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14. ABSTRACT- We hypothesize that genetic susceptibility to prostate cancer may be in part due to variations in the core circadian genes that regulate circadian rhythms and that serum sex steroid hormone levels modify the effect that circadian gene variations have on prostate cancer risk. To test this hypothesis, we genotyped and analyzed 256 SNPs in 10 circadian genes in a study of 1,169 prostate cases and 1,365 controls nested within the Prostate Cancer Prevention Trial (PCPT), a randomized placebo-controlled clinical trial to determine if finasteride (an inhibitor of androgen bioactivation) could prevent prostate cancer. Logistic regression analysis using SNPs in an additive model showed that variants in specific circadian genes are associated with prostate cancer risk and that this risk differed between men who took finasteride versus those who took the placebo. The strongest association was seen for a cluster of 9 SNPs in <i>NPAS2</i> , which was associated with total prostate cancer risk in the finasteride group but not in the placebo group. The most significant <i>NPAS2</i> SNP was rs746924 (finasteride group OR=1.5, p=9.6x10 ⁻⁵ versus placebo group OR=0.95, p=0.53). In stratified analysis, the same cluster of <i>NPAS2</i> variants and a second cluster of 9 SNPs on <i>PER3</i> were associated with low-grade cancers (Gleason sum <7) in the finasteride group but not in the placebo group. Interestingly, risk of high-grade cancers (Gleason sum 7+) in the finasteride group was not related to either the <i>NPAS2</i> or <i>PER3</i> clusters of SNPs but was associated with a cluster of 7 SNPs in <i>CRY1</i> . These findings suggest that it may be possible to use genotyping information to identify men who might benefit from chemoprevention by finasteride and other related drugs. We also found that variations in several circadian genes correlated with serum androgen levels and that these associations may be influenced by finasteride treatment. Most notably, a cluster of 12 SNPs in <i>NPAS2</i> were associated with percent change in serum testosterone levels between baseline and follow-up. These observations suggest that it is possible that the underlying biology between the association between variations in circadian genes and prostate cancer risk may involve androgens. Future studies are needed to replicate our findings, determine the functional role of the SNPs identified in our study especially as it related to androgen metabolism, and to determine the utility of genotyping information for chemoprevention strategies.					
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INTRODUCTION:

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in men in the United States. The only established risk factors for prostate cancer are race, age, and family history (1) but data from recent genome-wide association studies indicate that genetic susceptibility also play a role in the etiology of this disease. We propose that genetic susceptibility to prostate cancer may be in part due to variations in genes from a number of pathways including the core circadian genes that regulate circadian rhythms. This hypothesis is supported by observational studies on sleep duration (2), light at night (3), rotating shift workers (4, 5), and male airline pilots (6-8), which all suggest that circadian rhythm disruptions increase prostate cancer risk. The goal of this project is to test the hypothesis that variants in circadian genes alter the risk of prostate cancer and that serum sex steroid hormone levels modify the effect of circadian polymorphisms on prostate cancer risk. Our study is nested within the Prostate Cancer Prevention Trial (PCPT), a randomized placebo-controlled clinical trial to determine if finasteride (an inhibitor of androgen bioactivation) could prevent prostate cancer. Included in our study are 1,169 cases and 1,365 controls from the PCPT. Questionnaire data, such as age, body mass index, and diabetes status, as well as serum hormone measurements from before and mid-trial are available for these subjects, which makes the PCPT an ideal setting in which to test the hypothesis that genetic susceptibility to prostate cancer may be in part due to variations in the core circadian genes that regulate circadian rhythms and that serum sex steroid hormone levels modify the effect that circadian gene variations have on prostate cancer risk..

BODY:

Our study has three specific aims, all of which utilizes genotyping data that was generated as part of the grant. The following is a summary report of each task in the statement of work:

Task 1. Data management

We have been in constant communications with the PCPT Statistical Center at the Fred Hutchinson Cancer Research Center (Seattle, WA) since the project's inception. Genotyping data for this project has been completed and incorporated into the PCPT central database as are data from serum androgen assays (completed as part of a separate study but used for Aim 2 of this study). With the PCPT Statistical Center, we have completed the quality control analysis of the data (see Task 3 below).

Task 2. Develop and perform genotyping assays on 320 SNPs (including 40 putatively functional and 270 tag SNPs as well as additional SNPs to account for control SNPs and potential SNP assay failures) of circadian genes in 1,169 cases and 1,365 controls.

We completed all genotyping assays for the study. In total, genotyping was performed for 285 single nucleotide polymorphisms (SNPs) on 1,169 cases and 1,365 controls. Thirty five SNPs were not genotyped from the original list because they could not be designed on the chosen genotyping platform or were predicted to have very low (<5%) minor allele frequencies in the reference population (HapMap Caucasian population, CEU). Study subjects who were not included in the genotyping did not have sufficiently DNA for genotyping; for these subjects, alternative strategies, including use of serum, were considered but the assays were cost-prohibitive due to additional costs involved for sample processing. A comparison of select characteristics (e.g., age, body mass index, etc) between the genotyped versus not genotyped subjects showed no significant differences

between the 2 subsets of subjects and thus we do not believe bias was introduced due to the reduced sample size.

Task 3. Monitor quality of genotyping results on an ongoing basis

Quality of the genotyping was assessed for SNPs as well as for samples:

SNPs. We assessed SNP genotyping quality by calculating completion rates (i.e., percentage of subjects for whom genotypes were called), concordance rates (for any SNP, the percentage of replicate samples that had the identical genotype called), and Hardy-Weinberg Equilibrium (HWE) p-values. Based on data from all subjects combined (N=2,534), completion rates ranged from 49% to 100%. Specifically, of the 285 SNPs that were typed, completion rates were >75% for 265 (93%) SNPs and >95% for 209 (73%) SNPs. No significant differences in completion rates were seen between cases and controls. For concordance rates, we assessed data from 228 subjects (all control subjects) for whom duplicate DNA were typed for the 285 SNPs. Concordance rate between the 228 sets of duplicate samples ranged from 50.4% to 99.6%; Of the 285 SNPs, concordance rates were >75% for 271 SNPs (96%) and >95% for 197 SNPs (69%). We also assessed Hardy-Weinberg Equilibrium for all SNPs in the control population. HWE p-values ranged from <0.0001 to 1; of the 285 SNPs typed, 265 (82%) had HWE p-value >0.001. For inclusion in subsequent analysis, we included SNPs for which completion rates were >75%, concordance rates were >75%, and HWE p-values were >0.001. In total, 256 SNPs met these criteria.

Subjects. We assessed quality of the samples for each subject by the completion rates as defined as the percentage of SNPs that were successfully genotyped on each sample. Using data from the 256 SNPs that passed quality control described above, 2,126 subjects (83.8%) had data for over 250 SNPs (97.7% completion rate) and all 2,534 subjects had data for over 192 SNPs (75% completion rate). For inclusion in subsequent analysis, we included subjects for which completion rates were >75%. In total, 1,169 prostate cases and 1,365 controls were included in subsequent analysis (Table 1).

Task 4. Gather, ship, process, and archive biospecimens

The DNAs were shipped to and genotyped at the core genotyping facility at the University of Texas Health Science Center in San Antonio. This task was the most time consuming as the PCPT biorepository at the NCI had a backlog of requests for sample preparation for genotyping. In addition, the PCPT cohort changed genotyping laboratories for all PCPT genetic studies in 2010.

Task 5. Prepare hormone data from PCPT

As part of a separately funded study, we worked with the PCPT Statistical Center on analyzing data related to serum androgen levels as part of the PCPT Program Project. Dr. Ann Hsing, the PI of the current award, led the analysis and is the senior author of the recently published main manuscript describing the results (9). We use the androgen data from this previous study, including how the variables are categorized, in Aim 2 of the current study.

Tasks 6. Perform statistical analysis

Statistical analysis has been completed for main effects of SNPs in circadian genes on prostate cancer risk (Aim 1; Tables 2-3 & Figures 1-3) and serum androgen levels (Aim 3; Tables 4-5 &

Figures 4-6). We are currently finalizing the gene- and circadian pathway-based analyses. This part of the analysis was delayed due to the updating of the statistical software used for the analysis (10), which was released in August 2012 (AdaJoint; <http://dceg.cancer.gov/bb/tools/AdaJoint>). We anticipate this analysis will be completed by January 2013.

For Aim 2, we are currently analyzing the joint effects between SNPs and serum androgens on prostate cancer risk. This analysis requires a higher level of statistical analysis than Aims 1 and 3 and thus takes more time to accomplish. We anticipate this analysis to be completed by April 2013.

Task 7. Prepare scientific presentations & manuscripts

Preliminary data on a subset of the genotyping data was presented at the DoD PCRP IMPaCT Meeting in Orlando, FL in March 2011.

We are currently finalizing the gene- and circadian pathway-based analysis for Aims 1 and 3. Once the gene- and pathway-based analyses are complete, we will draft the manuscripts (separately for Aims 1 and 3) and anticipate submission of the manuscript to a peer-reviewed journal (e.g., Cancer Research, Cancer Prevention Research, etc) within 6 months time. Similarly, we anticipate completion of statistical analysis for Aim 2 by April 2013 with a subsequent manuscript to be drafted and submitted to a peer-reviewed journal within 6 month from end of analysis.

KEY RESEARCH ACCOMPLISHMENTS:

- Our study showed risks for prostate cancer related to variations in circadian genes are different between the finasteride group and the placebo group of the PCPT (Table 2). This suggests that finasteride modifies the effect that SNPs in circadian genes have on prostate cancer risk.
 - A cluster of 9 SNPs in *NPAS2* was associated with total prostate cancer risk in the finasteride group but not in the placebo group (Tables 2-3 & Figure 1). The most significant *NPAS2* SNP was rs746924 (finasteride group: OR=1.5, $p=9.6 \times 10^{-5}$ versus placebo group: OR=0.95, $p=0.53$); this SNP reached Bonferroni-corrected p-value threshold of 1.95×10^{-4} .
 - The same cluster of *NPAS2* SNPs and a cluster of 9 SNPs in *PER3* were associated with risk for low-grade prostate cancer in the finasteride treated group and not in the placebo group (Tables 2-3 & Figure 2).
 - For high-grade prostate cancer, neither the *NPAS2* nor the *PER3* SNP clusters were associated with risk in the finasteride group but a cluster of 7 SNPs in *CRY1* was associated with risk in the finasteride group but not in the placebo group (Tables 2-3 & Figure 3).
- Our study also showed correlation between some SNPs in specific circadian genes and serum androgen and SHBG levels (Table 4). These correlations also seem to be influenced by finasteride treatment (Table 4).
 - Most notably, 12 SNPs in *NPAS2* were associated with percent change in serum testosterone levels between baseline and follow-up (Tables 4-5 & Figure 4).
 - No obvious cluster of SNPs in any circadian gene was associated with baseline, follow-up, or percent change in 3 α diol G (Table 4 & Figure 5). Several individual SNPs in *CSNK1E*, *NPAS2*, and *PER3* were correlated with 3 α diol G at baseline and follow-up at $p < 0.01$.

- Several variants in *NPAS2* were associated with serum SHBG during finasteride treatment but not with change in SHBG levels between baseline and follow-up (Tables 4-5 & Figure 6)

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

- Presentations
 - DoD PCRP IMPaCT Meeting in Orlando, FL in March 2011.
- Manuscripts
 - At least two manuscripts to be submitted within 6-12 months of this report
- Informatics such as databases
 - Data from 285 SNPs have been added to the PCPT database at the statistical center.
- Funding applied for based on work supported by this award
 - R03 Circadian Genes and Aggressive Prostate Cancer in Caucasians and African Americans (PI: Ann Hsing, submitted July 2012)
- Employment or research opportunities applied for and/or received based on experience/training supported by this award
 - Co-PI (Lisa Chu) is now a Senior Staff Scientist at the Cancer Prevention Institute of California

CONCLUSION:

The goal of this project was to test the novel hypothesis that variants in circadian genes alter the risk of prostate cancer and that serum sex steroid hormone levels modify the effect of circadian polymorphisms on prostate cancer risk. Through our preliminary analysis of the data for prostate cancer risk (total, low- and high-grade cancers), we show that certain variants in specific circadian genes influences prostate cancer risk. We also show that the effects of the SNPs on prostate cancer risk are modifiable by treatment with finasteride. We see similar effects when restricting our analysis to low- and high-grade prostate cancers. These results show that it may be possible to develop methods to use genotyping information to select men who might benefit from chemoprevention. We also showed that some variations in circadian genes correlate with serum androgen levels and that this correlation may be influenced by finasteride treatment. These observations suggest that it is possible that the underlying biology between the association between variations in circadian genes and prostate cancer risk may involve androgens. Future studies are needed to replicate our findings, determine the functional role of the SNPs identified in our study especially as it related to androgen metabolism, and to determine the utility of genotyping information for chemoprevention trials.

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APPENDICES:

NONE

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Figure 6.	Correlation between individual circadian gene variants on serum sex hormone-binding globulin (SHBG) levels in the finasteride-treated men

Table 1. Select Characteristics of Study Subjects

Characteristic (categorical)	Placebo Group										Finasteride Group									
	Total					White					Minority					White				
	Controls		Cases		p-value	Controls		Cases		p-value	Controls		Cases		p-value	Controls		Cases		p-value
	n	%	n	%		n	%	n	%		n	%	n	%		n	%	n	%	
Number of Participants	1365		1169			667		642			118		43			422		450		
Body Mass Index (BMI; Baseline)					0.09															
Normal (BMI <25)	328	24.3%	324	28.0%		157	23.9%	192	30.2%		24	20.3%	7	16.3%		106	25.2%	117	26.2%	
Overweight (BMI 25 to <30)	718	53.2%	598	51.6%		357	54.4%	331	52.1%		63	53.4%	22	51.2%		234	55.7%	227	50.8%	
Obese (BMI >=30)	304	22.5%	237	20.4%		142	21.6%	112	17.6%		31	26.3%	14	32.6%		80	19.0%	103	23.0%	
Alcohol Consumption					0.25															
Non-drinker	320	23.4%	243	20.8%		150	22.5%	132	20.6%		33	28.0%	12	27.9%		99	23.5%	90	20.0%	
>0 to <30 g/day Alcohol	928	68.0%	816	69.8%		458	68.7%	455	70.9%		75	63.6%	29	67.4%		281	66.6%	308	68.4%	
>=30 g/day Alcohol	117	8.6%	110	9.4%		59	8.8%	55	8.6%		10	8.5%	2	4.7%		42	10.0%	52	11.6%	
Smoking Status					0.21															
Never Smoker	454	33.3%	414	35.4%		230	34.5%	229	35.7%		35	29.7%	15	34.9%		149	35.3%	159	35.3%	
Current Smoke	103	7.5%	70	6.0%		45	6.7%	34	5.3%		17	14.4%	7	16.3%		25	5.9%	26	5.8%	
Former Smoker	808	59.2%	685	58.6%		392	58.8%	379	59.0%		66	55.9%	21	48.8%		248	58.8%	265	58.9%	
Has Family History of Prostate Cancer	290	21.2%	245	21.0%	0.86	142	21.3%	135	21.0%		19	16.1%	7	16.3%		106	25.1%	101	22.4%	
Has Diabetes	109	8.0%	51	4.4%	<0.001	44	6.6%	21	3.3%		16	13.7%	3	7.0%		17	4.0%	21	4.7%	
Race					<0.0001															
White (Non-Hispanic)	1089	79.8%	1092	93.4%		667	100.0%	642	100.0%							422	100.0%	450	100.0%	
Black	130	9.5%	47	4.0%							49	41.5%	27	62.8%				81	51.3%	
Other	146	10.7%	30	2.6%							69	58.5%	16	37.2%				77	48.7%	
Gleason Sum																				
2-6			829	73.4%				499	80.3%				28	68.2%				283	65.2%	
7-10			301	26.6%				122	19.6%				13	31.8%				151	34.8%	
T-stage																				
T1 a/b/c			903	79.3%				506	80.8%				31	75.6%				341	78.0%	
T2 a/b/c			221	19.4%				113	18.1%				9	22.0%				90	20.6%	
T 3/4			14	1.2%				7	1.1%				1	2.4%				6	1.4%	
N-stage																				
N X/0			1110	99.5%				607	99.3%				41	100.0%				428	99.5%	
N 1/2			6	0.5%				4	0.7%									2	0.5%	
M-stage																				
M X/0			1113	99.7%				609	99.7%				41	100.0%				429	99.8%	
M1			3	0.3%				2	0.3%									1	0.2%	
Characteristics (continuous)	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age (Baseline)	63.61	0.06	63.44	0.06	0.46	63.75	5.66	63.48	5.59		62.14	4.95	61.51	4.98		64.33	5.76	63.58	5.57	
BMI (Baseline)	27.71	4.02	27.41	4.04	0.06	27.63	3.96	27.14	4.02		28.03	4.07	29.38	5.50		27.61	3.92	27.55	3.82	
Alcohol Consumption, g/day	9.15	14.03	10.02	14.71	0.12	9.27	13.81	9.48	13.39		9.00	16.64	6.65	10.14		9.71	14.49	11.50	16.95	
Pack-Years of Cigarettes Smoked	15.54	16.90	13.55	15.79	<0.01	16.03	17.55	13.18	15.41		14.90	15.86	10.99	14.45		15.72	16.96	14.41	16.44	

Table 2. Summary of variants in circadian genes and their associations with prostate cancer

Gene	# SNPs Genotyped	# SNPs associated with Total Prostate Cancer Risk				# SNPs associated with Low-Grade Prostate Cancer Risk				# SNPs associated with High-Grade Prostate Cancer Risk			
		Placebo Group		Finasteride Group		Placebo Group		Finasteride Group		Placebo Group		Finasteride Group	
		p<0.01	p<0.05	p<0.01	p<0.05	p<0.01	p<0.05	p<0.01	p<0.05	p<0.01	p<0.05	p<0.01	p<0.05
<i>ARNTL</i>	28	0	0	1	4	0	2	0	3	0	0	1	1
<i>CLOCK</i>	14	0	0	0	1	0	0	0	0	0	0	0	1
<i>CRY1</i>	22	1	4	0	1	1	5	0	0	0	0	3	7
<i>CRY2</i>	16	0	0	0	0	0	0	0	0	1	2	0	0
<i>CSNK1E</i>	23	0	2	0	1	0	3	0	0	1	2	0	0
<i>NPAS2</i>	79	1	3	7	9	0	1	6	10	1	4	0	1
<i>PER1</i>	17	0	1	0	1	0	0	0	0	0	1	0	0
<i>PER2</i>	24	0	1	0	0	0	0	0	0	1	5	0	0
<i>PER3</i>	30	0	0	0	3	0	1	2	9	1	6	0	1
<i>TIMELESS</i>	2	0	0	0	0	0	0	0	0	0	0	0	0
<i>Total</i>	255	2	11	8	20	1	12	8	22	5	20	4	11

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for total, low-, and high-grade prostate cancer in relation to SNPs in circadian genes with P-value <0.05 in the PCPT nested case-control study

p<0.01 p<0.05				Total Prostate Cancer Risk												Low Grade Prostate Cancer Risk												High Grade Prostate Cancer Risk																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
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				MAF		Controls	Cases	OR	95% CI	p-value	MAF		Controls	Cases	OR	95% CI	p-value	MAF		Controls	Cases	OR	95% CI	p-value	MAF		Controls	Cases	OR	95% CI	p-value	MAF		Controls	Cases	OR	95% CI	p-value																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					

Table 4. Summary of variants in circadian genes and their associations with serum androgens and sex hormone-binding globulin (SHBG)

Gene	# SNPs Genotyped	# SNPs associated with Testosterone at p<0.05			# SNPs associated with 3 α Diol G at p<0.05			# SNPs associated with SHBG at p<0.05		
		All controls	Finasteride controls		All controls	Finasteride controls		All controls	Finasteride controls	
		Baseline	Follow-up	% Change	Baseline	Follow-up	% Change	Baseline	Follow-up	% Change
<i>ARNTL</i>	28	0	0	0	2	2	3	0	0	4
<i>CLOCK</i>	14	0	7	0	0	0	0	3	0	5
<i>CRY1</i>	22	0	3	2	0	1	0	0	0	0
<i>CRY2</i>	16	4	0	1	0	0	0	0	2	1
<i>CSNK1E</i>	23	1	0	2	2	2	0	4	3	1
<i>NPAS2</i>	79	2	2	12	3	5	4	3	12	2
<i>PER1</i>	17	2	1	1	0	2	0	1	0	1
<i>PER2</i>	24	2	2	1	3	2	0	0	3	3
<i>PER3</i>	30	1	1	0	5	0	0	1	1	0
<i>TIMELESS</i>	2	0	0	0	0	0	0	0	0	1
<i>Total</i>	255	12	16	19	15	14	7	12	21	18

Table 5. Correlation between SNPs in circadian genes and serum androgens and SHBG with P-value <0.05 in the PCPT nested case-control study

Gene	SNP	Chr	Location	Testosterone												3α Diol G												Sex Hormone-Binding Globulin (SHBG)																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
				All Controls						Finasteride Group Controls						All Controls						Finasteride Group Controls						All Controls						Finasteride Group Controls																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																												
				Baseline			Follow-up			Percent Change			Baseline			Follow-up			Percent Change			Baseline			Follow-up			Percent Change			Baseline			Follow-up			Percent Change																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																									
				β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
ARNTL	rs12421920	11	13249759	-7.70	-26.63, 11.22	0.4252	-2.89	-37.89, 32.11	0.8713	-1.53	-9.6, 6.54	0.7102	0.05	-0.03, 0.13	0.2095	-0.28	-0.47, -0.09	0.0036	-0.19	-0.36, -0.03	0.0222	0.02	-0.03, 0.08	0.4199	0.05	-0.04, 0.14	0.2671	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.02	-0.08, 0.03	0.3621	-0.

Table 5. Correlation between SNPs in circadian genes and serum Androgens and SHBG with P-value<0.05 in the PCPT nested case-control study (cont.)

Gene	SNP	Chr	Location	Testosterone									3α Diol G									Sex Hormone-Binding Globulin (SHBG)								
				All Controls			Finasteride Group Controls						All Controls			Finasteride Group Controls						All Controls			Finasteride Group Controls					
				Baseline			Follow-up			Percent Change			Baseline			Follow-up			Percent Change			Baseline			Follow-up			Percent Change		
				β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
				β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
PER1	rs3809882	17	7999589	13.01	1.64, 24.37	0.0251	21.97	0.39, 43.55	0.0467	-0.10	-5.1, 4.89	0.9679	-0.03	-0.07, 0.02	0.3103	0.02	-0.1, 0.13	0.7749	0.04	-0.06, 0.14	0.4500	0.02	-0.01, 0.05	0.2147	0.05	0, 0.11	0.0535	-0.01	-0.05, 0.02	0.4626
	rs9894356	17	8006312	-13.37	-26.15, -0.58	0.0407	-18.22	-42.57, 6.14	0.1435	-1.77	-7.38, 3.84	0.5372	0.01	-0.04, 0.07	0.6730	0.02	-0.11, 0.15	0.7708	0.00	-0.12, 0.11	0.9559	0.01	-0.03, 0.05	0.5533	-0.03	-0.09, 0.04	0.3936	-0.01	-0.05, 0.03	0.5991
	rs9912048	17	8008535	8.54	-3, 20.09	0.1470	-6.16	-26.49, 14.16	0.5525	-2.71	-7.39, 1.96	0.2565	0.01	-0.04, 0.06	0.7787	0.11	0, 0.22	0.0431	0.05	-0.04, 0.15	0.2644	0.03	0, 0.07	0.0441	-0.04	-0.09, 0.01	0.1329	-0.05	-0.08, -0.02	0.0032
	rs7215658	17	8010164	4.10	-9.35, 17.55	0.5504	6.08	-18.37, 30.54	0.6261	-2.21	-7.84, 3.43	0.4433	-0.02	-0.08, 0.04	0.4643	-0.14	-0.28, -0.01	0.0318	-0.05	-0.16, 0.07	0.4302	0.00	-0.03, 0.04	0.8370	0.02	-0.04, 0.08	0.5309	-0.02	-0.06, 0.02	0.2630
	rs3027267	17	8090895	5.52	-15.07, 26.11	0.5995	-22.57	-58.64, 13.51	0.2210	-10.41	-18.8, -2.01	0.0156	0.03	-0.06, 0.12	0.5134	0.13	-0.06, 0.32	0.1759	0.04	-0.13, 0.2	0.6851	0.01	-0.05, 0.07	0.6751	-0.01	-0.1, 0.08	0.8420	-0.03	-0.08, 0.03	0.3323
PER2	rs7558403	2	239103749	-8.07	-19.51, 3.38	0.1673	-1.62	-22.2, 18.96	0.8777	-0.57	-5.21, 4.06	0.8084	-0.05	-0.1, 0	0.0343	0.03	-0.08, 0.14	0.6050	0.05	-0.05, 0.15	0.3126	-0.03	-0.06, 0	0.0821	-0.02	-0.07, 0.04	0.5722	0.02	-0.01, 0.05	0.1804
	rs4663863	2	239121733	7.12	-5.84, 20.07	0.2821	6.33	-17.59, 30.25	0.6044	-4.12	-9.62, 1.38	0.1430	0.06	0.01, 0.12	0.0251	0.00	-0.13, 0.13	0.9709	-0.06	-0.17, 0.05	0.2938	0.01	-0.03, 0.05	0.6309	0.06	0, 0.12	0.0556	-0.01	-0.05, 0.03	0.6269
	rs6722019	2	239128117	14.76	3.65, 25.87	0.0094	0.74	-19.41, 20.89	0.9426	1.11	-3.53, 5.75	0.6391	0.06	0.01, 0.1	0.0208	0.04	-0.07, 0.15	0.4350	-0.06	-0.15, 0.04	0.2168	0.03	0, 0.06	0.0690	-0.01	-0.06, 0.04	0.6875	-0.03	-0.06, 0	0.0353
	rs2305174	2	239133324	7.06	-9.77, 23.89	0.4112	9.04	-20.79, 38.87	0.5529	3.55	-3.36, 10.46	0.3143	-0.02	-0.1, 0.05	0.5498	-0.16	-0.33, 0	0.0497	-0.06	-0.2, 0.08	0.4118	0.00	-0.05, 0.04	0.9226	0.03	-0.05, 0.11	0.4096	0.00	-0.05, 0.05	0.9508
	rs56386336	2	239153948	-0.55	-15.56, 14.46	0.9427	-28.04	-56.47, 0.39	0.0539	0.28	-6.34, 6.9	0.9340	-0.01	-0.07, 0.06	0.8140	0.08	-0.08, 0.23	0.3331	-0.01	-0.14, 0.13	0.8912	-0.02	-0.06, 0.02	0.3211	-0.09	-0.17, -0.02	0.0132	-0.02	-0.06, 0.02	0.3567
	rs11894535	2	239177073	-7.84	-21.54, 5.87	0.2627	-39.70	-65.93, -13.47	0.0032	0.03	-6.04, 6.1	0.9931	0.02	-0.04, 0.08	0.4760	0.06	-0.08, 0.2	0.4280	-0.02	-0.14, 0.1	0.7646	-0.02	-0.06, 0.02	0.2999	-0.10	-0.17, -0.03	0.0037	-0.02	-0.06, 0.02	0.2406
	rs2304673	2	239185922	-1.93	-17.08, 13.23	0.8031	-32.10	-60.99, -3.21	0.0300	-0.80	-7.49, 5.9	0.8158	0.00	-0.07, 0.06	0.9714	0.08	-0.07, 0.24	0.3070	-0.02	-0.15, 0.12	0.8272	-0.02	-0.06, 0.02	0.3556	-0.09	-0.16, -0.01	0.0264	-0.02	-0.07, 0.02	0.2705
	rs7595976	2	239215744	-0.83	-12.09, 10.42	0.8848	12.99	-7.21, 33.19	0.2082	1.71	-2.96, 6.38	0.4728	0.00	-0.05, 0.05	0.9941	-0.07	-0.18, 0.04	0.1967	0.00	-0.09, 0.1	0.9261	0.00	-0.03, 0.03	0.8776	0.03	-0.02, 0.08	0.2984	0.03	0, 0.06	0.0456
	rs7599697	2	239231477	12.17	0.99, 23.35	0.0331	12.12	-7.8, 32.04	0.2337	-1.19	-5.75, 3.36	0.6084	-0.01	-0.06, 0.04	0.7006	0.06	-0.05, 0.16	0.3194	0.04	-0.06, 0.13	0.4618	0.01	-0.02, 0.05	0.3646	0.03	-0.02, 0.08	0.2149	-0.03	-0.06, 0	0.0756
	rs6737780	2	239235287	-11.22	-23.84, 1.39	0.0815	9.35	-13.57, 32.27	0.4243	5.31	0.03, 10.59	0.0496	0.01	-0.05, 0.06	0.8273	-0.10	-0.23, 0.02	0.0953	-0.05	-0.16, 0.05	0.3344	-0.02	-0.05, 0.02	0.3237	0.00	-0.06, 0.06	0.9332	0.04	0.01, 0.07	0.0236
PER3	rs1417986	1	7797734	-2.39	-13.54, 8.76	0.6744	4.39	-14.96, 23.75	0.6567	-0.64	-5.11, 3.82	0.7774	-0.08	-0.13, -0.03	0.0012	-0.03	-0.14, 0.07	0.5174	0.05	-0.04, 0.14	0.2765	0.00	-0.03, 0.03	0.8935	0.04	-0.01, 0.09	0.1146	0.00	-0.03, 0.03	0.8420
	rs2066293	1	7810543	-4.60	-16.76, 7.55	0.4580	8.37	-12.27, 29.01	0.4272	2.15	-2.63, 6.93	0.3789	-0.08	-0.13, -0.03	0.0020	-0.05	-0.16, 0.07	0.4168	0.03	-0.06, 0.13	0.5019	-0.01	-0.05, 0.02	0.4943	0.04	-0.02, 0.09	0.1949	0.01	-0.03, 0.04	0.7369
	rs2640908	1	7889941	-16.36	-30.65, -2.07	0.0251	-9.45	-34.04, 15.14	0.4518	3.14	-2.52, 8.8	0.2772	-0.06	-0.13, 0	0.0417	-0.07	-0.21, 0.06	0.2703	0.00	-0.12, 0.12	0.9991	-0.03	-0.07, 0.01	0.1686	-0.01	-0.08, 0.05	0.6754	0.02	-0.01, 0.06	0.2143
	rs707476	1	7918106	-6.00	-17.79, 5.8	0.3192	14.84	-6.72, 36.41	0.1781	2.20	-2.78, 7.17	0.3876	-0.05	-0.1, 0	0.0404	-0.08	-0.19, 0.04	0.1982	-0.03	-0.14, 0.07	0.5139	-0.02	-0.05, 0.02	0.3747	0.05	-0.01, 0.1	0.1138	0.03	0, 0.06	0.0817
	rs579992	1	7927981	-4.22	-22.67, 14.22	0.6539	0.63	-33.25, 34.51	0.9711	-1.53	-9.33, 6.27	0.7009	-0.11	-0.19, -0.03	0.0070	-0.06	-0.24, 0.12	0.5277	0.05	-0.11, 0.21	0.5747	-0.03	-0.08, 0.02	0.2677	0.02	-0.06, 0.11	0.5843	0.02	-0.03, 0.07	0.4554
	rs1040397	1	7952427	4.07	-7.29, 15.43	0.4828	20.84	0.31, 41.38	0.0473	1.14	-3.66, 5.94	0.6422	0.02	-0.03, 0.07	0.5007	0.01	-0.1, 0.13	0.8016	-0.02	-0.12, 0.08	0.7451	0.04	0.01, 0.07	0.0103	0.06	0, 0.11	0.0405	0.00	-0.03, 0.04	0.7952
TIMELESS	rs774047	12	56815922	5.22	-5.59, 16.03	0.3439	7.42	-11.97, 26.82	0.4535	-0.03	-4.5, 4.44	0.9891	-0.03	-0.07, 0.02	0.2335	-0.07	-0.17, 0.04	0.2222	-0.03	-0.12, 0.06	0.5082	0.01	-0.02, 0.04	0.4084	0.02	-0.03, 0.07	0.3700	-0.03	-0.06, 0	0.0241

Figure 1. Main effects of individual circadian gene variants on total prostate cancer risk in men in the PCPT by treatment group

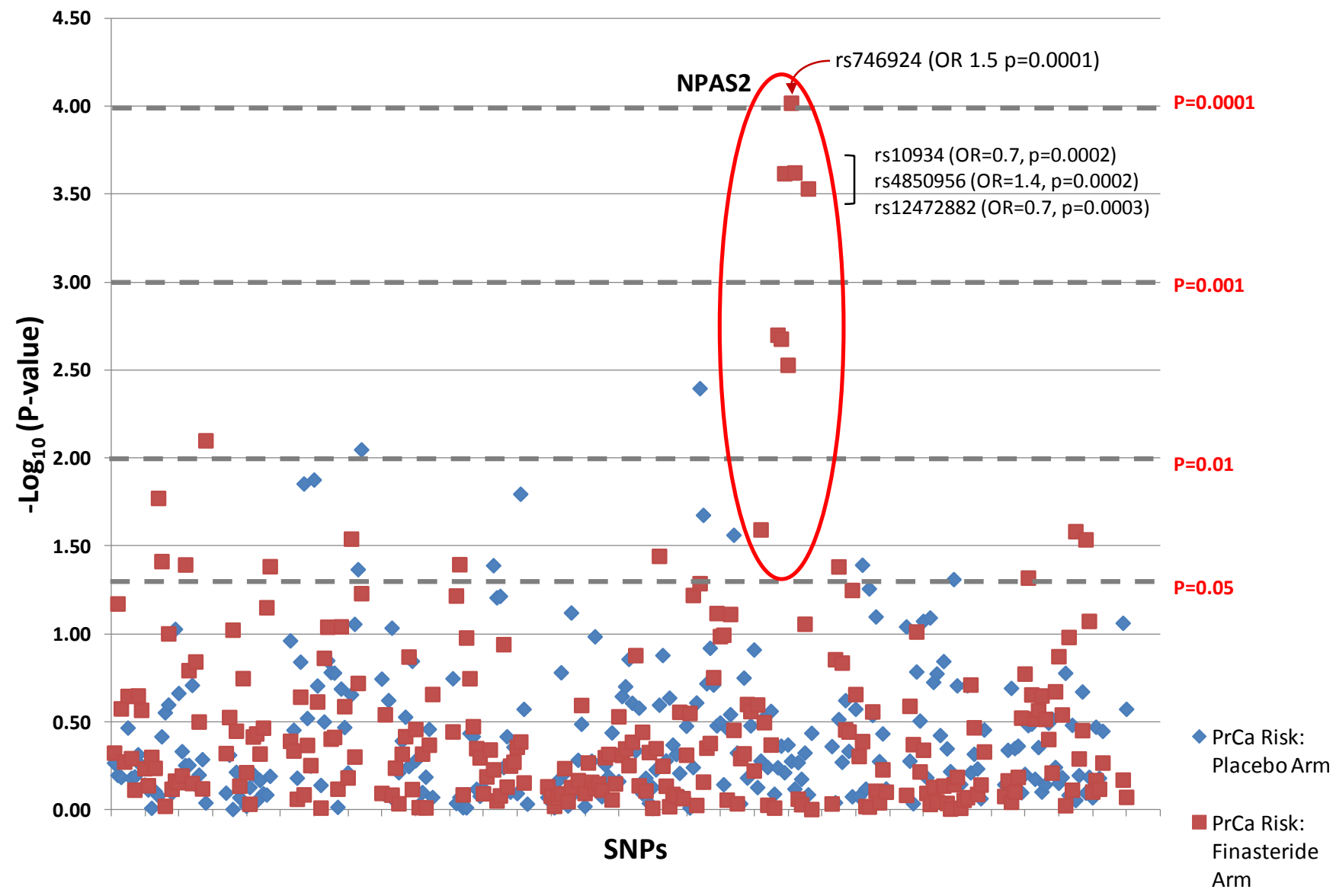


Figure 2. Main effects of individual circadian gene variants on low-grade prostate cancer risk in the PCPT by treatment group

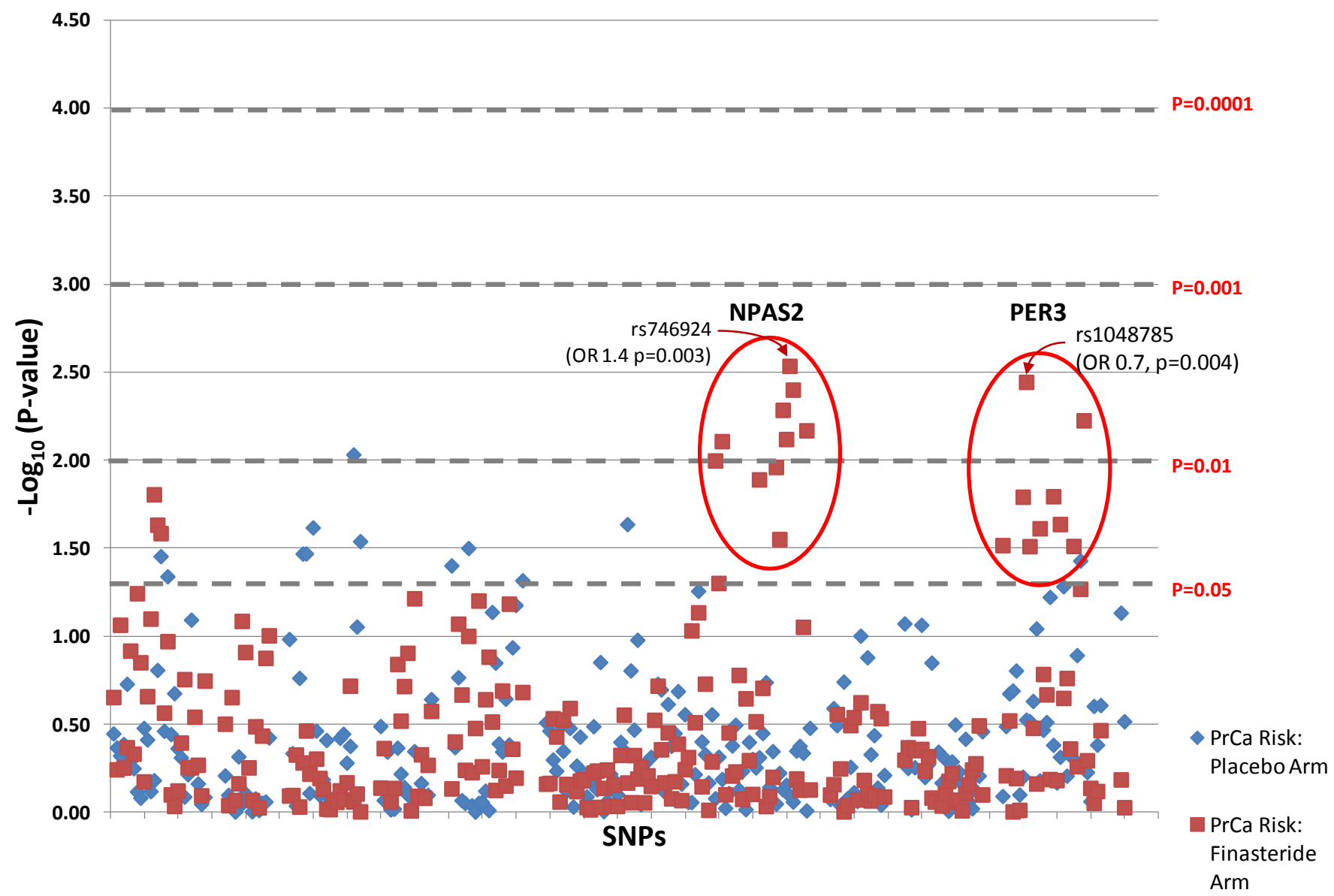


Figure 3. Main effects of individual circadian gene variants on high-grade prostate cancer risk in the PCPT by treatment group

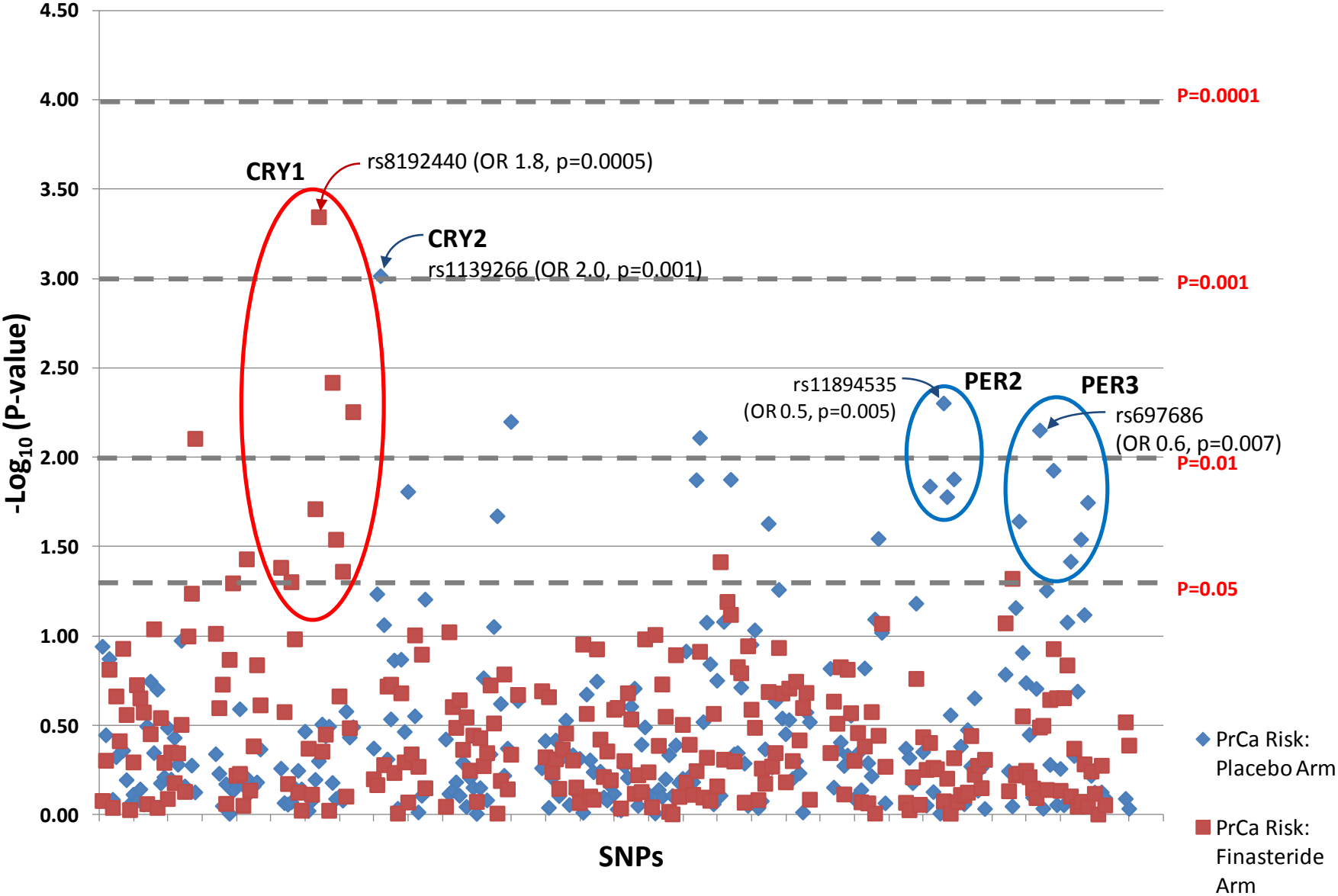


Figure 4. Correlation between individual circadian gene variants on total serum testosterone levels in the finasteride-treated men

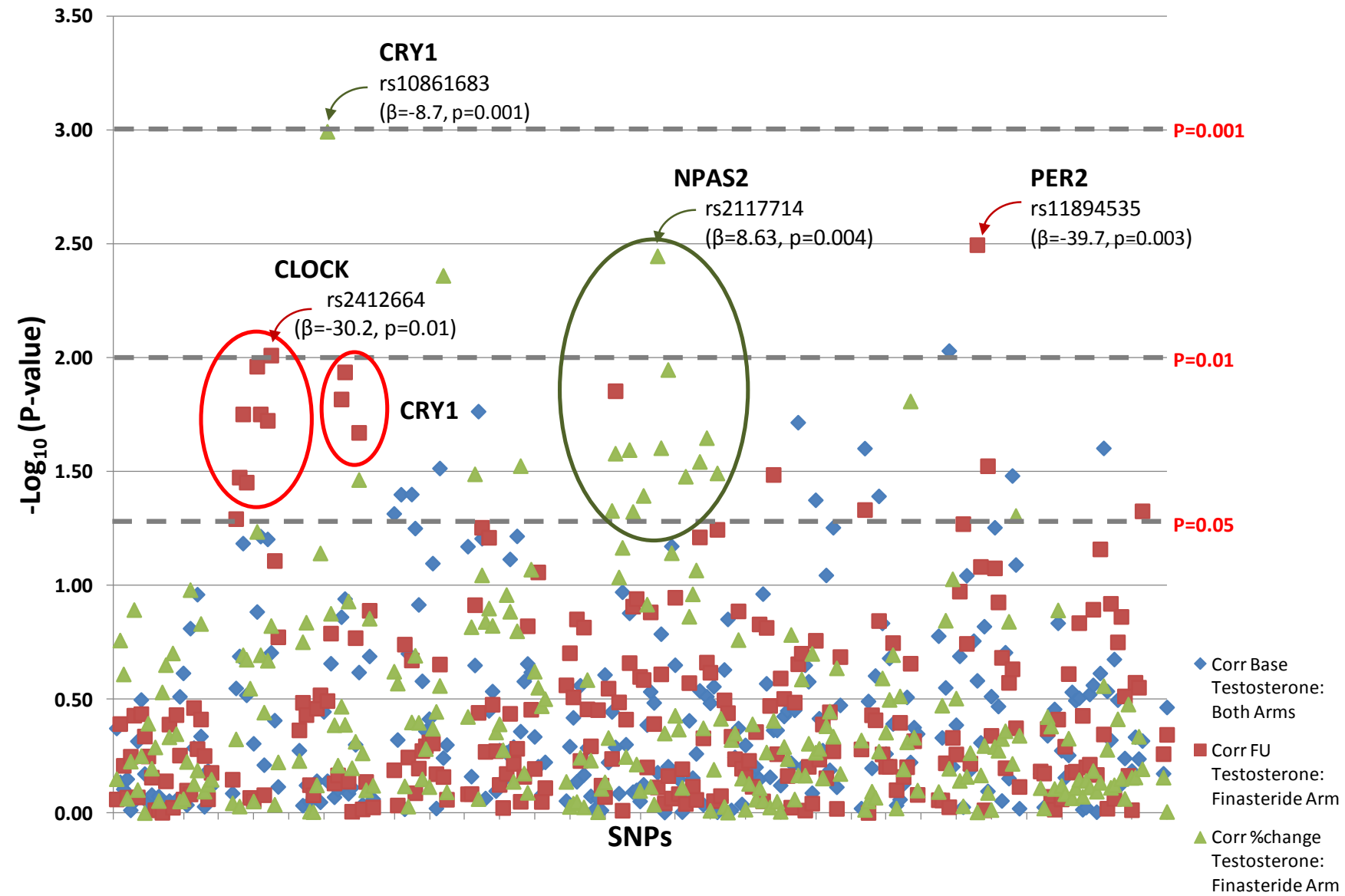


Figure 5. Correlation between individual circadian gene variants on serum 3α diol G levels in the finasteride-treated men

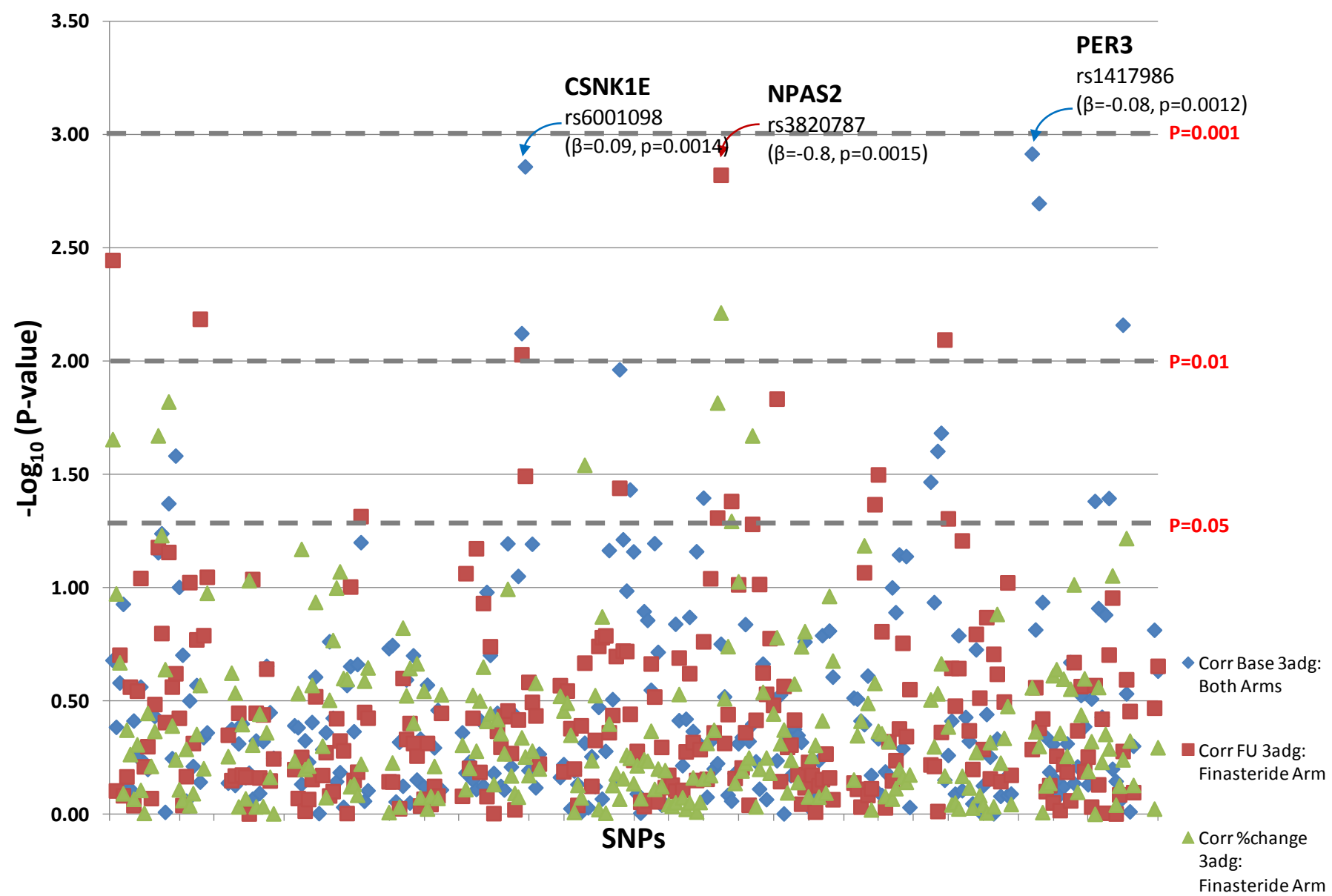


Figure 6. Correlation between individual circadian gene variants on serum sex hormone-binding globulin (SHBG) levels in the finasteride-treated men

