

Interactive Association Between Intronic Polymorphism (rs10506151) of the LRRK2 Gene and Type 2 Diabetes on Neurodegenerative Diseases

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Purpose: We investigated the interactive effect of rs10506151 polymorphism of the Leucine-rich repeat kinase 2 (LRRK2) gene and type 2 diabetes (T2D) on neurodegenerative disease (ND) risk.

Materials and Methods: Data of 17, 927 participants in the Taiwan Biobank (TWB) assessed between 2008 and 2015 were linked to healthcare records in the National Health Insurance Research Database (NHIRD). The odd ratios (ORs) and 95% confidence intervals (CIs) for NDs were determined using logistic regression analysis.

Results: There were 145 cases with NDs, and 28.28% (n = 41) of these individuals had T2D. Associations of neurodegenerative disorders with LRRK2 rs10506151 variant and T2D were not significant. The corresponding ORs (95% CI) for NDs were 1.06 (0.75–1.49) in CA/AA compared to CC individuals and 0.93 (0.63–1.39) in those with T2D compared to non-diabetic participants. However, we found evidence of a significant interaction between rs10506151 and T2D (p = 0.0073). After stratification by genotypes of rs10506151, the OR for NDs was 0.37 (CI, 0.17–0.82) in CA/AA individuals with T2D and 1.41 (0.88–2.27) in their CC counterparts. When CA/AA individuals with T2D represented the reference group, the OR (95% CI) was 1.74 (0.81–3.73) in CC individuals with no T2D, 2.47 (CI, 1.14–5.38) in CA/AA individuals with no T2D, and 2.34 (CI, 1.07–5.11) in CC individuals with T2D.

Conclusion: Our data indicated that the risk of NDs was significantly lower among diabetic individuals with combined CA/AA of the LRRK2 rs10506151 variant in Taiwan.

Keywords: polymorphism, neurodegenerative disorders, diabetes, variation

Introduction

Neurodegenerative diseases (NDs) such as Parkinson's disease (PD), Alzheimer's disease (AD), and multiple sclerosis, are significant life-threatening diseases in adults.¹ They are characterized by degeneration of specific neural clusters.² Some of the factors associated with neurological diseases include proteinopathy, hypovitaminosis D, and oxidative stress,^{3,4} even though they express separate pathophysiological features.⁵

Genetic factors are essential for providing insights into the pathogenesis of NDs. Attempts have been made to investigate mutations in specific ND-related genes.⁶ The LRRK2 gene is one of the genes that contribute to neurodegeneration, especially in PD.⁷ Several mutations of this gene have been investigated as risk factors for PD, though the mechanisms remain to be investigated.^{8,9} Among them, the rs10506151 polymorphism had been associated with a dramatic increase in PD risk

among Chinese individuals who were homozygous for the minor allele (rs10506151 A) in both additive and recessive models.¹⁰ Despite this, a prior study in Norway found no evidence of an association between the variant and PD.¹¹ It is not yet known whether rs10506151 could increase the risk of NDs.

Diabetes had also been associated with a higher risk of PD and other NDs.^{12–16} However, a case-control study in Japan reported inverse associations between T2D and PD risk.¹⁷ Diabetes mellitus and neurodegenerative conditions seem to share pathophysiological mechanisms. Importantly, Zhu and colleagues previously identified LRRK2 as one of the hub genes for T2D and AD.¹⁸

While the LRRK2 rs10506151 polymorphism dramatically increased PD risk in Chinese populations, such associations have not been reported in Taiwan. Therefore, this study investigated the interactive effects of rs10506151 polymorphism and T2D on neurodegenerative disease development in Taiwan Biobank.

Materials and Methods

Study Participants and Setting

We collected basic demographic, anthropometric, lifestyle, and genetic data of participants enrolled in TWB between 2008 and 2015. The disease information was collected from the NHIRD. Data from TWB were linked to electronic healthcare records in the NHIRD at the Health and

Welfare Data Science Center (HWDC). The biobank data are not freely available due to restrictions. The Institutional Review Board on Biomedical Science Research in Academia Sinica and the Governance Council of Taiwan Biobank had approved the TWB project.¹⁹ Biobank participants had provided written informed consent before enrollment. This study was approved by the Institutional Review Board of Chung Shan Medical University (CS1-20009).

Initial recruitment included 17,985 biobank participants. After excluding persons with incomplete questionnaires (N=37) and genotyping information (N=21), the final analysis included 145 participants with NDs and 17,927 control individuals. Among participants with NDs, 41 were identified with T2D.

Disease Assessment and Covariates

From the linked datasets, we identified participants with NDs including PD (ICD-9-CM: 332.0), other degenerative diseases of the basal ganglia (ICD-9-CM: 333.0), AD (ICD-9-CM: 331.0), dementia subtypes (ICD-9-CM: 290, 331.1, 331.2, 331.7, 331.8, and 331.9), hyperlipidemia (ICD-9-CM: 272), diabetes mellitus (ICD-9-CM: 250), and hypertension (ICD-9-CM: 401–405) based on at least two outpatient visits or inpatient hospitalization.

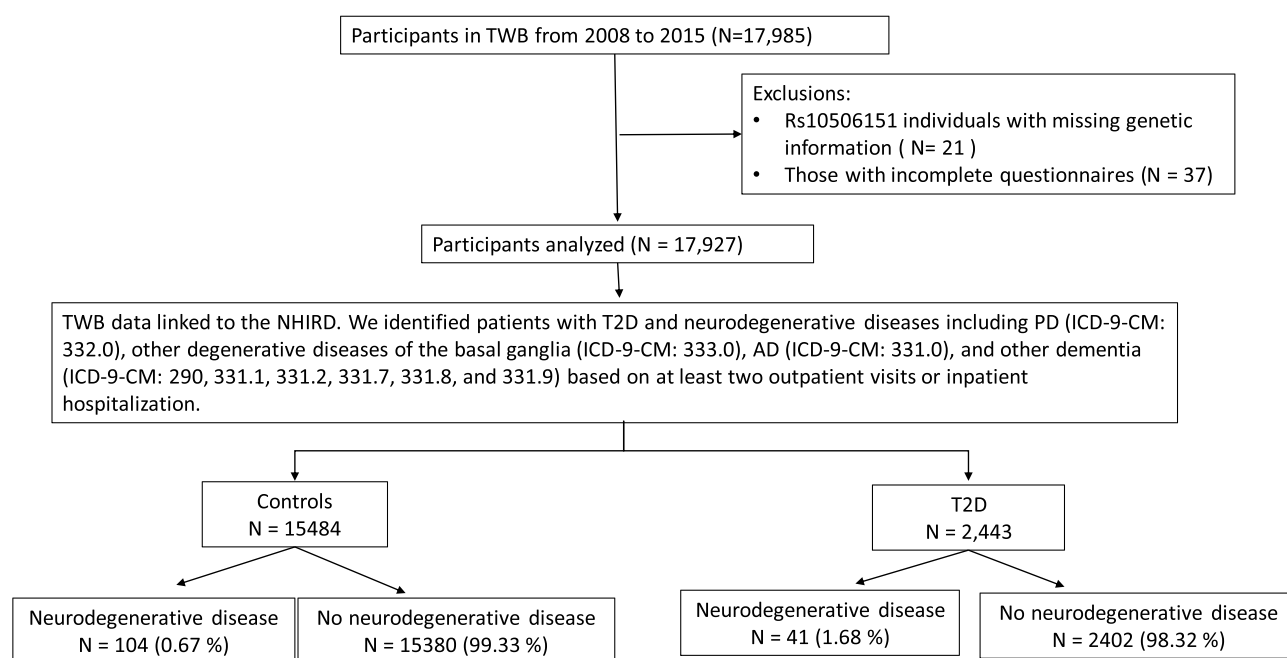


Figure I A flowchart showing study population.

Table I Demographic Characteristics of Study Participants with and without T2D

	Controls (N=15,484)		T2D (N=2443)		
	n (%)		n (%)		p-value
rs10506151 (LRRK2)					0.740
CC	9942	(64.21)	1573	(64.39)	
CA	4914	(31.74)	779	(31.89)	
AA	628	(4.06)	91	(3.72)	
Neurodegenerative disorder					<0.001
No	15,380	(99.33)	2402	(98.32)	
Yes	104	(0.67)	41	(1.68)	
Sex					0.001
Female	8064	(52.08)	1171	(47.93)	
Male	7420	(47.92)	1272	(52.07)	
Education					<0.001
Elementary School	720	(4.65)	316	(12.93)	
Junior & Senior High School	5935	(38.33)	1059	(43.35)	
University & above	8829	(57.02)	1068	(43.72)	
Smoking					<0.001
No	11,767	(75.99)	1751	(71.67)	
Yes	3717	(24.01)	692	(28.33)	
Alcohol intake					<0.001
No	13,931	(89.97)	2128	(87.11)	
Yes	1553	(10.03)	315	(12.89)	
Physical activity					<0.001
No	9421	(60.84)	1095	(44.82)	
Yes	6063	(39.16)	1348	(55.18)	
Hypertension					<0.001
No	12,693	(81.97)	1019	(41.71)	
Yes	2791	(18.03)	1424	(58.29)	
Hyperlipidemia					<0.001
No	11,930	(77.05)	576	(23.58)	
Yes	3554	(22.95)	1867	(76.42)	
Age	47.60	±10.78	56.86	±8.85	<0.001
BMI	24.09	±3.57	25.40	±3.83	<0.001

Notes: Data are presented as numbers (N) or percentage (%), or as mean ± standard deviation (SD). CC, CA, and AA represent genotypes of the rs10506151 variant.

Abbreviation: T2D, type 2 diabetes; BMI, body mass index.

Cigarette smokers were defined as people who smoked for at least six months and continued to smoke during assessment visits. Alcohol drinkers were defined as persons who reported drinking more than 150 mL of alcohol per week for at least six months and were still drinking during assessment visits. Physical activity included any exercise activity at least three times a week and lasting for at least 30 minutes each time. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Genetic Variant, Genotyping and Quality Control

In TWB, genotyping is performed on participants by the National Center for Genome Medicine in Academia Sinica. This is done using the custom Taiwan Biobank Axiom™ Genome-Wide Array Plate (Affymetrix, Santa Clara, CA, USA). In addition to the socio-demographic and lifestyle data, biological samples (including blood and urine samples) are collected from all participants during

Table 2 Odds of Having Neurodegenerative Diseases Among Study Participants

	OR	(95% CI)	p-value
Rs10506151 (ref: CC)			
CA+AA	1.06	(0.75–1.49)	0.747
T2D (ref: No)			
Yes	0.93	(0.63–1.39)	0.732
Sex (ref: Female)			
Male	1.04	(0.69–1.56)	0.867
Age	1.10	(1.08–1.13)	<0.001
Education (ref: Elementary School)			
Junior and Senior High School	0.50	(0.32–0.78)	0.002
University above	0.49	(0.31–0.79)	0.004
Smoking (ref: No)			
Yes	1.08	(0.68–1.71)	0.752
Alcohol intake (ref: No)			
Yes	0.93	(0.52–1.66)	0.803
Physical activity (ref: No)			
Yes	0.69	(0.49–0.97)	0.032
BMI	0.96	(0.91–1.01)	0.141
Hypertension (ref: No)			
Yes	1.68	(1.14–2.46)	0.008
Hyperlipidemia (ref: No)			
Yes	1.48	(1.01–2.17)	0.046

Note: CC, CA, and AA represent genotypes of the rs10506151 variant.

Abbreviations: OR, odds ratio; CI, 95% confidence interval; T2D, type 2 diabetes.

assessment visits for different assays. Details of the genotyping procedures have been described elsewhere.¹⁹ In this study, we chose the LRRK2 rs10506151 variant based on its previous associations with neurodegenerative diseases. This variant passed the quality control test: call rate (>95%), Hardy-Weinberg equilibrium test ($p > 1.0 \times 10^{-3}$), and minor allele frequency (>0.05).

Statistical Analysis

Our study outcome was NDs, while rs10506151 and T2D were the exposure variables. We performed descriptive analysis for these variables and covariates based on the presence or absence of T2D. The inclusion and exclusion

of study participants are shown in Figure 1. We used the *t*-test and Chi-square test for the continuous and categorical variables. We then used logistic regression analysis to determine the ORs and 95% CIs for the relationship between diabetes, LRRK2 (rs10506151), and NDs. We also tested for the presence of an interaction between the variant and T2D, followed by stratified analyses based on these variables. Our statistical tools included the statistical analysis system (SAS) 9.4 software (SAS Institute, Cary, NC, USA) and PLINK 1.09 beta.

Results

Table 1 shows a summary of the demographic characteristics of participants classified by T2D status. The mean age (SD, standard deviation) was 56.86 (8.85) in those with T2D and 47.60 (10.78) in control participants. There were 2443 participants with T2D and 145 with neurodegenerative diseases. Logistic regression analyses showed that the rs10506151 variant and T2D were not independently associated with NDs (Table 2). The OR (95% CI) for NDs was 1.06 (0.75–1.49) in CA/AA compared to CC individuals, and 0.93 (95% CI, 0.63–1.39) in those with T2D (using those with no T2D as reference). Associations with NDs were also seen for age, educational level, hyperlipidemia, and hypertension.

When we used a multivariate model with the interaction term (T2D X rs10506151), the effect was significant ($p=0.0073$). When stratified by genotypes (Table 3), the OR (95% CI) was 0.37 (0.17–0.82) in CA/AA individuals who had T2D and 1.41 (0.88–2.27) in their CC counterparts. Compared with the CC genotype (Table 4), CA/AA individuals with and without T2D had ORs (95% CI) of 0.42 (0.19–0.93) and 1.42 (0.96–2.11), respectively. When we used CA/AA and T2D as the reference group (Table 5), the OR (95% CI) was 1.74 (0.81–3.73) for CC and no T2D, 2.47 (1.14–5.38) for CA/AA and no T2D, and 2.34 (1.07–5.11) for CC and T2D.

Discussion

As far as we are aware, this is the first work to study the interactive effect of the intronic polymorphism (rs10506151) of the LRRK2 gene and T2D on NDs using large datasets (TWB and the NHIRD). Results indicated that the risk of NDs was significantly lower among individuals having both diabetes and CA/AA genotype in Taiwan. This work provides new insights even though more analyses are needed to better understand the impact of these findings.

Table 3 Odds Ratios for Having Neurodegenerative Diseases Based on Genotypes of rs10506151

	rs10506151 (CC)			rs10506151 (CA+AA)		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
T2D (ref: No)						
Yes	1.41	(0.88–2.27)	0.158	0.37	(0.17–0.82)	0.015
Sex (ref: Female)						
Male	1.03	(0.61–1.75)	0.900	1.00	(0.52–1.91)	0.996
Age	1.12	(1.08–1.15)	<0.001	1.09	(1.05–1.13)	<0.001
Education (ref: Elementary School)						
Junior & Senior High School	0.45	(0.26–0.79)	0.005	0.66	(0.30–1.44)	0.295
University & above	0.45	(0.25–0.80)	0.006	0.64	(0.27–1.47)	0.290
Smoking (ref: No)						
Yes	1.44	(0.82–2.52)	0.208	0.57	(0.25–1.33)	0.196
Alcohol intake (ref: No)						
Yes	0.73	(0.34–1.60)	0.433	1.50	(0.62–3.66)	0.368
Physical activity (ref: No)						
Yes	0.60	(0.39–0.92)	0.019	0.82	(0.46–1.47)	0.504
BMI	0.94	(0.87–1.00)	0.057	1.01	(0.93–1.10)	0.812
Hypertension (ref: No)						
Yes	1.42	(0.88–2.30)	0.148	2.28	(1.21–4.29)	0.011
Hyperlipidemia (ref: No)						
Yes	1.40	(0.86–2.29)	0.174	1.57	(0.85–2.90)	0.153

Note: CC, CA, and AA represent genotypes of the rs10506151 variant.

Abbreviations: OR, odds ratio; CI, 95% confidence interval; T2D, type 2 diabetes.

As noted earlier, a published study on LRRK2 found no association between rs10506151 and PD among Norwegians.¹¹ On the contrary, a significant relationship was observed between PD and this variant in Chinese populations.¹⁰ Both studies differ from the current research in that 1) they focused mainly on PD, whereas we assessed other forms of NDs. 2) We considered diabetes status and confounders, but they did not, and 3) their sample size was relatively smaller.

In our study, the rs10506151 variant was not significantly related to NDs (OR 1.06 (95% CI 0.75–1.49). These results seem to align with those reported by Toft and colleagues.¹¹ However, when we added the interaction terms (rs10506151 and T2D) in our model, we found that the interaction effect was significant. That is to say, the relationship between NDs and T2D was influenced by

the rs10506151 variant. Only those with combined CA/AA genotype who had T2D had the lowest risk of developing NDs.

In an attempt to localize susceptibility genes for alterations in the brain structure associated with stroke and dementia risk, Turner and colleagues²⁰ found that the MRI measures of structural brain injury were heritable in non-Hispanic black and white sibships ascertained through hypertensive sibling pairs. They concluded that the susceptibility loci for brain atrophy, ventricular volume, and leukoaraiosis identified by linkage analyses differed among MRI measures and between races. In Framingham,²¹ investigators noted that the SNP rs10506151 was associated with frontal and temporal brain volumes. That implies this SNP might be related to NDs.

Table 4 Odds Ratios for Neurodegenerative Diseases in Patients with and without T2D

	No T2D			T2D		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
Rs10506151 (ref: CC)						
CA+AA	1.42	(0.96–2.11)	0.080	0.42	(0.19–0.93)	0.033
Sex (ref: Female)						
Male	0.92	(0.57–1.48)	0.723	1.46	(0.66–3.25)	0.351
Age	1.09	(1.06–1.12)	<0.001	1.17	(1.09–1.25)	<0.001
Education (ref: Elementary School)						
Junior & Senior High School	0.45	(0.26–0.77)	0.004	0.70	(0.31–1.55)	0.377
University & above	0.48	(0.27–0.85)	0.012	0.47	(0.19–1.13)	0.093
Smoking (ref: No)						
Yes	0.98	(0.56–1.72)	0.954	1.33	(0.58–3.05)	0.496
Alcohol intake (ref: No)						
Yes	1.16	(0.60–2.26)	0.656	0.52	(0.15–1.82)	0.307
Physical activity (ref: No)						
Yes	0.69	(0.46–1.04)	0.073	0.62	(0.32–1.20)	0.155
BMI	0.97	(0.91–1.04)	0.359	0.95	(0.86–1.05)	0.309
Hypertension (ref: No)						
Yes	1.88	(1.20–2.94)	0.006	1.19	(0.58–2.43)	0.641
Hyperlipidemia (ref: No)						
Yes	1.73	(1.13–2.64)	0.012	0.73	(0.34–1.58)	0.429

Note: CC, CA, and AA represent genotypes of the rs10506151 variant.

Abbreviations: OR, odds ratio; CI, 95% confidence interval; T2D, type 2 diabetes.

Associations between T2D and the risk of NDs are yet to be clarified.^{22,23} Prior studies reported associations between diabetes and NDs including but not limited to PD.^{12–16} However, a case-control study in Japan found that T2D was inversely related to PD risk.¹⁷ In this study, we found that the odds ratio for having NDs was not significant among individuals with T2D.

Certain NDs seem to be influenced by metformin.²⁴ A population-based study in Taiwan showed that metformin was linked to a higher risk for PD in patients with T2D.²² In another observational study, sulfonylurea was associated with a higher risk of PD in Taiwanese patients with T2D.²³ Nevertheless, the risk appeared much reduced when combination therapy with metformin was applied. In the current study, we attempted to analyze the effect of

metformin use (using ‘no metformin use’ as reference) in those with T2D. We found that the OR for having NDs in metformin users was 1.05 (95% CI 0.55–2.02) as shown in [Supplementary Table 1](#). In Orkaby’s study,²⁵ metformin was associated with a lower risk of subsequent dementia in veterans below the age of 75. Other studies found that metformin may reduce AD risk based on its ability to sensitize neuronal insulin resistance.^{26,27} According to another study, metformin may be used as a future therapy for NDs.²⁸ However, according to some authors, treatment with metformin might rather stimulate the development of AD.²⁹

One limitation of our study is that we did not focus on a specific disease because the sample size was not adequate. Before performing quality control on samples ($n =$

Table 5 The Odds of Having Neurodegenerative Diseases Based on Rs10506151 Genotype and T2D

	OR	(95% CI)	p-value
Rs10506151 genotype and T2D (ref: CA+AA & T2D)			
CC & no T2D	1.74	(0.81–3.73)	0.153
CA+AA & no T2D	2.47	(1.14–5.38)	0.023
CC & T2D	2.34	(1.07–5.11)	0.033
Sex (ref: Female)			
Male	1.04	(0.69–1.56)	0.851
Age	1.10	(1.08–1.13)	<0.001
Education (ref: Elementary School)			
Junior & Senior High School	0.51	(0.33–0.80)	0.003
University & above	0.50	(0.31–0.80)	0.004
Smoking (ref: No)			
Yes	1.08	(0.68–1.71)	0.753
Alcohol intake (ref: No)			
Yes	0.94	(0.52–1.68)	0.832
Physical activity (ref: No)			
Yes	0.68	(0.48–0.95)	0.026
BMI	0.96	(0.91–1.01)	0.149
Hypertension (ref: No)			
Yes	1.71	(1.16–2.50)	0.006
Hyperlipidemia (ref: No)			
Yes	1.48	(1.01–2.17)	0.045

Note: CC, CA, and AA represent genotypes of the rs10506151 variant.

Abbreviations: OR, odds ratio; CI, 95% confidence interval.

19,500), 165 participants were identified with NDs. Of these, 47 had PD, 10 had AD, 9 had other degenerative diseases of the basal ganglia, and 119 had other dementia. Of note, some of these individuals had more than one condition. To benefit from a larger sample size, NDs jointly included PD, other degenerative diseases of the basal ganglia, AD, and other dementia as stated above. Despite the limitation, our results may provide new directions for research in NDs. That is to say, the interactive effect of T2D or its medications and LRRK2 mutation on

neurodegenerative conditions is worthy of further investigation.

Conclusion

We found that among the four subpopulations categorized by rs10506151 genotypes and diabetes status, the risk of NDs was significantly lower among individuals having T2D and CA/AA genotype in Taiwan. These preliminary findings expand knowledge about the genetics of NDs and may be relevant to studies investigating disease-modifying therapies for

neurodegenerative conditions. Despite these, there is a need for more investigations.

Abbreviations

T2D, type 2 diabetes; OR, odds ratio; CI, 95% confidence interval; BMI, body mass index; LRRK2, Leucine-rich repeat kinase 2; NHIRD, National Health Insurance Research Database; TWB, Taiwan Biobank; PD, Parkinson's disease; AD, Alzheimer's disease; SNP, single nucleotide polymorphism.

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Disclosure

The authors report no conflicts of interest in this work.

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