in vivo *33*: 1685-1690 (2019)
doi:10.21873/invivo.11656

C-Reactive Protein Gene Variants and Their Serum Levels in Early Adult-onset Type 2 Diabetes Mellitus

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Abstract. *Background/Aim: C-Reactive protein (CRP) is a common marker of inflammation. Elevated CRP levels have been associated with increased risk of development of type 2 diabetes mellitus (T2DM). This study aimed to evaluate the association of CRP gene polymorphisms with early-onset T2DM and the effect of genetic variants on CRP level. Materials and Methods: In total, 948 individuals with early-onset (n=271) or late-onset (n=677) T2DM were enrolled in the study. Five single-nucleotide polymorphisms (SNPs) in the CRP gene, namely rs3093077, rs2808630, rs1800947, rs11265263, and rs11265265, were selected for genotyping, and CRP levels were measured. Results: Genotypic, allelic, and haplotype frequencies of these five SNPs were not significantly different between patients with early- and those with late-onset. T2DM Higher serum CRP levels were independently associated with the C-allele of rs3093077 and T-allele of rs11265265 (p<0.001). Furthermore, the C-allele of rs3093077 was associated with higher CRP level in both early- (p=0.016) and late-onset (p<0.001) T2DM. Conclusion: CRP gene variants may contribute to the risk of early-onset T2DM by affecting the serum CRP level.*

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Key Words: C-Reactive protein, polymorphism, early-onset, type 2 diabetes, Taiwan.

Type 2 diabetes mellitus (T2DM) is currently a major public health concern worldwide (1). During the past two decades, the prevalence of T2DM in young adults has steadily increased (2-4). A major risk factor strongly associated with early-onset T2DM is obesity in children, adolescents and young adults (5-7). From extensive experimental, clinical, and epidemiological studies, obesity has been linked to activation of innate immunity-related inflammatory signaling pathways. Inflammatory cytokines, such as interleukin-6 (IL6) and tumor necrosis factor-alpha (TNFα), and acute-phase reactants such as C-reactive protein (CRP) can block major anabolic cascades downstream of insulin signaling, thereby disrupting insulin homeostasis and increasing the risk of T2DM (8, 9). Studies have shown that reduction of inflammation and the ensuing acute-phase reactant responses through exercise, medication, or nutrition improves insulin sensitivity and delays disease onset (8).

Current evidence indicates that the risk of developing T2DM is regulated by lifestyle and genetic factors. Heterogeneity in the genetic determinants of T2DM development has been identified by candidate gene and genome-wide association studies (GWAS) across multiple populations (10-13). The influence of innate immunity-related inflammation genes combined with various lifestyle factors may affect serum levels of cytokines and inflammatory markers, that may play a pivotal role in susceptibility to T2DM. Therefore, investigation of the association between variants of inflammation-related genes and the risk of T2DM may help develop better approaches for early detection and prevention.

Table I. *Characteristics of patients with type 2 diabetes mellitus at entry, grouped by age of onset (early: <45 years; late: ≥45 years).*

		Early-onset (n=271, 28.6 %)	Late-onset (n=677, 71.4%)	*p*-Value
Gender (%)	Male	158 (58.3)	321 (47.4)	0.002
Age (years)	Mean±SD	50.7±9.2	62.6±8.4	<0.001
Diabetic duration (years)	Mean±SD	12.1±8.8	8.2±6.2	<0.001
BMI (kg/m^2)	Mean±SD	25.4±4.2	25.0±3.6	0.231
Waist to hip ratio	Mean±SD	0.91±0.06	0.92±0.07	0.013
Glu-AC (g/dl)	Mean±SD	145.6±42.2	144.5±42.9	0.721
Insulin (μU/ml)	Mean±SD	15.0±12.9	15.2±17.3	0.824
HbA1c (%)	Mean±SD	8.03±1.50	7.91±1.47	0.291
CRP (mg/l)	Mean±SD	0.26±0.42	0.34±1.01	0.093
DR, n (%)	Present	57 (27.4)	112 (22.2)	0.139
ACR, n (%)	<30 mg/g	173 (67.6)	388 (59.4)	0.067
	30-300 mg/g	62 (24.2)	205 (31.4)	
	>300 mg/g	21 (8.2)	60 (9.2)	
eGFR, n (%)	>90 ml/min/1.73 m^2	189 (69.7)	371 (54.8)	<0.001
	60-90 ml/min/1.73 m^2	63 (23.2)	200 (29.5)	
	<60 ml/min/1.73 m^2	19 (7.0)	106 (15.7)	

ACR: Albumin-to-creatinine ratio; BMI: body mass index; DR: diabetic retinopathy; eGFR: estimated glomerular filtration rate; Glu-AC: fasting glucose; HbA1c: hemoglobin A1c; CRP: C-reactive protein.

Recent evidence from linkage and GWAS studies has implicated a region of chromosome 1q21-23 encompassing the *CRP* gene with risk of T2DM development in various ethnic populations (14-16). CRP, a common marker of inflammation, is an acute-phase reactant regulated by cytokines, predominantly IL6 and TNFα. CRP plays a critical role in T2DM by its action on pancreatic β-cells and is thought to be an early risk factor for T2DM (17). *In vitro* studies have shown an association between the serum level of high-sensitivity CRP and β-cell dysfunction and insulin resistance (18, 19). Moreover, elevation of high-sensitivity CRP in diabetic patients has been associated with an increased risk of diabetic vasculopathy (18, 20-22). Furthermore, several single-nucleotide polymorphisms (SNPs) in the *CRP* gene have been reported to be associated with serum CRP level, insulin sensitivity, and T2DM incidence (23). Based on these observations, we investigated the association between variants of the *CRP* gene and early-onset T2DM in the Han Chinese population of Taiwan.

Materials and Methods

Patient and data collection. In total, 948 patients with T2DM (age >20 years) from the China Medical University Hospital in Taiwan were enrolled in the study, and informed consent was acquired from all patients. Diabetes was diagnosed based on the patient medical records and fasting plasma glucose level using the American Diabetes Association Criteria (24). Patients with type 1 diabetes, gestational diabetes, and maturity-onset diabetes of the young were excluded from this study. According to the age recommended by the American Diabetes Association for T2DM screening in adults, patients with type 2 diabetes were segregated into two subgroups: (i) early-onset diabetes (n=271; age at diagnosis, at least 20 years but less than 45 years) and (ii) late-onset diabetes (n=677; age at diagnosis, 45 years or more). Data regarding age, sex, duration of disease, weight, height, and circumference of waist and hip (waist-to-hip ratio) of each patient were obtained from questionnaires. Blood samples for genomic DNA isolation were collected by venipuncture, and serological tests, including fasting glucose, hemoglobin A1c, and CRP, were performed at the time of enrollment. The study was approved by the Medical Ethics Committee of the China Medical University Hospital, Taichung, Taiwan (approval number: CMUH103-REC2-071) and performed according to the tenets of the Declaration of Helsinki for research involving human subjects.

SNP selection and genotyping. Five SNPs of *CRP* gene rs3093077, rs2808630, rs1800947, rs11265263, and rs11265265 (positions: 159709846, 159711078, 159713648, 159740727, and 159743766 bp, respectively) were selected from the Illumina Hap550K chip (12), which has been used previously for GWAS in the Han Chinese population of Taiwan. SNPs were selected by applying the following criteria: (i) a threshold minor allelic frequency in the HapMap CHB population of 0.10 for tag SNPs; and (ii) a genotyping score ≥0.6, as recommended by the manufacturer (Illumina, Inc., San Diego, CA, USA) to ensure a high genotyping success rate. In order to avoid redundancy, markers with pairwise r^2 correlations ≥0.8 for any selected marker were not genotyped. Deviation from the Hardy–Weinberg equilibrium was not observed for any SNP. For genotyping, all blood samples were de-identified prior to analysis, and only the project investigator had access to the link for individual identities. Laboratory personnel involved in genotyping were blinded to the age at diabetic onset of the study patients. Genomic DNA was extracted from peripheral blood leukocytes using Genomic DNA kit (Qiagen, Valencia, CA, USA), and genotyping was performed using an allele-specific extension and ligation assay (Illumina) according to the manufacturer's instructions.

Table II. *Genotypic and allelic frequencies of C-reactive protein (CRP) gene variants for patients with early and late-onset type 2 diabetes mellitus.*

CRP SNP ID		Early-onset N (%)	Late-onset N (%)	*p*-Value[a]	OR (95% CI)b	*p*-Value[b]
rs3093077	A/A	172 (63.5)	465 (68.7)	0.271	1.00 (ref)	
	A/C	86 (31.7)	188 (27.8)		1.24 (0.91-1.69)	0.178
	C/C	13 (4.8)	24 (3.5)		1.46 (0.73-2.94)	0.281
Allele	A	430 (79.3)	1118 (82.6)	0.100	1.00 (ref)	
	C	112 (20.7)	236 (17.4)		1.23 (0.96-1.59)	0.100
rs2808630	T/T	189 (69.7)	449 (66.3)	0.573	1.00 (ref)	
	T/C	75 (27.7)	206 (30.4)		0.87 (0.63-1.18)	0.365
	C/C	7 (2.6)	22 (3.2)		0.76 (0.32-1.80)	0.526
Allele	T	453 (83.6)	1104 (81.5)	0.294	1.00 (ref)	
	C	89 (16.4)	250 (18.5)		0.87 (0.67-1.13)	0.294
rs1800947	C/C	225 (83.0)	559 (82.6)	0.744	1.00 (ref)	
	C/G	44 (16.2)	109 (16.1)		1.00 (0.68-1.47)	0.988
	G/G	2 (0.7)	9 (1.3)		0.55 (0.12-2.58)	0.443
Allele	C	494 (91.1)	1227 (90.6)	0.722	1.00 (ref)	
	G	48 (8.9)	127 (9.4)		0.94 (0.66-1.33)	0.722
rs11265263	C/C	165 (60.9)	393 (58.1)	0.725	1.00 (ref)	
	A/C	92 (33.9)	246 (36.3)		0.89 (0.66-1.20)	0.451
	A/A	14 (5.2)	38 (5.6)		0.88 (0.46-1.66)	0.688
Allele	C	422 (77.9)	1032 (76.2)	0.445	1.00 (ref)	
	A	120 (22.1)	322 (23.8)		0.91 (0.72-1.16)	0.445
rs11265265	C/C	129 (47.6)	320 (47.3)	0.400	1.00 (ref)	
	C/T	109 (40.2)	293 (43.3)		0.92 (0.68-1.25)	0.600
	T/T	33 (12.2)	64 (9.5)		1.28 (0.80-2.04)	0.301
Allele	C	367 (67.7)	933 (68.9)	0.613	1.00 (ref)	
	T	175 (32.2)	421 (31.1)		1.06 (0.85-1.31)	0.613

OR: Odds ratio; CI: confidence interval. [a]Chi-squared test comparing patients with early-onset type 2 diabetes with late-onset type 2 diabetes. [b]Logistic regression model, univariate analyses.

Statistical analyses. The distributions of genotypic and allelic frequencies of the polymorphisms in patients with early-onset (age <45 years) and late-onset (age ≥45 years) T2DM ware analyzed using the chi-squared or Fisher exact test for differences in proportions. Odds ratios (OR) were calculated for associations with genotypic and allelic frequencies with a 95% confidence interval (CI) using unconditional logistical regression. The effect of the *CRP* gene SNP genotype on serum CRP level was analyzed using a general linear regression model after logarithmic transformation of CRP data. All statistical analyses were conducted using IBM SPSS Statistics 22 (IBM Co., Armonk, NY, USA), and *p*-values of less than 0.05 (two-sided) were considered significant.

Results

In our database, 28.6% (n=271) of patients had early-onset T2DM (mean age at diagnosis=38.6±4.7 years), and 71.4% (n=677) had late-onset T2DM (mean age at diagnosis= 54.47±6.4 years). Clinical and biomedical parameters of patients with early-onset and late-onset T2DM are compared in Table I. We recorded a higher number of men, younger individuals, longer disease duration, and lower percentage of those with an estimated glomerular filtration rate <60 ml/min/1.73 m^2 in those with early-onset T2DM. None of the observed characteristics, including body mass index, waist-to-hip ratio, and serological marker levels (*i.e.* fasting glucose insulin, hemoglobin A1c, and CRP), in this study showed significant differences between these two groups. Furthermore, no significant differences in prevalence of diabetic retinopathy and albumin-to-creatinine ratio were observed.

In order to identify SNPs associated with early-onset T2DM, five SNPs within *CRP* were genotyped. The genotypic and allelic frequencies of these five polymorphisms were not significantly different between patients with early-onset and late-onset T2DM (Table II). Furthermore, we investigated the association between the CRP haplotype and susceptibility to early-onset T2DM, and no significant difference was found (Table III).

The effect of genotype on serum CRP level was also investigated (Table IV). A significant effect (both $p<0.001$) of the C-allele of SNP rs3093077 and T-allele of SNP rs11265265 on elevation of serum CRP level was observed in multivariate regression analysis after adjusting for gender, DM duration, and BMI. In addition, we stratified the patients with T2DM according to early- or late-onset, and the C-allele of rs3093077 was significantly associated with elevation of serum CRP level in both the early- and late-onset groups ($p=0.016$ and $p<0.001$, respectively). However,

Table III. *Haplotype analysis of gene encoding C-reactive protein (CRP).*

Haplotype*	Early-onset, N (%)	Late-onset, N (%)	OR (95% CI)[b]	*p*-Value[a]
ATCCC	243 (47.6)	596 (46.6)	1.00 (ref)	
ATCAC	52 (10.2)	147 (11.5)	0.87 (0.61-1.23)	0.426
ATGAC	48 (9.4)	127 (9.9)	0.93 (0.64-1.33)	0.683
ACCCT	73 (14.3)	217 (17.0)	0.83 (0.61-1.12)	0.215
CTCCT	94 (18.4)	192 (15.0)	1.20 (0.90-1.60)	0.213

OR: Odds ratio; CI: confidence interval. **rs3093077/rs2808630/rs1800947/rs11265263/rs11265265*. [a]Logistic regression model, univariate analyses.

Table IV. *Effect of single nucleotide polymorphisms (SNPs) of the gene encoding C-reactive protein (CRP) on serum CRP level by genotype in serum from patients with type 2 diabetes mellitus (T2DM).*

SNP		CRP level (mg/l)*					
	Genotype	Total T2DM N=946	*p*-Value[a]	Early-onset N=271	*p*-Value[a]	Late-onset N=677	*p*-Value[a]
rs3093077	A/A	0.12±0.47	<0.001	0.13±0.45	0.016	0.12±0.47	<0.001
	A/C	0.24±0.44		0.17±0.43		0.28±0.44	
	C/C	0.35±0.59		0.33±0.62		0.36±0.59	
rs2808630	T/T	0.15±0.46	0.488	0.14±0.46	0.624	0.16±0.47	0.290
	C/T	0.19±0.47		0.15±0.46		0.20±0.47	
	C/C	0.22±0.54		0.40±0.32		0.16±0.58	
rs1800947	C/C	0.18±0.46	0.129	0.17±0.45	0.338	0.18±0.47	0.147
	C/G	0.09±0.49		0.02±0.48		0.12±0.50	
	G/G	0.18±0.40		0.54±0.56		0.09±0.34	
rs11265263	A/A	0.19±0.44	0.432	0.30±0.55	0.764	0.15±0.39	0.602
	A/C	0.13±0.48		0.05±0.44		0.16±0.49	
	C/C	0.18±0.46		0.19±0.45		0.18±0.47	
rs11265265	C/C	0.10±0.45	<0.001	0.12±0.45	0.113	0.10±0.44	<0.001
	C/T	0.21±0.47		0.15±0.43		0.24±0.48	
	T/T	0.25±0.51		0.26±0.51		0.25±0.51	

*Data are geometric means with geometric standard deviation. [a]*p*-Value for general linear model adjusted for gender, body mass index and duration.

the T-allele of rs1126265 was only significantly associated with elevation of CRP level in the group with late-onset T2DM ($p<0.001$).

Discussion

Polymorphisms of several inflammation-related candidate genes such as those for toll-like receptor 4, ILα, IL6 and TNFα have been reported to contribute to T2DM (17, 25). However, only a few studies have examined the influence of genetics on age at T2DM diagnosis, and no high impact genes have been directly linked to T2DM onset. This study investigated five SNPs (rs3093077, rs2808630, rs1800947, rs11265263, and rs11265265) of the *CRP* gene and their association with early-onset T2DM. None of the selected SNPs were significantly associated with early-onset T2DM. It is possible that the SNPs examined in this study may not play important roles in T2DM development at an early age or might not capture all possible genetic variations in the *CRP* gene. Further studies exploring other *CPR* variants within this population, as well as experiments addressing genetic changes and their relationship to protein function, will help to identify the true causal variants of T2DM. In addition, the non-significant results of the association between the *CRP* gene and early-onset T2DM may be due to the sample size. Thus, the study may not have been sufficiently powered to detect a weak association between *CRP* genotype and early-onset T2DM.

Several SNPs, including rs1800947 (G1059C) (26-28), rs2794521 (A1009G) (29), rs3091244, and rs1205 (26), of *CRP* gene have been associated with concentrations of circulating CRP in patients of different ethnicities with different diseases. The relationship between *CRP* variants and serum CRP level was also explored in our T2DM study

population. A significant genetic effect on serum CRP level was observed in this study. SNPs rs3093077 and rs11265265 were associated with CRP level in patients with T2DM. Among these SNPs, rs3093077 was previously reported to be associated with CRP level in different populations, including in Denmark (30), the Framingham Heart Study cohort in America (31), the United Kingdom (32), and Taiwan (33), but not in Italians (34). SNP rs3093077 is located in the 3' flanking region of the CRP gene. It often contains a transcription unit to regulate formation of the 3' end of the message and may also contain enhancers or other protein-binding sites. SNPs in this region of *CRP* have been shown to affect the serum CRP level (29).

Furthermore, studies have shown that obesity can influence CRP concentration by stimulating overexpression of cytokines such as IL6 and TNFα (26). In addition, the effect of gender on CRP level has been shown in previous studies. Sheu *et al*. found that the *CRP* rs2794521 GG genotype was associated with lower serum CRP concentrations in a group of elderly men (29). Hence, we adjusted for the effect of BMI and gender in a multivariate model, and the results showed that the serum CRP level was affected by the *CRP* gene independently. The results highlight the importance of the interplay between genetic and lifestyle factors in phenotypic development of complex traits.

Conclusion

In conclusion, this study provides evidence for the association of serum CRP level and CRP gene polymorphisms in patients with T2DM, although a significant association between polymorphisms of the *CRP* gene and age at T2DM diagnosis was not observed.

Conflicts of Interest

None of the Authors have any financial interests to disclose.

Authors' Contributions

FJ Tsai and WL Liao conceived and supervised all works; YC Huang and WL Liao designed, analyzed and drafted the article; CC Chen, TY Wang, TTH Nguyen, YH Chen, CM Wu, and YW Chang participated interpretation the data. All Authors read and approved the final article.

Acknowledgements

The Authors thank the National Center for Genome Medicine, Taipei, Taiwan for providing support services for data coordination, subject recruitment, and project management.
Grant support: This work was supported in part by research grants from China Medical University Hospital (DMR-107-056 and DMR-108-036), Taichung City, Taiwan; and from Academia Sinica (AS-BD-108-9), Taipei City, Taiwan.

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Received June 20, 2019
Revised July 9, 2019
Accepted July 12, 2019