitive impairment. Demographic and clinical data were obtained through structured interviews with patients and their caregivers or from medical records. Cognitive screening utilized the Mini-Mental State Examination (MMSE) [32]. A thorough diagnostic evaluation included structural brain imaging, blood tests, neuropsychological assessment, and cerebrospinal fluid (CSF) analysis for Alzheimer's disease biomarkers. CSF collection and preanalytical processing followed standardized protocols [33]. CSF biomarkers of AD: $A\beta_{42}$, $A\beta_{42/40}$, p-tau_{181} and total-tau were measured using Innotest (Fujirebio)® immunoassays as previously described [28].

The second study group consisted of PD patients recruited from the Department of Neurology, University Medical Centre Ljubljana, Slovenia, between October 2016 and April 2018, as part of a retrospective pharmacogenetics study of dopaminergic treatment. Inclusion criteria are listed elsewhere [30,31]. Demographic and clinical data were obtained through structured interviews with patients

and their caregivers or from medical records. Presence of dementia in PD patients was determined based on the prescription of anti-dementia medication.

The third group was the control group and included Slovenian subjects recruited within the PREPARE clinical study of the Ubiquitous Pharmacogenomics project, between May 2017 and June 2020 [34]. Only individuals above 65 with no signs or symptoms of neurological disorders were included.

The study protocols received approval from the Slovenian Ethics Committee for Research in Medicine (0120–523/2017-4; KME 42/05/16; KME 44/12/16). All subjects gave written informed consent in accordance with the Declaration of Helsinki and agreed to the use of their DNA samples and clinical data for future pharmacogenomic studies.

2.2. Single nucleotide polymorphism selection

Common SNPs were selected for the analysis based on their functionality and previously proved effects on relevant pathological phenotypes. Among the three selected SNPs, two were in *GLP1R* (rs10305420 and rs6923761) and one in *GIPR* (rs1800437). All SNPs are located in the coding region, are non-synonymous or affect splicing according to the SNP function prediction tool [35] and have a minor allele frequency (MAF) above 20 %. Further details on the genetic variants investigated in this study are presented in Table 1.

2.3. DNA isolation and genotyping

For DNA extraction, peripheral blood samples from all participants were collected during our previous studies [28–31]. Genomic DNA was isolated using the FlexiGene DNA Kit (Qiagen, Hilden, Germany) or E.Z.N.A.® SQ Blood DNA Kit II (Omega Bio-tek, Inc., Norcross, GA, USA). All the SNPs were genotyped with the respective KASP assays (KBiosciences, Herts, UK and LGC Genomics, UK) according to manufacturer's instructions. None of the genotype distributions deviated from the Hardy–Weinberg equilibrium in control group (pHWE values were 0.057, 0.655 and 0.542, for rs10305420, rs6923761 and rs1800437, respectively). As a quality control, 10 % of the samples were genotyped in duplicate. All the results were consistent.

2.4. Statistical analysis

The central tendency and variability of continuous variables were summarized using the median and the interquartile range (25th to 75th percentile), while categorical variables were described using frequencies. In the control cohort, the chi-squared test was used for the assessment of agreement of genotype frequencies with Hardy-Weinberg equilibrium. We used both dominant and additive genetic models in the analyses.

To evaluate the associations of selected SNPs and clinical data with the risk for AD or PD and with the occurrence of dementia in PD patients (categorical variables), we used binary univariable logistic regression and calculated odds ratios (ORs) and 95 % confidence intervals (95%CIs). Adjustments for age and sex were performed in multivariable logistic regression analyses. The effects of genotypes on biochemical parameters in AD patients (continuous variables) were evaluated using the nonparametric Mann-Whitney *U* test and Kruskal-Wallis test, as the variables were not normally distributed according to Shapiro-Wilk normality test.

A significance threshold of 0.050 was set for p-values. All statistical tests were two-sided. For all statistical analyses, IBM SPSS Statistics, version 27.0 (IBM Corporation, Armonk, NY, USA) was used.

Table 1
Clinical characteristics of Alzheimer's disease patients.

Characteristic	Category/Unit	Cut-off value	AD patients (N = 62)
Sex	Male, N (%)		27 (43.5)
	Female, N (%)		35 (56.5)
Age at recruitment	Years, median (25–75 %)		77 (74–81)
Education	Years, median (25–75 %)		11 (8–12) [1]
Height	cm, median (25–75 %)		168 (160–172) [8]
Weight	kg, median (25–75 %)		63 (55–77) [7]
BMI	kg/m^2, median (25–75 %)		24.5 (21–27) [9]
Diabetes	No (%)		50 (80.6)
	Yes (%)		11 (17.7) [1]
MMSE[a]	Score, median (25–75 %)		20 (15–24) [12]
$A\beta_{42}$	pg/mL, median (25–75 %)	>570 pg/mL	688 (538.5–772) [1]
$A\beta_{42/40}$ ratio	Median (25–75 %)	>0.07	0.06 (0.04–0.06) [3]
Total tau	pg/mL, median (25–75 %)	<400 pg/mL	778 (573.5–991) [1]
p-tau_{181}	pg/mL, median (25–75 %)	<60 pg/mL	98 (82.5–128) [1]

BMI: body mass index; MMSE: The Mini-Mental State Examination.
Numbers of missing data of each characteristic is presented in [] brackets.
[a] MMSE score bellow 24 is considered indicative of dementia.

3. Results

3.1. Alzheimer's disease and Parkinson's disease patients' characteristics

Among 62 AD patients, there were 27 male and 35 female. The median age at enrolment was 77 (74–81) years. 11 (17.7 %) AD patients had diabetes. AD patients had decreased $A\beta_{42}$ and $A\beta_{42/40}$ ratio and increased total and p-tau according to locally validated biomarker cut-off levels (Table 1), consistent with AD biomarker profile. Their median MMSE score was 20 (15–24). The characteristics of AD patients are presented in Table 1.

Among the 229 PD patients, there were 131 males and 98 females. Patients' median age at enrolment was 72.2 (65.7–78.0) years. 15 (6.6 %) PD patients had diabetes. Other relevant clinical characteristics of PD patients are presented in Table 2.

The control group included 21 males and 41 females with a median age of 69 years (66.5–73.0). None of the subjects had any neurological disorders, however 9 (14.5 %) had diabetes.

3.2. Association of genetic variants with the occurrence of Alzheimer's and Parkinson's disease

GLP1R rs10305420 was significantly associated with AD risk (Table 3). Heterozygotes had increased risk for AD development (OR = 3.23; 95 % CI = 1.47–7.08; p = 0.003). Additionally, carriers of at least one T allele also had increased risk for AD development under the dominant model (OR = 2.89; 95 % CI = 1.39–6.00; p = 0.004). After adjustment for sex and age, the associations remained significant both for heterozygotes (OR = 3.48; 95 % CI = 1.37–8.82; p = 0.009) and for carriers of at least one T allele (OR = 3.25; 95 % CI = 1.36–7.79; p = 0.008).

GLP1R rs10305420 was also significantly associated with the increased risk for PD in heterozygotes (OR = 2.61; 95 % CI = 1.39–4.89; p = 0.003). Carriers of at least one T allele also had increased risk for PD under the dominant model (OR = 2.44; 95 % CI = 1.38–4.34; p = 0.002). After adjustment for sex and age (age at diagnosis for PD patients), both associations remained significant. Heterozygotes still showed increased risk for development of PD (OR = 3.60; 95 % CI = 1.79–7.23; p < 0.001), while carriers of at least one T allele still presented with increased risk for PD development as well (OR = 3.31; 95 % CI = 1.75–6.26; p < 0.001).

Other *GLP1R* and *GIPR* polymorphisms showed no association with either AD or PD risk (Table 3).

3.3. Association of GLP1R and GIPR variants with biochemical parameters of Alzheimer's disease

In the AD group, we assessed the associations between *GLP1R* and *GIPR* polymorphisms and CSF biomarker levels. Both *GLP1R* polymorphisms were associated with higher $A\beta_{42/40}$ ratio (Table 4). Carriers of at least one polymorphic rs10305420 T allele were more likely to have higher $A\beta_{42/40}$ ratio (p = 0.041). Similarly, carriers of at least one polymorphic rs6923761 A allele (p = 0.050) tended to have higher $A\beta_{42/40}$ ratio. Furthermore, carriers of at least one polymorphic A allele in *GLP1R* rs6923761 had lower p-tau than non-carriers (p = 0.022). No associations with biomarker levels were observed for *GIPR* rs1800437.

3.4. Association of GLP1R and GIPR variants with Parkinson's disease dementia

We assessed whether the tested *GLP1R* or *GIPR* genetic variants influence the risk for dementia in PD patients. *GIPR* rs1800437 heterozygotes had increased odds for cognitive decline (OR = 2.06; 95 % CI = 1.16–3.67; p = 0.014), which remained significant even after adjustment for significant clinical parameters (Table 2), namely age at diagnosis and taking dopamine receptor agonists (OR = 1.92; 95 % CI = 1.05–3.51; p = 0.034). Furthermore, carriers of at least one C allele were more likely to develop dementia (OR = 2.07; 95 % CI = 1.18–3.65; p = 0.012), which also remained significant after adjustment for the clinical parameters (OR = 1.95; 95 % CI = 1.08–3.52; p = 0.027). *GLP1R* SNP showed no associations with PD related dementia (Table 5).

Table 2
Clinical characteristics of Parkinson's disease patients.

Characteristic		All patients (N = 229)
Sex	Male (%)	131 (57.2)
	Female (%)	98 (42.8)
Ever being treated with DAs [4]	No (%)	57 (25.3)
	Yes (%)	168 (74.7)
Dementia	No (%)	157 (68.6)
	Yes (%)	72 (31.4)
Diabetes	No (%)	214 (93.4)
	Yes (%)	15 (6.6)
Age at recruitment	Median (25%–75 %), years	72.2 (65.7–78.0)
Age at diagnosis	Median (25%–75 %), years	62.0 (54.8–71.2)

DAs: Dopamine receptor agonists.
This cohort of PD patients was already presented in Ref. [28].
Numbers of missing data of each characteristic is presented in [] brackets.

Table 3
Association of genetic variants with the occurrence of Alzheimer's and Parkinson's disease.

SNP	Genotype	OR (95 % CI)	p value	OR_{adj} (95 % CI)[a]	p_{adj} value[a]	OR (95 % CI)	p value	OR_{adj} (95 % CI)[a]	p_{adj} value[a]
Alzheimer's disease						Parkinson's disease			
***GLP1R* rs10305420**	**CC**	Ref.		Ref.		Ref.		Ref.	
	TC	**3.23 (1.47–7.08)**	**0.003**	**3.48 (1.37–8.82)**	**0.009**	**2.61 (1.39–4.89)**	**0.003**	**3.60 (1.79–7.23)**	**<0.001**
	TT	2.01 (0.64–6.30)	0.232	2.60 (0.66–10.17)	0.171	2.03 (0.82–5.00)	0.124	2.61 (0.98–6.92)	0.054
	TC + TT	**2.89 (1.39–6.00)**	**0.004**	**3.25 (1.36–7.79)**	**0.008**	**2.44 (1.38–4.34)**	**0.002**	**3.31 (1.75–6.26**	**<0.001**
***GLP1R* rs6923761**	**GG**	Ref.		Ref.		Ref.		Ref.	
	GA	0.97 (0.46–2.05)	0.930	1.37 (0.56–3.37)	0.493	0.87 (0.49–1.57)	0.650	0.81 (0.43–1.52)	0.506
	AA	1.39 (0.42–4.54)	0.591	2.89 (0.69–12.01)	0.145	0.48 (0.17–1.40)	0.180	0.51 (0.16–1.62)	0.256
	GA + AA	1.04 (0.51–2.12)	0.917	1.57 (0.66–3.72)	0.304	0.81 (0.46–1.42)	0.454	0.76 (0.41–1.39)	0.370
***GIPR* rs1800437**	**GG**	Ref.		Ref.		Ref.		Ref.	
	GC	1.51 (0.72–3.19)	0.275	1.52 (0.63–3.70)	0.353	1.27 (0.70–2.33)	0.436	1.22 (0.64–2.33)	0.547
	CC	0.28 (0.03–2.64)	0.266	0.27 (0.02–3.32)	0.303	0.50 (0.14–1.80)	0.289	0.37 (0.09–1.53)	0.171
	GC + CC	1.31 (0.64–2.69)	0.464	1.30 (0.55–3.06)	0.547	1.14 (0.64–2.03)	0.649	1.07 (0.58–1.99)	0.820

Statistically significant data is presented with bold text.
[a] Adjustments made for sex and age.

4. Discussion

The main finding of our study is that *GLP1R* and *GIPR* genetic variability affects the occurrence of AD and PD and is also associated with PD dementia and CSF biomarkers of AD in AD patients. *GLP1R* rs10305420 polymorphism was associated with the development of both AD and PD. Furthermore, both investigated *GLP1R* polymorphisms were associated with CSF AD biomarker levels, thus supporting their role in AD pathology. On the other hand, *GIPR* rs1800437 was associated with the risk of developing dementia in PD.

We found a consistently increased risk for the occurrence of both AD and PD in *GLP1R* rs10305420 heterozygotes and carriers of at least one polymorphic allele. Furthermore, we report an increased risk for development of PD-related dementia in *GIPR* rs1800437 heterozygotes and carriers of at least one polymorphic allele. No studies on genetic variability of incretin receptors in relation to PD-related dementia have been published to date. However, a study conducted in a Chinese Han population reported that the *GLP1R* rs3765467 was significantly associated with PD development, whereas *GLP1R* rs6923761, which was assessed in our study, was not. We could assign this to the differences in study populations [27]. The investigated SNPs were previously mainly associated with metabolic disorders and psychiatric diseases [13–25], however studies in the neurodegeneration field are lacking. Only one study focused on genetic variation of antidiabetic drug targets and reported a lower risk for AD associated with *GLP1R* polymorphisms [26].

Both *GLP1R* rs10305420 and rs6923761 polymorphisms showed associations with higher $A\beta_{42/40}$ under the dominant model when compared to carriers of the wild type allele. Similarly, lower p-tau181 was observed in carriers of at least one *GLP1R* rs6923761 polymorphic allele under dominant model. The observed potentially protective effect of *GLP1R* genetic variability on disease hallmarks is another important addition to the knowledge about the role of incretin receptor is in the course of AD. Multiple studies highlighted the neuroprotective role of GLP-1 analogues on Aβ and tau pathology in AD *in vivo* [36–39]. As it has been shown in AD mouse models, GLP-1 analogues enhance the expression of insulin degrading enzyme [40,41]. The decline of insulin degrading enzyme was also observed in AD patients and negatively correlated with the amount of $A\beta_{42}$ in brain [42]. Concurrently elevated tau phosphorylation and inactivated insulin pathway has been found in type-2 diabetes animal models (summarized in Ref. [43]), while phosphorylated insulin receptor substrate 1 co-localized with neurofibrillary tangles, composed of tau fibrils, in the brains of AD patients [44]. Although pathophysiological evidence supports the role of insulin signalling in the brain, we are among the first to show an association between AD CSF Aβ and p-tau levels and genetic variability of *GLP1R*. Elevated total and p-tau181 and reduced $A\beta_{42}$ and $A\beta_{42/40}$ levels are associated with AD. Discrepancies in associations between *GLP1R* genotypes with AD risk and *GLP1R* genotypes and AD biomarker levels are present, thus further research is needed to better understand the effect of genetic variability in incretin receptors on AD pathology. Furthermore, if CSF biomarkers of AD were measured in the control group, this could provide additional information for more thorough understanding of the observed effect. However, during this study, obtaining CSF from control group participants was not feasible.

Our study showed the association between genetic variants in incretin receptors and the occurrence, of two most common

Table 4
Association of *GLP1R* and *GIPR* polymorphisms with cerebrospinal fluid biomarkers in AD patients.

SNP	Genotype	Aβ (pg/ml)	p value	$Aβ_{42}/_{40}$ ratio	p value	Total tau (pg/ml)	p value	pTau (pg/ml)	P value
***GLP1R* rs10305420**	**CC**	711 (547.5–818)	0.350	0.04 (0.03–0.06)	0.057	802 (565–1027.5)	0.440	110 (81–144.5)	0.308
	TC	602 (513.5–764.5)		0.06 (0.05–0.07)		806 (597.5–991)		98 (87.5–124.5)	
	TT	716 (577.25–790.25)		0.06 (0.05–0.08)		642.5 (516.5–878.25)		95.5 (74.5–111.25)	
	TC + TT	653 (518.5–772)	Pdom = 0.294	0.06 (0.05–0.07)	Pdom = **0.041**	750 (562.5–968)	Pdom = 0.760	97 (85.5–123.5)	Pdom = 0.294
***GLP1R* rs6923761**	**GG**	714.5 (552.75–773.75)	0.551	0.05 (0.03–0.06)	0.129	838 (565.5–1064.75)	0.375	115.5 (83.25–146.75)	0.071
	GA	653 (514–774)		0.06 (0.05–0.07)		719 (524–969)		94 (77–123)	
	AA	616 (553.5–768.5)		0.06 (0.05–0.07)		758.5 (712.25–834.5)		97.5 (93.75–106.25)	
	GA + AA	638 (522–774)	P_{dom} = 0.307	0.06 (0.05–0.07)	P_{dom} = **0.050**	748 (559–921)	P_{dom} = 0.161	97 (79–119)	P_{dom} = **0.022**
***GIPR* rs1800437**	**GG**	753 (593.75–1071.75)	0.288	0.06 (0.04–0.08)	0.228	592 (462.5–954)	0.629	91 (70.5–127)	0.472
	GC	725 (530–1005)		0.06 (0.05–0.09)		571 (344–881)		81 (56–114)	
	GC + CC	724.5 (548.5–799.75)	P_{dom} = 0.178	0.06 (0.04–0.07)	P_{dom} = 0.581	762.5 (576.75–1055.25)	P_{dom} = 0.572	99 (87.25–133.75)	P_{dom} = 0.659

Statistically significant data is presented with bold text.

Table 5
Association of *GLP1R* and *GIPR* polymorphisms with the occurrence of PD dementia.

Gene	Genotype	OR (95 % CI)	p-value	OR_{adj} (95 % CI)[a]	p_{adj} value[a]
***GLP1R* rs10305420**	**CC**	Ref.			
	TC	1.154 (0.624–2.135)	0.648	1.064 (0.556–2.034)	0.852
	TT	1.394 (0.597–3.257)	0.443	1.360 (0.559–3.317)	0.497
	TC + TT	1.207 (0.674–2.160)	0.526	1.128 (0.611–2.083)	0.700
***GLP1R* rs6923761**	**GG**	Ref.			
	GA	0.630 (0.353–1.123)	0.117	0.667 (0.364–1.221)	0.189
	AA	0.577 (0.148–2.254)	0.429	0.504 (0.122–2.088)	0.345
	GA + AA	0.624 (0.356–1.096)	0.101	0.648 (0.360–1.166)	0.148
***GIPR* rs1800437**	**GG**	Ref.			
	GC	**2.058 (1.155–3.669)**	**0.014**	**1.922 (1.052–3.513)**	**0.034**
	CC	2.273 (0.483–10.684)	0.299	2.297 (0.459–11.490)	0.312
	GC + CC	**2.073 (1.177–3.653)**	**0.012**	**1.947 (1.079–3.516)**	**0.027**

Statistically significant data is presented with bold text.
[a] Adjustments made for age at diagnosis and DAs.

neurodegenerative diseases, AD and PD. Although not fully consistent, our findings further support the importance of incretin receptors in AD and PD. Assessment of selected polymorphisms in a bigger cohort of AD patients could provide better insight into development of the disease. Furthermore, lumbar puncture with CSF analysis was not performed in PD patients and control group participants but could provide more thorough understanding of observed effects. Considering the beneficial effect of GLP-1 agonists on the motor function in PD [10] and protective effect on brain metabolism in AD [45], their use in both diseases might be considered in clinical practice. Thus, it would be important to further understand the role of genetic variability of incretin receptors in response to incretin analogues. Also, assessing the genetic variability of *GIP* and *GCG*, gene encoding for GLP-1, could be beneficial. Although rare and not fully elucidated, their effect could contribute to the more thorough evaluation of the effect of incretin hormones on development of neurodegenerative diseases. With the knowledge about the pharmacodynamics of GLP-1 agonists in relation to genetic parameters the treatment could be tailored to the individual patient's needs.

We are aware of few limitations of this study. In comparison to PD group, AD group is relatively small. The size difference was due to different recruitment strategy in both syndromes, as AD patients were included prospectively. However, this did not create a bias as the genotype frequencies of all of the investigated polymorphisms are comparable between both diseases. Considering inclusion criteria, selection of subjects for the control group was not completely random, as patients with different comorbidities were included. A larger and more homogenous control group could be beneficial in potential further analysis.

5. Conclusions

Our study revealed significant associations between common functional polymorphisms in incretin receptor genes *GLP1R* and *GIPR* in AD and PD. The effect on the occurrence of dementia in PD patients and CSF AD biomarker levels was also observed. To confirm the clinical relevance of the outcomes, a study on a bigger cohort should be performed. However, we believe that our findings support the importance of *GLP1R* and *GIPR* in neurodegeneration and could foster further research in the area of impaired insulin metabolism in neurodegenerative diseases. Furthermore, our findings also support the concept of pharmacogenetic/personalized patient management and warant further research on the potential implementation of GLP-1 agonists in AD and PD treatment.

CRediT authorship contribution statement

David Vogrinc: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Sara Redenšek Trampuž:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Tanja Blagus:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Maja Trošt:** Writing – review & editing, Resources, Methodology, Investigation. **Milica Gregorič Kramberger:** Writing – review & editing, Resources, Methodology, Investigation. **Andreja Emeršič:** Writing – review & editing, Resources, Methodology, Investigation. **Saša Čučnik:** Writing – review & editing, Resources, Methodology, Investigation. **Katja Goričar:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Vita Dolžan:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data and code availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Vita Dolzan reports financial support was provided by Javna Agencija za Raziskovalno Dejavnost republike Slovenije. Vita Dolzan reports a relationship with Javna Agencija za Raziskovalno Dejavnost RS that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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