AMPK γ2 subunit gene *PRKAG2* polymorphism associated with cognitive function as well as diabetes in old age

Eosu Kim

Department of Medicine

The Graduate School, Yonsei University

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Directed by Professor Byoung-Hoon Oh

The Doctoral Dissertation
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Doctor of Philosophy

Eosu Kim

December 2010

This certifies that the Doctoral Dissertation of Eosu Kim is approved.

Thesis Supervisor: Byoung-Hoon Oh

Dong Goo Kim: Thesis Committee Member#1

Jong Rak Choi: Thesis Committee Member#2

Ho-Geun Yoon: Thesis Committee Member#3

Chang Hyung Hong: Thesis Committee Member#4;

The Graduate School
Yonsei University

December 2010

ACKNOWLEDGEMENTS

I would like to express deep appreciation to Professor. Byoung-Hoon Oh who has leaded me to becoming a geriatric psychiatrist. In addition, to the practical founders and contributors of this study, Prof. Chang Hyung Hong and Kang Soo Lee, the two outstanding geriatric psychiatrists. Geriatric psychiatry taught me that the final stage in life is the premier as it is in all that have stages.

However, until I majored in this subspecialty, namely, old age psychiatry, I did not realize that the whole figure of my present life in younger middle age (especially, the relationship with others) is a key predictor of the successful and healthy aging in the final stage of my life.

Ironically, just prior to the moment that I receive my Ph.D. degree in geriatric psychiatry, I thus came to really doubt the qualification of me as a specialist for geriatric mental health, because I find myself having screwed up 'the present' in order to complete this Ph.D. dissertation at the expense of time, energy, and even affection of the principal persons around me as well as my time, energy, and affection towards them.

Now I recall the names of some of these thankful ones in my heart. Yehwon Lee, my wife, who allowed me to dare to explore the world, waiving her better rights she always deserves; Dayune, my daughter, who is always waiting for her Dad, thankfully, never forgetting him; Jin Sung Kim, Dad, Jae Sook Lee, Mom, who have sacrificed their better lives for my development; Kwan Hyung Lee & Kyung Ae Yeom who made the best to me, and lastly, as always the last but never least, Ji Hoon Lee and Hwasu Kim. Finally, Zong Ha Yune, my spiritual guide who is now with the Father in Heaven. If he were alive still, he would never permit me to go on studying.

This time, for the space consideration, I would like to omit the names of Prof. Minsun Park, Ms. Hyun-Jung Kim, Prof. Young-Chul Jung, Jae-Jin Kim, Hyun-Sang Cho, & Prof. Kee Namkoong, although their contribution to the present of me is invaluable.

December 2010
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ABSTRACT

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Eosu Kim

Department of Medicine
The Graduate School, Yonsei University

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Metabolic and cognitive disorders are closely related. However, the mechanism underlying this relationship is still under a debate. AMP-activated protein kinase (AMPK) is a key regulator of energy metabolism. Energy metabolism deficiency has been consistently implicated in the pathogenesis of cognitive decline such as Alzheimer's disease as well as metabolic disorders including diabetes. This study aimed to examine whether the AMPK γ2 gene, *PRKAG2* -26 C/T polymorphism is associated with cognitive functions and diabetes in the Korean community elderly aged from 60 to 80 (n = 1,609). Multivariate logistic regression analysis showed a significant association between the -26C/T single-nucleotide polymorphism (SNP; CC versus CT/TT) and cognitive impairment (OR, 1.6; 95% CI, 1.1-2.2) after adjusting for age, gender,

education, smoking, alcohol drinking, depression, waist circumference and the number of APOE e4 allele. Moreover, this SNP (CC/CT versus TT) was also related to the presence of diabetes (OR, 1.8; 95% CI, 1.2-2.8). Importantly, the relationship between the SNP and cognitive impairment was still significant in persons who had no diabetes (P = 0.015). Further analyses with subpopulation (n = 546) revealed that CC homozygotes relative to T-allele carriers had significantly better performances in verbal and visual memory and attention. These findings collectively supports a hypothesis that AMPK has a role in cognitive functioning, as well as metabolic functioning, in humans even when excluding the potential secondary effect of diabetes on cognition. Further longitudinal study with larger sample size and additional SNPs is warranted.

Key words: AMPK, genetic polymorphism, cognitive function, diabetes

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Department of Medicine
The Graduate School, Yonsei University

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I. INTRODUCTION

Metabolic and cognitive disorders constitute the great burden of aging society worldwide [1]. Furthermore, growing body of evidence indicates that these two disorders are closely related. For instance, the metabolic syndrome and its individual components such as diabetes, central obesity, and hypertension, have been found to increase the risk of cognitive decline or dementias [2-5].

Underlying mechanism of this linkage is not clearly identified yet. One of the most plausible mechanisms, cerebrovascular dysfunction secondary to such metabolic disturbances seems unable to explain the whole picture [3,5-6]. It is known that diabetes increases the risk of not only vascular dementia but also Alzheimer's disease (AD) [4,6], with the latter being the most common [2]. In addition, it was also found that persons suffering diabetes already showed mild

cognitive deficits even when they had no dementia relative to age-matched healthy persons [7].

More fundamentally, there could be a certain common factor that has independent influence on both metabolic and cognitive impairments while not necessarily developing both. Energy metabolism deficiency such as mitochondrial dysfunction may be a reasonable candidate in this regard, given that it has been consistently suggested as a pathoetiology of each of cognitive and metabolic disorders [8-10]. Further elucidation of such underlying mechanisms linking the two conditions would provide newer insight for the pathogenesis of cognitive aging or dementia.

AMP-activated protein kinase (AMPK) is a metabolic enzyme well known as a 'master switch' for energy homeostasis [11]. AMPK is involved in a variety of important metabolic processes such as glucose uptake/utilization, fatty acid oxidation, and cell growth/death. Its activity is also required for mitochondrial biogenesis [12]. Metabolic disturbances including diabetes, obesity, fatty liver disease [13] or even life span [14] have been known to be related to AMPK activity. Interestingly, the degree of AMPK activation in response to energy stress was shown to be decreased by aging [15], which is a well defined risk factor for both metabolic and cognitive impairments.

Neuronal cell is characteristically vulnerable to energy imbalance. Glucose/energy metabolism is crucial for normal functioning of neurons in that they have highly metabolic demands but little own energy reservoir. Thus, it is

very likely that AMPK activity is also important for healthy cognitive functioning as well as neuronal survival [16]. Indeed, Dagon et al. [17] firstly suggested the AMPK involvement in cognition by showing that activation of hippocampal AMPK enhances cognitive ability of mice, increasing neuronal survival under the metabolic stresses.

An analysis of genetic polymorphisms would be a good alternative way of such assaying a target enzyme activity *in vivo* to identify the potential of the target molecule involvement in some phenotypes in humans. Expectedly, following the several animal studies showing the crucial involvement of AMPK in metabolic regulations [18-19], subsequent studies have shown that polymorphisms in AMPK gene are associated with the risk of various forms of metabolic disorders, such as diabetes, hypercholesterolemia, and hypertriglyceridemia [20-23]. However, there has been no, to our knowledge, report to date showing the relationship between the AMPK gene polymorphism and cognitive functions.

Therefore, this study aimed to examine if a single-nucleotide polymorphism (SNP), namely, – 26 C/T polymorphism in 5'-flanking region of AMPKγ2 subunit gene *(PRKAG2)* is associated with the greater risk of cognitive impairment as well as diabetes in Korean old age.

II. MATERIALS AND METHODS

1. Study Population

Study subjects were part of the Gwangju Dementia and Mild Cognitive Impairment Study (GDEMCIS), an ongoing prospective cohort study of community-dwelling elderly people, all of whom are ethnic Koreans aged over 60 years at initial, living in Gwangju, a city with both urban and agricultural districts, located in south of Seoul, the capital city of Korea. More description about GDEMCIS was detailed in prior literature [24]. Informed consent was obtained after providing a full description of the study to subjects and their relatives. This study was approved by the Severance Mental Health Hospital Institutional Review Board.

Of 2,137 persons at baseline, only 1,862 persons with age ranging 60 to 80 were subjects of interest of the current study. We limited the subjects' age to 80 or below in order to avoid the potential floor effect of age on cognitive functions. Previous genetic study showed that the effect of *APOE* genotype on cognition is weakened in those with higher age above 80 [25]. Genotyping data for both *APOE* and *PRKAG2* were available in 1,648 persons. Additional 39 subjects were excluded from the analyses by the following exclusion criteria: 1) a history of or current neurological disorders such as significant head trauma, carbon monoxide gas intoxication, stroke, Parkinson's disease, and active epilepsy, 2) a history of or current psychiatric disorders such as schizophrenia, mental retardation, severe depression or mania, and substance/alcohol

dependence or current taking psychotropic medications, 3) active treatment for cancer in the previous 5 years. Finally, 1,609 persons were included for the final analyses.

2. Measurements

The Korean version of Mini-Mental State Examination (MMSE-K)[26] was administered to all participants. MMSE-K is a Korean version of MMSE [27] modified and validated to adjust scores for people who had no formal education. A registered nurse and clinical psychologist conducted this cognitive screening and anthropometric measurement. Mood status was evaluated using Korean Short version of Geriatric Depression Scale (GDS) [28]. Field investigators trained by senior psychiatrists and clinical psychologists performed Some of the participant completed a neuropsychological battery, which includes Digit span (Forward, Backward) for attention and working memory, Seoul Verbal Learning Test for verbal memories, the simplified Rey-Osterrieth Complex Figure Test for visual memories, the Korean version of Boston naming test for naming ability and a Stroop test for fronto-executive function. Collateral information was obtained to verify a subject's self-reports from at least one close family member or reliable informant acquainted with the subject.

3. Genotyping (TaqMan assay)

For genotyping, the collected blood was added to Vacutainer (BD, Franklin

Lakes, NJ) containing acid citrate dextrose and stored in a – 80 °C freezer. The genotyping of AMPK γ2 gene (*PRKAG2*) – 26 C/T SNP was screened using the TaqMan fluorogenic 5' nuclease assay (ABI, Foster City, CA, USA). The final volume of polymerase chain reaction (PCR) was 5uL, containing 10ng of genomic DNA and 2.5ul TaqMan Universal PCR Master Mix, with 0.13ul of 40X Assay Mix (Assay ID C_2684958_10). Thermal cycle conditions were as follows: 50℃ for 2 min to activate the uracil N-glycosylase and to prevent carry-over contamination, 95℃ for 10 min to activate the DNA polymerase, followed by 45 cycles of 95℃ for 15 s and 60℃ for 1 min. All PCR were performed using 384-well plates by a Dual 384-Well GeneAmp PCR System 9700 (ABI, Foster City, CA, USA) and the endpoint fluorescent readings were performed on an ABI PRISM 7900 HT Sequence Detection System (ABI, Foster City, CA, USA). Duplicate samples and negative controls were included to ensure accuracy of genotyping. *APOE* genotyping was conducted as described in elsewhere [24].

4. Statistical Analyses

To compare the baseline characteristics of participants, t test or X^2 analysis was used as appropriate. Firstly we conducted a multivariate linear regression analysis to examine the relationship between – 26C/T polymorphism of AMPK γ2 gene and MMSE-K score with adjustment for age, gender, education, smoking, alcohol use, waist circumference, depression scores, and copy number

of Apo E e4. Then we conducted multivariate adjusted logistic regression analyses to examine whether the - 26 C/T polymorphism was associated with odds of cognitive impairment or the presence of diabetes. Cognitive impairment was defined as MMSE-K score less than 18 for this cut-off value has been used to indicate severe cognitive impairment or as a proxy measure to diagnose dementia [27]. We used CC homozygote (reference) versus T-allele carriers (CT/TT), as independent variables and age, gender, education, smoking, alcohol use, waist circumference, depression scores, and copy number of Apo E e4 as covariates. Choice of the genetic model for the SNP was determined by crude comparison of mean scores (MMSE) or percentage of the presence of diabetes among three genotypes (CC, CT, TT); a minor allele dominant model [CC homozygotes versus T-allele carriers (CT/TT)] was applied to cognitive impairment, and a recessive model (CC/CT versus TT) to diabetes. With a smaller number of subjects (n = 546) who had completed neuropsychological battery test data, we applied general linear model to identify which cognitive domains included in the neuropsychological battery are specifically associated with the - 26 C/T polymorphism. In this regression analysis, the same covariates used for the logistic regression were used. Among various cognitive domains which are included in the neuropsychological battery, we were primarily interested in verbal and visual memory and attention, which were firstly examined. Then we secondarily analyzed regarding fronto-executive functions, which have a large number of sub-domains. A 2-tailed type I error of 0.05 or

less was used for statistical significance in all analyses, which were carried out using SPSS 17.0 (Chicago, IL, USA).

III. RESULTS

1. Characteristics

General characteristics of the subjects are described in Table 1, showing the comparison between CC homozygotes and T-allele carriers. The number of persons belonging to each genotype was 788, 673, and 148 for CC homozygote (49.0%), CT heterozygote (41.8%), and TT homozygote (9.2%), respectively. These genotype frequencies was similar with those of a previous report in the Chinese population [22], conforming to Hardy-Weinberg equilibrium ($p = 0.80$).

2. Relationship with Cognitive Function

At first, we conducted a multivariate linear regression analysis, which showed that the -26C/T polymorphism of AMPK γ2 gene was significantly associated with MMSE-K score with adjustment for age, gender, education; metabolic risk factors (waist circumference, smoking, and alcohol use); depression score and the copy number of APOE e4 allele.

In subsequent logistic regression analyses, we found the -26C/T polymorphism was significantly associated with cognitive impairment≤(17 MMSE score; Table 2). As expected, age and education were related to

cognitive impairment (increased age, OR = 1.11, 95% CI: 1.07-1.16, P < 0.001; higher education year, OR = 0.70, 95% CI: 0.66-0.76, P < 0.001), whereas gender had no association with cognitive impairment (P = 0.26). Higher depression score was also significantly associated with cognitive impairment (OR = 1.07, 95% CI: 1.03-1.12, P = 0.001).

Table 1. Characteristics of participants according to - 26 C/T polymorphism of *PRKAG2*

	- 26 C/T polymorphism of *PRKAG2* (n = 1,609)	
	CC homozygotes (n = 788)	T-carriers (CT/TT) (n = 821)
Age (year) *	71.0 ± 5.3	70.4 ± 5.1
Gender (female, n)	520 (66.0%)	550 (67.0%)
Education (year)	5.3 ± 4.6	5.0 ±4.5
Alcohol use (n; none/previous/current)	529/64/195	560/73/188
Smoking (n; none/previous/current)	570/109/109	602/128/91
Waist circumference (cm)	85.7 ± 9.0	85.8 ± 9.5
BMI (kg/cm2)	24.7 ± 6.5	24.5 ± 3.0
Depression score	6.5 ± 4.4	6.6 ± 4.5
MMSE score **	23.1 ± 4.2	22.6 ± 4.4
Cognitive impairment (n; MMSE $\leq$ 17) **	69 (8.8%)	103 (12.5%)
Copy number of *APOE* ε4 allele (n; 0/1/2)	655/126/7	692/124/5

* P < 0.05, ** P < 0.01 in independent t test or Pearson X^2 test. BMI, body mass index; MMSE, Mini-Mental State Exam.

However, contrary to the previous findings [29], waist circumference was not

found to be associated with cognitive impairment in the current study (P = 0.74). The same multivariate logistic regression analysis only with persons who had MMSE-K score 10 or higher (n = 1,593) showed almost identical results (data not shown).

Table 2. Odds ratios for cognitive impairment by - 26 C/T polymorphism of *PRKAG2 [CC (reference) versus CT/TT]*

	B (SE)	Wald	P-value	Odds Ratio (95% Confidence Interval)
Unadjusted	0.40 (0.16)	5.99	0.01	1.49 (1.08 – 2.06)
Adjusted Model 1	0.45 (0.18)	6.31	0.01	1.57 (1.10 – 2.23)
Adjusted Model 2	0.44 (0.18)	6.01	0.01	1.56 (1.09 – 2.22)
Adjusted Model 3	0.44 (0.18)	6.00	0.01	1.56 (1.09 – 2.22)

Models adjusted for age, education, and gender (Model 1); (Model 1) + waist circumference, alcohol, smoking and depression (Model 2); (Model 2) + the copy number of *APOE* e4 allele (Model 3). SE, standard error.

To identify cognitive domains which are specifically associated with the -26C/T SNP, we conducted a multivariate analysis of covariance with smaller population (n = 546) who had complete data of the neuropsychological battery which indicates performances in various cognitive domains. It showed that CC homozygotes had significantly higher performances in verbal and visual memories and attention measured by the immediate/delayed verbal and nonverbal free recall, and Digits Forward tests, respectively (Table 3). To avoid

the potential of the floor effect, we repeated the same analyses by excluding persons who had zero point in the delayed verbal recall, and then found that statistical significances still remained (data not shown).

Table 3. Estimated marginal means of neuropsychological test scores according to -26C/T polymorphism of *PRKAG2*

Neuropsychological tests	- 26 C/T polymorphism of *PRKAG2* (n = 546)		
	CC homozygotes (n = 267)	T-carriers (CT/TT) (n = 279)	P-value*
Verbal memory			
Immediate free recall	3.7 (3.6-3.9)	3.4 (3.2-3.6)	0.02
Delayed free recall	5.8 (5.5-6.1)	5.0 (4.7-5.3)	< 0.0001
Recognition	19.9 (19.4-20.3)	19.4 (18.9-19.8)	0.11
Nonverbal memory			
Immediate free recall	11.6 (11.2-12.1)	10.9 (10.4-11.4)	0.03
Delayed free recall	11.3 (10.8-11.8)	10.6 (10.1-11.1)	< 0.05
Recognition	16.0 (15.5-16.5)	15.4 (14.9-15.9)	0.12
Attention/Working memory			
Digits Forward	5.2 (5.0-5.3)	4.8 (4.6-4.9)	< 0.01
Digits Backward	2.9 (2.8-3.0)	2.8 (2.6-2.9)	0.15

* Multivariate ANCOVA with adjustment for age, education, gender, waist circumference, alcohol, smoking, depression, and the copy number of *APOE* e4 allele

As exploratory outcomes, we also compared the several fronto-executive

functions between CC and CT/TT genotypes, and found that CC homozygotes relative to T-allele carriers had higher performances in Controlled Oral Word Association Test (COWAT-Animal; P = 0.020) and Korean-Color Word Stroop Test (K-CWST-number of error; P = 0.005). However, these additional findings might be results from the statistical noise in that various sub-items are included in such executive function tests.

3. Relationship with Diabetes

We found that the -26C/T polymorphism was also related to the presence of diabetes (Table 4) conforming to the previous finding in Chinese population [22].

Table 4. Distribution of diabetic patients according to the - 26 C/T polymorphism of *PRKAG2*

	- 26 C/T polymorphism of *PRKAG2* (n = 1,609)			X^2 test
	CC (n = 788)	CT (n = 673)	TT (n = 148)	
Diabetes (n, %)	90 (11.4%)	85 (12.6%)	29 (19.6%)	P = 0.023

Logistic regression analyses showed that minor allele homozygotes (TT) had higher odds of having diabetes relative to C-allele carriers (CC/CT) when adjusting for all the same variables used as covariates in the above multivariate logistic regression analyses for cognitive impairment (Table 5). As expected, the greater waist circumference was significantly associated with the higher odds of presence of diabetes (OR = 1.04, 95% CI: 1.02-1.06, P < 0.0001). Given these

findings, we examined again the relationship between the SNP and cognitive impairment in persons without diabetes to exclude the potential secondary effect of diabetes on cognitive function. Importantly, we found that the SNP (CC versus CT/TT) was still related to cognitive impairment even in persons having no diabetes (n = 1,405) in univariate (OR = 1.46, 95%CI = 1.04 – 2.05, P = 0.027) and full-term multivariate analyses (OR = 1.59, 95%CI = 1.10 – 2.31, P = 0.015). Finally, in order to exclude the potential of secondary cognitive impairment from stroke, we repeated the analyses with persons without a history of stroke (n = 1,506) and found that the – 26C/T polymorphism was still significantly associated with the higher odds of cognitive impairment as well as the presence of diabetes (data not shown).

Table 5. Odds ratios for the presence of diabetes by - 26 C/T polymorphism of *PRKAG2 [CC/CT (reference) versus TT]*

	B (SE)	Wald	P-value	Odds Ratio (95% Confidence Interval)
Unadjusted	0.58 (0.22)	6.88	0.01	1.79 (1.16 – 2.77)
Adjusted Model 1	0.57 (0.22)	6.46	0.01	1.76 (1.14 – 2.73)
Adjusted Model 2	0.59 (0.23)	6.90	0.01	1.81 (1.16 – 2.81)
Adjusted Model 3	0.59 (0.23)	6.96	0.01	1.81(1.17 – 2.82)

Models adjusted for age, education, and gender (Model 1); (Model 1) + waist circumference, alcohol, smoking and depression (Model 2); (Model 2) + the copy number of *APOE* e4 allele (Model 3). SE, standard error.

IV. DISCUSSION

This study shows that the -26C/T SNP of AMPK γ2 gene, *PRKAG2*, is associated with the presence of cognitive impairment as well as diabetes in old age. T-allele carriers (CT and TT) were related to increased chance of having cognitive impairment relative to CC homozygotes, while TT homozygotes had higher incidence of diabetes. This finding was corroborated by the further analyses showing that the CC homozyotes relative to T-allele carriers had better performances in attention, verbal/visual recall memories, and some fronto-executive functions.

These cognitive domains have been reported to be relatively impaired in persons with metabolic disorders such as diabetes, central obesity or hypertension [29-30]. In addition, a recent investigation showed that poorer verbal memory and executive function at baseline predict greater likelihood of AD conversion from MCI [31]. For we only used a proxy measure for severe cognitive impairment (MMSE≤ 17) instead of a straightforward diagnosis of AD, it should be examined in a future study whether this polymorphism of AMPK gene has a role in risk modification of AD development.

AMPK is a heterotrimeric enzyme consisting of a catalytic α subunit and two regulatory subunits (β and γ), with each coded by two or three genes (α1~2, β1~2, γ1~3). Among various SNPs reported in these AMPK genes, we selected the – 26C/T SNP in AMPKγ2 gene as a single target by considering our

hypothesis and the size and ethnicity of our population (Korean). Our original hypothesis is that AMPK gene polymorphism is associated with both metabolic and cognitive impairments. The – 26C/T SNP was recently reported to increase the risk of diabetes in Chinese population [22] while other SNPs in α2, β1 or β2 subunit gene were not associated with diabetes in Japanese population [32]. Especially, γ subunit is a key regulatory subunit of AMPK, as it was shown that deficiency in this subunit causes neurodegeneration [33]. We also posed priority in SNPs reported in Chinese or Japanese studies. And, as this study is preliminary in nature to evaluate the relationship of AMPK gene polymorphisms to cognitive function, we first chose only a single target SNP to avoid statistical noise considering our relatively small sample size.

There could be several explanations for the current finding of the relationship between AMPK and cognition. First, the AMPK polymorphism might affect the mitochondrial function with age-dependent manner. AMPK's activity is known to be crucial for normal mitochondrial biogenesis in response to energy stress [12], and there has been increasing evidence that mitochondrial dysfunction has a causative role in neurodegenerative diseases [8] as well as in metabolic disorders [9]. Second, AMPK activity is recently found to have a positive role in modulating the amyloid beta production and tau phosphorylation [34-35], both of which are the hallmarks of AD pathogenesis. Thus it could be postulated that the SNP-dependent difference in basal activity of AMPK might exert a 'long-term' effect on AD-related pathology accumulation

during aging, just as the case of APOE genotype [36]. Third, AMPK activity has been known to affect neuronal survival via modulating the key processes such as neurogenesis, neuroapoptosis, neuroinflammation, and autophagy [16,37-38]. Genetic variants of AMPK might contribute to some of these survival processes during aging. Further study would be needed for the identification of detailed role of AMPK and its genetic variants in cognitive function.

This human genetic finding adds evidence to these previous suggestions from animal studies that AMPK has a role in modulating cognitive function as well as in metabolic function. No significant association was observed between the - 26C/T SNP and waist circumference which is known to well represent the individual's metabolic status related to cardiovascular risks [39]. However, it was found that the - 26C/T SNP was significantly associated with the presence of diabetes. Thus this study showed the double association of AMPK with metabolic and cognitive disturbances as was originally hypothesized.

Notably, recent animal study has shown that the level of AMPK activity is decreased during aging [15], which reminds that glucose/energy metabolism is decreased during aging [40]. Such reduction of AMPK activity during aging was suggested to contribute to impaired energy metabolism in older age relative to younger age. Though measured AMPK activity in rat muscles, this finding suggests that aging-associated decrease in AMPK activity might contribute to aging-associated cognitive impairment and that the SNP-dependent functional difference in such decrease of AMPK activity could be responsible for

inter-individual variation in cognitive impairment during aging. This speculation may seem likely when considering that late-onset, sporadic AD, and many other metabolic disorders as well, are thought to be manifested in later life as the result of long-term accumulative effects of subtle metabolic disturbance [36,41]. Interestingly, agents known to modulate AMPK activity were found to not only improve metabolic disturbances [18,42] but also reverse the consequences of aging processes [43-44].

Several limitations should be considered in the interpretation of our results. This is a cross-sectional study, so it can not suggest the cause-and-effect relationship between the SNP and cognitive functions. A longitudinal observation should be conducted to identify whether age-associated cognitive decline is dependent of AMPK genetic variants. However, genetic information can be an inborn risk factor exerting long-term cumulative effects on cognitive and metabolic functions throughout the individual's life. Thus, with a presumption that the great majority of all subjects had normal cognitive functioning in their younger age, this cross-sectional study may suggest the genotype-and-phenotype relationship which is manifested by aging effect.

Definition of phenotypes and diagnostic issue are also problematic areas. We used a proxy measure of dementia (MMSE-K score $\leq$ 17) instead of more comprehensive diagnostic work-up. In addition, MMSE, though it is widely used to represent global cognitive functioning, may not be so sensitive to represent a specific biological endophenotype accounting for the differences in

cognitive functioning among individuals. Only small portion of entire cohort has been received comprehensive neuropsychological tests that can measure individual domains of cognitive functions. With these reasons, the current study cannot address if the – 26 C/T SNP is associated with a risk of any form of dementias or simply with of cognitive aging. On the other hand, some of community-dwelling elders included in this study must have various types of dementias. There is a potential of a bias in the results caused by excluding the uncooperative demented elderly. In addition, we did not depend on more objective measurement tools or objective medical records, but on the self- and/or collateral verbal reports regarding the past history of physical illnesses including diabetes that may seriously confound our results.

Using small sample size and only a single target SNP is also an important limitation of this study, although choosing a single target SNP was to avoid reduction of statistical power caused by multiple comparisons in a small sample size. .

V. CONCLUSION

We found that the major allele homozygotes (CC) of – 26C/T polymorphism of AMPK γ2 gene might be protective against cognitive impairment during aging while minor allele homozygotes (TT) more vulnerable to diabetes. With some inevitable limitations of a cross-sectional population study, our data

collectively support a hypothesis that AMPK gene polymorphism is a common contributing factor involved in both cognitive and metabolic dysfunctions in humans, and also suggest in part that cognitive impairment in diabetes might not be totally dependent on the vascular dysfunction secondary to diabetes. An extended and longitudinal study with multiple target SNPs is warranted.

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ABSTRACT(IN KOREAN)

인지기능 및 당뇨병과 관련된 AMPK 감마2 유전자 PRKAG2의 유전다형성

<지도교수 오 병 훈>

연세대학교 대학원 의학과

김 어 수

대사장애 및 인지장애는 서로 깊이 연관되어 있는 것으로 밝혀지고 있으나, 그 연관성에 대한 구체적인 기전에 대해서는 논란 중이다. AMP-활성 단백질 인산화효소(AMP-activated protein kinase, AMPK)는 에너지대사의 중추적 조절 효소다. 에너지대사의 이상은 알츠하이머병을 포함한 인지감퇴와 대사질환, 양쪽 모두에 중요한 병인론으로 주목받고 있다. 따라서 본 연구에서는 AMPK 감마2 유전자의 단일유전다형성(*PRKAG2* -26 C/T polymorphism)이 대한민국 지역사회 노인(60세 – 80세)의 인지기능 및 당뇨병과 관련되는지를 조사하였다. 나이, 성별, 교육연수, 흡연력, 음주력, 우울점수, 허리둘레, APOE e4 유전자형의 개수 등을 통제한 다변량 로지스틱 회귀분석에서 -26 C/T 유전다형성은 인지장애와 유의한 관계가 있음이 밝혀졌다(CC 대 CT/TT, OR, 1.6; 95% CI, 1.1-2.2). 더 나아가, 이는

당뇨병의 존재와도 연관된 것으로 밝혀졌다 (CC/CT 대 TT, OR, 1.8; 95% CI, 1.2-2.8). 중요한 것은, 당뇨가 없는 노인들을 대상으로 분석을 반복했을 때도 이 유전다형성과 인지기능과의 관계가 유의하게 관찰되었다는 것이다. 추가적인 소그룹 분석에서 CC 유전형을 가진 사람들은 CT/TT군 보다 언어 및 시각 즉각/지연 회상과 주의력 검사에서 유의하게 높은 평균점수를 보였다. 본 연구결과는 AMPK가 당뇨에 의한 이차적인 인지감퇴를 배제하더라도, 인지장애와 대사장애에 동시에 영향을 미치는 공통인자라는 것을 시사한다. 향후 더 큰 집단에서 전향적 연구를 통해 이러한 결과를 확인해야 할 것이다.

핵심되는 말: AMPK, 유전다형성, 인지기능, 당뇨