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PERIOD2 Variants Are Associated with Abdominal Obesity, Psycho-Behavioral Factors, and Attrition in the Dietary Treatment of Obesity

MARTA GARAULET, PhD, **M. DOLORES CORBALÁN-TUTAU, PhD**, **JUAN A. MADRID, PhD**, **JUAN C. BARAZA, PhD**, **LAURENCE D. PARNELL, PhD**, **YU-CHI LEE, MS**, and **JOSE M. ORDOVAS, PhD**

M. Garaulet is a physiology professor, Department of Physiology, University of Murcia, Murcia, Spain, and the Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University School of Medicine, Boston, MA. M. D. Corbalán-Tutau is a doctoral student, J. A. Madrid is a physiology professor, and J. C. Baraza is a nutrition associate professor, Department of Physiology, University of Murcia, Murcia, Spain. L. D. Parnell is a computational biologist, Y.-C. Lee is a doctoral student, and J. M. Ordovas is director of nutrition and genomics laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University School of Medicine, Boston, MA

Abstract

The purpose of this research was to test for association between polymorphisms in the circadian clock–related gene *PERIOD2 (PER2)* and attrition in patients prone to withdrawal from a behavioral weight-reduction program based on the Mediterranean diet. A total of 454 overweight/obese participants (women=380, men=74), aged 20 to 65 years, who attended outpatient clinics specializing in obesity between January and December 2008, were studied. Anthropometric, biochemical, and dietary-intake variables were analyzed. Effectiveness of the program was assessed, and a questionnaire of barriers to weight loss was considered. Multivariate analysis and logistic regression models were performed. Results indicate that *PER2* polymorphisms rs2304672C>G and rs4663302C>T were associated with abdominal obesity ($P<0.05$). Participants who withdrew from treatment were significantly more obese and had more barriers to lose weight ($P<0.05$). They also displayed a lower likelihood of planning eating in advance and experiencing stress with dieting than those who completed treatment. Frequency of rs4663307 minor allele was significantly greater in withdrawers than in those who successfully completed treatment ($P<0.05$). Logistic regression analysis showed that rs2304672 C>G minor allele carriers had a greater probability of dropping out, displaying extreme snacking, experiencing stress with dieting, eating when bored, and skipping breakfast than noncarriers. *PER2* is implicated in attrition in weight-loss treatment and may modulate eating-behavior–related phenotypes. These findings could represent a step toward personalized health care and nutrition based on a combination of genotyping and psycho-behavioral characterization.

Address correspondence to: Marta Garaulet, PhD, Department of Physiology, Faculty of Biology, University of Murcia, Campus de Espinardo, s/n 30100. Murcia, Spain. garaulet@um.es.

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One of the great challenges in obesity treatment is to develop techniques of eating behavior to significantly curtail attrition (1,2). Attrition and the achievement of weight-loss objectives depend largely on the capacity of a patient to modify lifestyle habits in an effective and sustained way. During this process, most patients encounter a variety of obstacles (1,2) that include losing motivation, being prone to stress-related eating, and being liable to eat when bored.

Interindividual differences in eating behavior and compliance with a weight-loss regimen may be heritable (3). Studying candidate genes to examine eating patterns, de Krom and colleagues (4) found that obese carriers of common polymorphisms in the leptin or leptin receptor genes showed increased risk to display extreme snacking behavior. Polymorphisms in cholecystokinin and serotonin receptor 2C also have been associated with eating patterns, satiety, and effectiveness of weight-loss treatments (4,5).

Recent clinical and epidemiologic studies, adding to the already complex field of obesity research, show interesting links between chronobiology and obesity. Shift work, sleep deprivation, and bright-light exposure at night have been associated with increased adiposity and prevalence of metabolic syndrome (6). Moreover, variants of the *CLOCK* gene have been associated with energy intake and obesity (7–9). The *PERIOD2* (*PER2*) gene is a second key component of the molecular mechanism that generates circadian rhythms in mammals. A missense mutation in human *PER2* has been linked to psycho-behavioral factors such as diurnal preference (10), advanced sleep phase syndrome (11), seasonal variations in mood and behavior, and winter depression (12). It has been shown that mPer2−/− mice display feeding abnormalities resembling that of the night eating syndrome, which has combined features of a circadian rhythm disorder and an eating disorder (13). However, the particular role of *PER2* on eating behavior and attrition in a weight-loss program in human participants is not known. The aim of this study was to characterize common traits of patients prone to withdrawal from a behavioral weight-reduction program based on the Mediterranean diet in an obese population. A second aim was to test for potential association between polymorphisms in the circadian clock-related gene *PER2* and attrition.

SUBJECTS AND METHODS

This study included all overweight/obese participants (body mass index [BMI] >25 and <40) within the age range 20 to 65 years (n=454) who attended five outpatient obesity clinics in the city of Murcia, located in southeastern Spain. The period of the study covered 12 months from the beginning to the end of 2008. A total of 50 participants was excluded from the study; this group included those patients receiving treatment with thermogenic or lipogenic drugs; diagnosed with diabetes mellitus; and with chronic renal failure, hepatic diseases, or cancer.

All procedures followed good clinical practice. Written consent was obtained from each patient before participation and study principles, including genotyping, were approved by the Research Ethics Committee of the Virgen de la Arrixaca Hospital. Patient data were codified to guarantee anonymity.

Patients were enrolled in a dietary treatment based on Mediterranean diet principles. Characteristics of the weight-reduction program have been described elsewhere (2,14). Individual energy requirements were calculated from the Harris-Benedict formula and total energy expenditure was calculated according to physical activity. About 600 kcal/day were then subtracted from the total energy expenditure (15). Final dietary energy contents ranged from 1,200 to 1,800 kcal/day for women and 1,500 to 2,000 kcal/day for men to induce an approximate loss of 0.5 to 1 kg/week (1 to 2 lb/week). Nutritional education, physical activity, and behavioral techniques, including stimulus control, self-monitoring, positive reinforcement, and cognitive behavioral therapy were also used.

Weight and height were determined by digital electronic balance (SecaAlpha, Igmy, France) and a Harpenden digital stadiometer (Harpenden, Pfifter 450, Badem, Padum Aveny, Carlstads, NJ). Total body fat was measured by bioelectrical impedance using TANITA TBF-300 (TANITA Corporation of America, Arlington Heights, IL). Body fat distribution was assessed by measuring waist circumference at the umbilicus and hip circumference at its widest, over the great trochanters (16). All data were collected by trained personnel following Spanish Society for the Study of Obesity norms (17). Plasma concentrations of glucose, total cholesterol, total hemoglobin, and uric acid were determined from venous blood samples after overnight fast with commercial kits (Roche Diagnostics GmbH, Mannheim, Germany).

To evaluate food habits, initial nutrient intake was determined by a 24-hour dietary recall the day before starting the treatment. Interviews were conducted from Monday to Friday, including 24-hour recalls of food intake from weekend and weekdays. Total energy intake and macronutrient composition were analyzed with the nutritional evaluation program Grunumur (version 1, 2006, University of Murcia, Murcia, Spain) (18) enlisting Spanish food-composition tables (19).

Participants were required to complete the Barriers to Weight Loss checklist (1,2) with careful explanation by a dietetics practitioner to ensure thorough understanding by participants. The 29 questions were classified in seven sections: meal recording, weight control, and weekly interviews; eating habits; portion size; food and drink choice; manner of eating; and other obstacles to weight loss (1). Lastly, summing the scores of all questions yielded a barriers-to-weight-loss score for each participant (2).

For *PER2* genotyping, tag single nucleotide polymorphisms (SNPs) were selected as effective proxies for untyped SNPs in strong linkage disequilibrium (LD) with Tagger (20) based on HapMap Caucasian European Utah data (21) with a minor allele frequency ≥0.10 and a minimum $r2$ of 0.8. SNP selection used three criteria: literature reports of genetic associations or biological function of interest, bioinformatics functional assessment, and LD structure. SNP rs2304672 C>G was genotyped because it was the tagSNP for a large LD block (LD1); it resides in the 5′ untranslated region of *PER2* and bioinformatics functional assessment (22) suggested important changes to mRNA structure; and it was previously linked to psychobehavioral factors (10–12). SNP rs4663302 C>T was chosen because it tags another LD block, it resides 6554 bp upstream of the transcription start site of *PER2*, and has a high minor allele frequency in the Caucasian European Utah population (0.34).

DNA was isolated from blood samples using DNA isolation kits (Qiagen, Valencia, CA). Genotyping was performed with TaqMan assays with allele-specific probes on the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA) according to standardized protocols (23).

Statistical Analyses

A Student *t* test was used to analyze differences between those patients who completed and those who withdrew from treatment. Analysis of variance and Student *t* test were applied to compare crude means across genotype groups. Different genetic inherent models were tested, applying a dominant model in the final analyses for *PER2* SNP rs2304672 C>G, whereas rs4663307 required a recessive model. Multivariate adjustments of the associations by analysis of covariance and estimated adjusted means were performed. Analyses were adjusted for sex, age, initial BMI, and treatment center. The statistical homogeneity of the effects by sex was tested in the corresponding regression model with interaction terms. Logistic regression models were fitted to estimate odds ratio (OR) and 95% confidence interval (CI) of barriers to losing weight associated with attrition, and to detect eating behaviors associated with *PER2* polymorphisms. Statistical analyses employed SPSS (version 15.0, 2007, SPSS Inc, Chicago, IL). A two-tailed *P* value of <0.05 was considered statistically significant. Values in text are expressed as mean±standard error of the mean.

RESULTS AND DISCUSSION

Circadian clocks are composed of proteins that generate self-sustained circadian oscillations through positive and negative transcriptional/translational feedback loops. PERs (periods), together with cryptochromes, are key elements in this system, responsible for negative regulation (6). In our population, minor allele frequencies for two *PER2* polymorphisms were 6.7% for SNP rs2304672 C>G and 35.9% for rs4663302 C>T. *PER2* genotype frequencies did not deviate from Hardy-Weinberg equilibrium for rs2304672 (*P*=0.117) nor for rs4663302 (*P*=0.669).

Significant associations between abdominal obesity and *PER2* genotypes were identified after adjusting for sex, age, treatment center, and initial BMI. For rs4663302 C>T, homozygotes for the minor allele (ie, TT) had significantly higher waist circumference than CT+CC individuals (104.4±1.1 vs 101.8±0.4) (*P*=0.021) and waist-to-hip ratio (0.91±0.01 vs 0.89±0.001) (*P*=0.012). In contrast, G allele carriers of rs2304672 C>G showed the lowest waist-to-hip ratio values (0.87±0.01 vs 0.9±0.003) (*P*=0.015).

One aim of this study was to characterize common traits of patients prone to withdraw from a weight-reduction program. Attrition was considered as the percentage of participants who withdrew before reaching a personal weight-loss goal, typically losing at least 10% of initial weight. Data show that those patients who withdrew from treatment before achieving their weight-loss goals were significantly more obese at the beginning of the treatment and displayed a significantly greater barriers-to-weight-loss score (Table 1). Furthermore, dissecting the weight-loss barrier score by logistic regression analysis indicated that participants who dropped out experienced more frequent stress with dieting (OR 1.47, 95% CI 1.00 to 2.16) (*P*=0.042) and planned eating less frequently than those who successfully

finished the treatment (OR 0.62, 95% CI 0.41 to 0.93) (*P*=0.023). These characteristics could be related to the individual chronotype. Another obstacle to losing weight in this population included feeling stress because of dieting. Participants not completing the program were twice as likely to experience stress with dieting than those who completed it (OR 2.02, 95% CI 1.36 to 3.02) (*P*=0.0001). It has been reported that in some participants, dieting, with its self-imposed restriction, is associated with stress and a number of adverse psychosocial outcomes such as body dissatisfaction, fear of weight gain, and disaffectedness (24,25).

The *PER2* rs4663302 C>T polymorphism was related to attrition (Table 1). Indeed, the presence of the T allele was significantly greater among participants who dropped out than in those who completed treatment (Table 1). No significant differences between both groups were found for rs2304672 C>G, likely because of the low minor allele frequency (6.7%). However, when logistic regression model was used to test the association of *PER2* SNPs with attrition and barriers to weight loss related to eating behavior, results for rs2304672 C>G showed that G allele carriers had a greater probability of attrition, displaying extreme snacking, experiencing stress with dieting, eating when bored, and skipping breakfast than CC noncarriers (Table 2). Computer predictions indicated that this polymorphism, which maps 12 residues upstream of the translation start codon, could alter the secondary structure of the transcript, yielding differential translatability between the two alleles. This observation agrees with changes in folding of the 5′ untranslated region of human *PER2* mRNA predicted by Carpen and colleagues (10).

Previous findings suggested that extreme snacking disrupts the circadian system and vice versa. As light and food are the two main synchronizing factors of central and peripheral oscillators, respectively, it is conceivable that when daily periodic signals of feeding time are suppressed by constant snacking, those circadian rhythms driven by peripheral oscillators become desynchronized from the rhythms controlled by the suprachiasmatic nucleus and entrained by light (6).

Recently it was demonstrated in a large Spanish population (N=34,974) (26) that constant snacking and skipping breakfast are eating behaviors highly associated with obesity. These two eating practices present in G allele carriers of *PER2* rs2304672 C>G could account for the higher degree of attrition and could affect not only short-term weight-loss results, but also long-term maintenance of weight loss.

One limitation of our work is the relatively low number of participants considering the low frequency of the genetic variant *PER2* rs2304672 C>G, particularly among the male population.

CONCLUSIONS

This study provides novel evidence supporting the hypothesis that genetic variation at *PER2* is related to attrition in a weight-treatment program, psychobehavioral characteristics, and eating behavior traits in patients with obesity. Moreover, data support that *PER2* variation is associated with abdominal fat distribution. Future studies may more effectively treat obesity

by identifying *PER2* genetic variants, as these are useful to detect participants more susceptible to dropping out and to personalize behavioral and cognitive techniques.

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Table 1

Comparison between participants who completed and who did not complete treatment for weight reduction based on the Mediterranean diet in research to test for association between polymorphisms in the circadian clock-related gene *PERIOD2* (*PER2*) and obesity treatment attrition

Characteristic	Completed (n=239)	Did not complete (n=215)	*P* value
	←——*mean±standard deviation*——→		
Initial anthropometric			
Age (y)	39.2±11.2	39.3±12.1	0.930
Body mass index	30.2±4.8	32.7±5.4	0.0001*
Body fat (%)	36.5±7.4	38.7±7.5	0.003*
Hip (cm)	112.4±9.3	116.6±10.5	0.0001*
Waist (cm)	100.2±13.2	104.3±14.8	0.002*
Waist-to-hip ratio	0.9±0.7	0.9±0.9	0.671
Glucose (mmol/L)[a]	90.3±23.4	91.2±21.3	0.694
Cholesterol (mmol/L)[b]	175±41	171±40	0.284
Uric acid (mg/dL)[c]	4.4±1.5	4.4±1.5	0.770
Hemoglobin (g/L)[d]	15.0±9.4	14.0±2.4	0.131
Initial behavior habits			
Energy intake (kcal/d)	1,860±708	1,947±711	0.212
Carbohydrates (g/d)	145.7±52.2	151.3±53.2	0.277
Carbohydrates (%)	40.0±11.2	39.2±9.7	0.782
Proteins (g/d)	65.1±27.0	66.0±26.6	0.730
Proteins (%)	17.0±3.8	16.6±3.4	0.252
Fats (g/d)	78.1±39.3	79.8±37.6	0.639
Fats (%)	42.9±11.6	44.1±9.6	0.259
Exercise (MET[e]/wk)	3,993±4155	4,295±4,728	0.478
Total barriers score[f]	4.5±7.5	6.5±8.3	0.011*
Final effectiveness of the treatment			
Total weight loss (kg)	13.2±0.3	4.5±0.3	0.0001*
Percentage of weight loss (%)	15.0±0.3	5.4±0.3	0.0001*

Characteristic	Completed (n=239)		Did not complete (n=215)		*P* value
Rate of weight loss[g] (kg)	0.5±0.2		0.3±0.3		0.0001*
Length of treatment	30.7±16.8		21.6±17.5		0.0001*
***PER2* polymorphism**	*n*	%	*n*	%	
PER2 rs2304672					
CC	196	52.9	26	48.2	
GG+CG	28	51.8	174	47.0	0.885
PER2 rs4663302					
CT+CC	192	52.2	33	61.1	
T/T	21	38.8	176	47.8	0.046*

[a] To covert mmol/L glucose to mg/dL, multiply mmol/L by 18.0. To convert mg/dL glucose to mmol/L, multiply mg/dL by 0.0555. Glucose of 6.0 mmol/L=108 mg/dL.

[b] To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.026. Cholesterol of 5.00 mmol/L=193 mg/dL.

[c] To convert mg/dL uric acid to μmol/L, multiply mg/dL by 59.48. To convert μmol/L uric acid to mg/dL, multiply μmol/L by 0.017. Uric acid of 4.0 mg/dL=238 μmol/L.

[d] To convert g/L hemoglobin to g/dL, multiply g/L by 0.1. To convert g/dL hemoglobin to g/L, multiply g/dL by 10. Hemoglobin of 15 g/L=1.5 g/dL.

[e] MET=metabolic equivalents.

[f] Total barriers score for each subject was calculated by summing the scores to each question from the Barriers to Weight Loss Checklist.

[g] Rate of weight loss (kg) is considered as the weight loss per week, whereas percentage of weight loss refers to the initial weight.

* Statistical significance.

Table 2

Odds ratio (OR) and 95% confidence intervals (CIs) for risk of attrition and having barriers related to eating behaviors across *PERIOD2* (*PER2*) (rs2304672) genotype groups in research to test for association between polymorphisms in the circadian clock-related gene *PER2* and obesity treatment attrition[a]

	Attrition		Extreme Snacking		Stress with Dieting		Are You Liable to Eat when Bored?		Skipping Breakfast	
Genotype group	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
CC (n=376)	1		1		1		1		1	
GG+CG (n=54)	2.12	(1.09–4.10)	2.66	(1.25–5.62)	1.92	(1.01–3.62)	2.21	(0.96–5.05)	1.90	(1.02–3.53)
P value	0.025		0.014		0.040		0.043		0.044	

[a]Adjusted for age, sex, initial body mass index, and clinic.