

Polymorphic Variation in Human Circadian Genes in Mental Illness

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Abstract: Over a seven-year period, we collected DNA samples from upwards of 2,000 subjects suffering from various forms of mental illness. PCR-amplified material from all exons of nine genes (*BMAL1*, *BMAL2*, *CRY1*, *CRY2*, *CLOCK*, *NPAS2*, *PER1*, *PER2* and *PER3*) involved in controlling circadian rhythm was subjected to denaturing HPLC (dHPLC) analytic methods to identify polymorphic variations. DNA samples with aberrant chromatographic behavior were directly sequenced in order to define the identities of polymorphic variants. 2012 subjects were screened for genetic variations (GVs) in *PER1* and *PER3*. A subset of these 2012 subjects (288 subjects) was randomly selected for rapid additional screening for GV in *BMAL1*, *BMAL2*, *CRY1*, *CRY2*, *CLOCK*, *NPAS2* and *PER2*. We report here all GV identified in these nine genes, as well as pertinent characteristics of the subjects identified with exonic GV producing changes in amino acid sequence. We have categorized and ranked these GV in order to identify those that we judge to have the most compelling likelihood of functionally affecting the product of the relevant gene. The majority of our most compelling GV were found in the *PER3* gene. Overall, we identified almost twice as many GV in *PER3* as in *PER1*. Comparison of the conservation of amino acid sequences of *PER1*, *PER2* and *PER3* in all species from which their genes have been fully sequenced shows that *PER3* is significantly less conserved than *PER1* and *PER2*. Such observations indicate that *PER3* may be under less stringent selective pressure than the paralogous *PER1* and *PER2* genes. We have also demonstrated that one of our most highly ranked GV, a double mutation in *PER3* that changes amino acid residues 414 (P414A) and 416 (H416R) directly adjacent to the nuclear export sequence, affects *PER3* nuclear localization. Surprisingly, this identical GV was observed independently in 4 unrelated patients. We further consider possible implications of other apparently compelling GV on protein function. It is our hope that publication of this work on www.mcknightlab.com will facilitate resolution of the hypothesis that functionally relevant GV in the genes controlling circadian rhythm

might be involved in the pathophysiology of some forms of mental illness.

Introduction: The behavior of most organisms shows 24-hour rhythmicity controlled by an endogenous circadian timing system that is synchronized to daily and seasonal changes in external time cues. The mammalian circadian timing system is composed of a hierarchy of dispersed oscillators in most cells and peripheral tissues. These oscillators consist of interconnected genes whose products generate a self-sustaining transcriptional-translational feedback cycle having a free-running period of about 24 hours. This oscillatory cycle can be entrained by photic input to the master clock localized within the bilaterally paired suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The SCN receives photic input from the retinohypothalamic tract, which projects neuronal output principally to the hypothalamus, midline thalamus and basal forebrain (reviewed in 1 and 2). The entrainment of the master clock to light is believed to be the mechanism by which circadian oscillators are synchronized to local time. Circadian oscillators can also be entrained by daily cycles of restricted food availability (3,4,5,6,7).

The function of the highly organized circadian timing system is generally understood to anticipate environmental changes that implement physiology and behavior at biologically advantageous times. Although human life is largely organized into a 24-hour schedule consisting of periods of wakefulness and sleep, modern technology permits us to readily escape temporal constraints that would otherwise be imposed by the natural environment. Because human physiology has not maintained pace with technology, we are now faced with medical and social implications of circadian rhythms. For example, performing tasks at times of the day when psychomotor capabilities are suboptimal can confer functional and safety consequences in normally healthy individuals, such as shifting work schedules in medical personnel, airplane pilots, air traffic controllers, security workers, military personnel, and commercial truck drivers (reviewed in 8). In addition, efficacy and toxic side effects of some medications in the treatment of serious medical disorders like cancer may also depend on timing of delivery in

relation to circadian rhythms (reviewed in 9). Furthermore, malfunctions of the human circadian timing system have been implicated in myriad medical disorders, including breast cancer (10,11,12,13,14,15,16), chronic sleep disorders in the elderly, bipolar disorder, depression, and seasonal affective disorder (SAD) (reviewed in 17 and 18).

The extent to which circadian disturbances are causal manifestations of a medical disorder or secondary downstream effects of any given disease is unknown. Much research to date has pursued identification of polymorphisms in human circadian genes in subjects with medical disorders having a strong circadian component. For example, two rare single nucleotide polymorphisms have been found in *CLOCK* (T3117G and G3125A) in a small number of individuals with affective disorder (17). More strikingly, a C to T nucleotide substitution in position 3111 of human *CLOCK* cDNA has been associated with sleep disturbances (18,19), recurrence rate in mood disorders (20), and morningness-eveningness preference (21). The morningness–eveningness dimension is a continuum upon which individuals are arranged from the morning-type (“lark”) to the evening-type (“owl”). Most individuals fall into an intermediate group, and this continuum is associated with individual differences in academic, professional and sport performance, as well as personality traits and psychopathologic risk factors (22,23,24,25).

PER2 has also been associated with an autosomal dominant familial form of advanced sleep phase syndrome (ASPS) by virtue of a missense mutation that replaces a critical serine residue, normally phosphorylated by CKIε, with glycine (26). This mutated human *PER2* is hypophosphorylated (26), which might induce faster accumulation of *PER2* and accelerate clock feedback loops, effectively shortening the circadian period.

In *PER3*, an amino acid polymorphism (V647G) located close to a putative CKIε phosphorylation site has been identified in some individuals with delayed phase sleep syndrome (DSPS) (27). This polymorphism has also been associated with self-reported diurnal preference in other study subjects (28). Furthermore, a varying length polymorphism (four or five repeating units) has been identified in a region of *PER3* containing several putative CKIε phosphorylation sites in patients with extreme diurnal preference and DSPS (29). In this population, the longer allele was associated with morningness and the shorter allele was associated with eveningness, and 75% of DSPS subjects were homozygous for the shorter allele.

The well-recognized association between circadian alterations and psychiatric conditions in humans (reviewed in 30 and 31) has prompted the hypothesis that mutations or allelic variations in genes controlling circadian rhythm may be associated with clinical symptoms in patients with forms of mental illness characterized by circadian abnormalities. Traditional linkage and association studies on the various genes involved in circadian rhythm, however, have thus far failed to establish a relationship with mental illness (32,33,34). In this study, we have adopted a more direct

approach to this hypothesis by identifying specific genetic variations (GVs) in genes controlling circadian rhythms from genetic material of study subjects gathered from multiple psychiatric clinics. Our goal was to identify GV in circadian genes as candidates for future genetic studies on the role of circadian rhythm in mental illness.

Methods:

PCR Amplification: All exons in *BMAL1*, *BMAL2*, *CLOCK*, *PER1*, *PER2*, *PER3*, *CRY1*, *CRY2* and *NPAS2* were amplified by standard PCR. Specific primer sequences used for PCR amplification are listed in Appendix 1.

Selection of Study Subjects: Designated study subject diagnosis relied on clinical reports from the clinics from which study subjects were enrolled. Diagnoses were made by psychiatrists or clinically trained nursing staff following normal standards of psychiatric care. There was no standardization of clinical interview for diagnosis. Study subjects were not evaluated by standardized research-structured interview design. Diagnosis and family history for these individuals who did not consent to release of personal information was classified as Unknown. Study subjects were broadly classified according to DSM IV diagnostic criteria (Mood Disorders, Anxiety Disorders, Childhood Disorders, Eating Disorders, Personality Disorders, Psychotic Disorders, Substance Related Disorders, and Schizoaffective Disorder).

Mood disorders comprise Major Depressive Disorder (MDD), Depression Not Otherwise Specified (NOS), Bipolar Disorder (types I and II), Cyclothymic Disorder, and Dysthymic Disorder. Anxiety Disorders comprise Acute Stress Disorder, Agoraphobia, Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, Panic Disorder, Posttraumatic Stress Disorder, Separation Anxiety Disorder, Social Phobia, and Specific Phobia. Childhood Disorders comprise Attention-Deficit/Hyperactivity Disorder and Conduct Disorder. Because no study subjects were diagnosed with Conduct Disorder, this category was re-designated as Attention Deficit/Hyperactivity Disorder (ADHD). Eating Disorders comprise Anorexia Nervosa and Bulimia Nervosa. Personality Disorders comprise Antisocial Personality Disorder, Avoidant Personality Disorder, Borderline Personality Disorder, Dependent Personality Disorder, Histrionic Personality Disorder, Narcissistic Personality Disorder, Obsessive-Compulsive Personality Disorder, Paranoid Personality Disorder, Schizoid Personality Disorder, and Schizotypal Personality Disorder. Psychotic Disorders comprise Brief Psychotic Disorder, Psychotic Disorder NOS, Schizophreniform Disorder, Schizophrenia, and Shared Psychotic Disorder. Substance Related Disorders comprise Alcohol Dependence, Amphetamine Dependence, Cannabis Dependence, Cocaine Dependence, Hallucinogen Dependence, Inhalant Dependence, Nicotine Dependence, Opioid Dependence, Phencyclidine Dependence, and Sedative Dependence.

RESULTS

General characteristics of the study population are summarized in **Tables 1** and **2**. The majority (63.32% in all subjects and 70.49% in the smaller subset) carried a diagnosis of Mood Disorder, most frequently Major Depressive Disorder (48.1% in all subjects and 52.08% in the smaller subset). The next largest diagnosis within Mood Disorder for both groups was Depression NOS (9.44% in all subjects and 11.81% in the smaller subset). The family history of psychiatric illness was

unknown in a large percentage of study subjects in both groups (48.81% in all subjects and 45.14% in the smaller subset). Within all subjects, 40.26% had a family history of mood disorder. Within the smaller subset, 42.71% had a family history of mood disorder. The majority of study subjects in both groups were Caucasian (73.06% in all subjects and 82.99% in the smaller subset) and female (57.50% in all subjects and 55.56% in the smaller subset)

TABLE 1: STUDY SUBJECT DIAGNOSES	ALL SUBJECTS (n=2012)		SUBSET (n=288)	
	NUMBER	PERCENT (%)	NUMBER	PERCENT (%)
1) MOOD DISORDERS	1274	63.32%	203	70.49%
Major Depressive Disorder	969	48.16%	150	52.08%
Bipolar Disorder	190	9.44%	34	11.81%
Depression NOS	77	3.83%	14	4.86%
Cyclothymic Disorder	1	0.05%	0	0.00%
Dysthymic Disorder	21	1.04%	2	0.69%
Adjustment Disorder	7	0.35%	1	0.35%
Unspecified Subtype	9	0.45%	2	0.69%
2) ANXIETY DISORDERS	70	3.48%	7	2.43%
Generalized Anxiety Disorder	12	0.60%	0	0.00%
Obsessive-Compulsive Disorder	14	0.70%	3	1.04%
Panic Disorder	21	1.04%	0	0.00%
Social Phobia	3	0.15%	1	0.35%
Post-Traumatic-Stress Disorder	5	0.25%	1	0.35%
Unspecified Subtype	15	0.75%	2	0.69%
3) ATTENTION-DEFICIT HYPERACTIVE DISORDER	44	2.19%	16	5.56%
4) EATING DISORDER	7	0.35%	2	0.69%
Anorexia-Nervosa	1	0.05%	0	0.00%
Bulimia-Nervosa	4	0.20%	2	0.69%
Unspecified Subtype	2	0.10%	0	0.00%
5) PERSONALITY DISORDERS	0	0.00%	0	0.00%
6) PSYCHOTIC DISORDERS	38	1.89%	6	2.08%
Psychotic Disorder NOS	8	0.40%	0	0.00%
Schizophrenia	29	1.44%	6	2.08%
Delusional Disorder	1	0.05%	0	0.00%
7) SUBSTANCE RELATED DISORDERS	36	1.79%	2	0.69%
Alcohol Dependence	21	1.04%	1	0.35%
Cocaine Dependence	2	0.10%	0	0.00%
Opioid Dependence	9	0.45%	0	0.00%
Sedative Dependence	1	0.05%	0	0.00%
Polysubstance Dependence	3	0.15%	1	0.35%
8) SCHIZOAFFECTIVE DISORDER	2	0.10%	1	0.35%
9) UNKNOWN	557	27.68%	50	17.36%
10) NO DIAGNOSIS	23	1.14%	9	3.13%

TABLE 2: SUBJECT DEMOGRAPHICS	ALL SUBJECTS		SUBSET	
	NUMBER	PERCENT (%)	NUMBER	PERCENT (%)
FAMILY HISTORY				
1) Mood Disorders	810	40.26%	123	42.71%
2) Anxiety Disorders	115	5.72%	13	4.51%
3) Attention-Deficit Hyperactive Disorder	47	2.34%	12	4.17%
4) Eating Disorders	2	0.10%	0	0.00%
5) Personality Disorders	2	0.10%	0	0.00%
6) Psychotic Disorders	34	1.69%	2	0.69%
7) Substance-Related Disorders	31	1.54%	2	0.69%
8) Schizoaffective Disorder	1	0.05%	0	0.00%
9) Unknown	982	48.81%	130	45.14%
10) None	134	6.66%	26	9.03%
ETHNICITY				
1) Caucasian	1470	73.06%	239	82.99%
2) African American	57	2.83%	4	1.39%
3) Hispanic	51	2.53%	11	3.82%
4) Asian	18	0.89%	1	0.35%
5) Indian	3	0.15%	0	0.00%
6) Caucasian / African American	1	0.05%	0	0.00%
7) Caucasian / Hispanic	3	0.15%	1	0.35%
8) Any Other Combination	3	0.15%	0	0.00%
9) Other	20	0.99%	4	1.39%
10) Unknown	386	19.18%	28	9.72%
SEX				
1) Male	626	31.11%	126	43.75%
2) Female	1157	57.50%	160	55.56%
3) Unknown	229	11.38%	2	0.69%

All GVs discovered are listed in **Tables 3-5**, and the results for each particular gene are discussed in detail below. GVs are reported as intronic vs. exonic, and exonic GVs are further divided into “Exonic Changes (meaningful),” defined as producing an amino acid change, and “Exonic Changes (silent),” defined as preserving the amino acid. GVs are reported by convention as: Gene, Exon, Original Amino Acid - (Original Codon) – Amino Acid Position – New Amino Acid – (New Codon). For example, the GV designation *BMAL2*, E2, S(TCT) 37 F(TTT) indicates that the original codon TCT, within exon 2 of the *BMAL2* gene, which codes for amino acid

S, has been changed to the new codon TTT, which codes for the amino acid F, at amino acid position 37 within the *BMAL2* gene product. Exon designation was included in the original listing in order to aid other investigators who might wish to utilize any of these GVs in their studies. For more in-depth discussion of GVs in *PER1* and *PER3*, the exon designation was eliminated. No intronic GVs in any of the genes studied were present in readily identifiable splicing regulatory sequences, and as such these are not discussed in detail beyond their listing in **Tables 3-5**.

Table 3: GVs identified in Subset Population in *BMAL1*, *BMAL2*, *CRY1*, *CRY2*, *CLOCK*, *NPAS2* and *PER2*.

GENE	INTRONIC CHANGES		EXONIC CHANGES (SILENT)		EXONIC CHANGES (MEANINGFUL)			
	Exon	Description	Exon	Description	Frequency	Exon	Description	Frequency
<i>BMAL1</i>	2	-15 C→T	NONE			NONE		
	4	-8 T→C						
	5	+31 C→T						
	6	-35 A→G						
<i>BMAL2</i>	2	-42 C→T	NONE			2	S(TCT) 74 F(TTT)	1.04%
	4	-26 A→G				5	K(AAA) 203 R(AGA)	5.56%
	8	-78 C→T				8	N(AAC) 340 S(AGC)	0.69%
	10	-42 A→G						
	13	-16 A→G						
<i>CRY1</i>	9	+15 6bp INS	5	G(GGC) 212 G(GGT)	1.04%	NONE		
	10	+52 A→T						
	11	+32 A→G						
<i>CRY2</i>	2	-4 A→G	NONE			NONE		
	2	+47 C→G						
	4	+14 G→A						
	6	-41 A→T						
	7	+50 G→A						
	8	-16 C→T						
	9	-38 G→A						
	10	-32 C→T						
	10	+3 G→A						
	11	+60 C→G						
<i>CLOCK</i>	3	-106 A→G	8	F(TTT) 233 F(TTC)	0.69%	7	S(TCT) 208 C(TGT)	1.74%
	3	+5 A→T	17	N(AAT) 588 N(AAC)	47.2%	12	L(CTT) 395 I(ATT)	0.35%
	5	+30 G→A	20	S(TCA) 816 S(TCC)	3.13%			
	8	-10 A→G						

Table 3: (cont) GVs identified in Subset Population in *BMAL1*, *BMAL2*, *CRY1*, *CRY2*, *CLOCK*, *NPAS2* and *PER2*.

GENE	INTRONIC CHANGES			EXONIC CHANGES (SILENT)			EXONIC CHANGES (MEANINGFUL)		
	Exon	Description	Exon	Description	Frequency	Exon	Description	Frequency	
<i>NPAS2</i>	2	-17 G→A	7	V(GTG) 219 V(GTA)	10.1%	12	T(ACA) 394 A(GCA)	2.43%	
	9	+21 2bp INS	11	Y(TAC) 354 Y(TAT)	31.6%	14	S(TCG) 472 L(TTG)	12.85%	
	10	+5 C→T	19	T(ACC) 711 T(ACT)	37.5%				
	10	-6 G→A							
	10	-63 C→T							
	11	+27 G→A							
	11	+43 G→A							
	11	+82 C→A							
	11	-105 A→T							
	12	+27 T→A							
	15	-16 C→T							
	17	+31 C→G							
	19	+21 1bp INS							
	19	+51 G→A							
	20	+7 G→A							
	<i>PER2</i>	2	-88 A→C	4	L(CTG) 156 L(CTA)	49.0%	17	R(CGA) 773 Q(CAA)	0.35%
3		-31 C→T	4	T(ACC) 174 T(ACT)	0.35%	18	V(GTC) 903 I(ATC)	2.10%	
3		-43 T→C	16	A(GCA) 655 A(GCG)	2.08%				
3		+59 A→G	16	A(GCG) 664 A(GCA)	0.35%				
3		+18 A→T	16	S(TCG) 665 S(TCA)	0.35%				
4		-23 2bp INS							
5		-15 A→G							
7		+45 C→T							
8		-58 C→T							
12		+4 C→T							
12		+18 C→T							
13		+13 1bp INS/DEL							
14		-51 C→T							
16		+28 7bp DEL							
16		+13 7bp INS/DEL							
17		+13 C→T							
19	-17 G→T								
20	+35 G→A								

***BMAL1*:** Table 3 shows that in 288 study subjects, only 4 GVs were found in *BMAL1*. All of these GVs were intronic.

***BMAL2*:** Table 3 shows that in 288 study subjects, 5 intronic GVs and 3 exonic GVs were found in *BMAL2*. All 3 exonic *BMAL2* GVs produce amino acid changes: (1) ***BMAL2*, E2, S(TCT) 74 F(TTT)**, (2) ***BMAL2*, E5, K(AAA) 203 R(AGA)**, and (3) ***BMAL2*, E8, N(AAC) 340 S(AGC)**. Details of these 3 meaningful exonic GVs in *BMAL2* are outlined below.

1. **BMAL2, E2, S(TCT) 74 F(TTT)**

- **Frequency:** 1.04% (3/288)
- **Diagnoses:** 100% (3/3) Mood Disorder (1 with MDD and 2 with Bipolar Disorder)
- **Family History:** 100% (3/3) family history of Mood Disorder
- **Ethnicity:** 100% (3/3) Caucasian
- **Sex:** 66.7% (2/3) female, 33.3% (1/3) male

2. **BMAL2, E5, K(AAA) 203 R(AGA)**

- **Frequency:** 5.56 % (16/288)
- **Diagnoses:** 62.5% (10/16) Mood Disorder (8 with MDD, 1 with Bipolar Disorder, and 1 with Dysthymic Disorder).
25% (4/16) Unknown.
6.25% (1/16) ADHD
6.25% (1/16) Schizophrenia.
6.25% (1/16) Schizoaffective Disorder
- **Family History:** 31.3% (5/16) family history of Mood Disorder.
18.8% (3/16) no family history of psychiatric illness.
43.8% (7/16) unknown family history.
6.25% (1/16) family history of ADHD.
6.25% (1/16) family history of Schizophrenia.
- **Ethnicity:** 100% (16/16) Caucasian.
- **Sex:** 68.8% (11/16) female, 31.2% (5/16) male

3. **BMAL2, E8, N(AAC) 340 S(AGC)**

- **Frequency:** 0.69% (2/288)
- **Diagnoses:** 100% (2/2) Mood Disorder (MDD).
- **Family History:** 50.0% (1/2) family history of Mood Disorder.
50.0% (1/2) unknown family history.
- **Ethnicity:** 100% (2/2) African-American.
- **Sex:** 100% (2/2) female

We believe that the three GV's producing amino acid changes in BMAL2 are unlikely to have functional effects on the protein. For example, although amino acids S and F differ substantially in their properties, the GV **BMAL2, E2, S(TCT) 74 F(TTT)** occurs in a poorly conserved area of the protein and is unlikely to have any functional consequences.

hBMAL2	59	PSQSGIMTEKVVVEKLSQNPLTYLLSTRIEISASSGSRVEDGEHQVKMKAFR----EAHSQ
dogBMAL2	50	PSQSGIMTEKVMVEKLSKNPFITYLLSTRIEISASSGSRMEDGEQQVKMNQVLFLLREAHSQ
btBMAL2	7	PSRSGIMKEKVMVEKLSQNPFITCLLSTRVEMSAFSCSRMEDGEQQVKIKS----FREAHSQ
mBMAL2	14	PLQSEFMTDTTVEISLPQNPFFASLLSTRITGVSAVPSG-----TREAHSQ
ratBMAL2	7	LLQSEFRITDAMVENLPRSPFTSVLSTRITGVAVPNC-----TREAHSQ
gallBMAL2	40	NPITKPAITTSFNNSVVEIIPRKRKGSDDSDNQDTVEVDGDPQKRNEDEEHLKIKDFREAHSQ
danioBMAL2	1	-----MDNLEMKASANLDEDMEDDAGRSEDDQHLKIKCIREFHSQ

Furthermore, although the GV **BMAL2, E5, K(AAA) 203 R(AGA)** occurs in the PAS domain of BMAL2, the amino acids K and R do not differ substantially in their properties, and indeed either K or R is present at this position in BMAL2 across species. Therefore, this change is extremely unlikely to have a functional effect on human BMAL2 function.

hBMAL2	190	AEGFLFVVGCEGRGKILFVSKSVSKILNYDQASLTGQSLFDFLHPKDVAKVKEQLSSFDIS
dogBMAL2	185	AEGFLFVVGCEGRGKILFVSKSVSKILNYDQASLTGRSLFDFLHPKDVAKVKEQLSSSDIS
btBMAL2	138	AEGFLFVVGCEGRGKILFVSKSVSRILNYDQASLIGQSLFDFLHPKDVSKVKEQLSSSDIS
mBMAL2	131	AEGFLFVVGCEGRIFVSKSVSKTLRYDQASLIGQSLFDFLHPKDVAKVKEQLS-CDGS
ratBMAL2	124	AEGFLFVVGCEGGRIFVSKSVSKTLHYDQASLMGQSLFDFLHPKDVAKVKEQLS-CDVS
gallBMAL2	175	ADGFLFVVGCEGRGKILFVSESVCKILNYDQTSLIGQSLFDYLHPKDVAKVKEQLSSSDVS
danioBMAL2	116	ADGFLFVVGCEGRGKILFVSESVSKTLNYSRTELIGQSLFDYVHPKDIGKVKEQLSASELY

BMAL2, E8, N(AAC) 340 S(AGC) occurs at a poorly conserved site in the protein, where serine residues also exist in other species, and is thus unlikely to have any functional consequences.

hBMAL2	309	RKFYTIHCTGYLRSWPPNIVGMEEERNSSKKNNSNFTCLVAIGRLQPYIVPQNSGEINVKPK
dogBMAL2	304	RKFCTIHCTGYLRSWPPNIVGLEEERDNKKNSSNFTCLVAIGRLHPYIVPQNSGEIKVKPK
btBMAL2	257	RKFCTVHCTGYLRSWPPNIAAGMEEERDNKKDRSNFTCLVAVGRLQPHIIVPQNSGEIKVKPK
mBMAL2	248	RKFHTVHCTGYLRSWPLNVVGMEEKESGGGKDSGPLTCLVAMGRLHPYIVPQKSGKINVRP
ratBMAL2	243	RKFHTIHCTGYLRSWPPNVVGTTEKEMGSGKDSGPLTCLVAMGRLQPYIVPVPKNGKINVRP
gallBMAL2	294	RKYCTIHCTGYMKNWPPSEVGVVEEENDVEKNSSNFNCLVAIGRLHPYIVPQKSGEIKVKA
danioBMAL2	236	QRYCTVHCTGYMRTWPTRQLATEGEAEADKESSEHFSCLVAMGRVHPHTLPQANGEIKVKPK

CRY1: Table 3 shows that in 288 study subjects, 3 intronic GVs and 1 silent exonic GV, **CRY1, E5, G(GGC) 212 G(GGT)** (1.04% frequency), were found in *CRY1*.

CRY2: Table 3 shows that in 288 study subjects, 10 GVs were identified in *CRY2*. All of these GVs were intronic.

CLOCK: Table 3 shows that in 288 study subjects, 4 intronic GVs and 5 exonic GVs were found in *CLOCK*. Three of the exonic GVs in *CLOCK* were silent: (1) **CLOCK, E8, F(TTT) 233 F(TTC)** (0.69% frequency), (2) **CLOCK, E17, N(AAT) 588 N(AAC)** (47.2% frequency) and (3) **CLOCK, E20, S(TCA) 816 S(TCC)** (3.13% frequency). Two of the exonic GVs in *CLOCK* were found to produce amino acid changes: (1) **CLOCK, E7, S(TCT) 208 C(TGT)** (1.74% frequency) and (2) **CLOCK, E12, L(CTT) 395 I(ATT)** (0.35% frequency). Details of these 2 meaningful exonic GVs in *CLOCK* are outlined below.

1. **CLOCK, E7, S(TCT) 208 C(TGT)**

- **Frequency:** 1.74% (5/288)
- **Diagnoses:** 100% (5/5) with Mood Disorder (3 with MDD, 1 with Bipolar Disorder, and 1 with Depression NOS)
- **Family History:** 40.0% (2/5) family history of Mood Disorder
40.0% (2/5) unknown family history
20.0% (1/5) no family history of psychiatric illness
20.0% (1/5) family history of ADHD.
- **Ethnicity:** 80.0% (4/5) Caucasian
20.0% (1/5) Hispanic
- **Sex:** 100% (5/5) male

2. **CLOCK, E12, L(CTT) 395 I(ATT)**

- **Frequency:** 0.35% (1/288)
- **Diagnosis:** Mood Disorder (MDD)
- **Family History:** Mood Disorder
- **Ethnicity:** Caucasian
- **Sex:** female

We believe that these two GVs producing amino acid changes in *CLOCK* are unlikely to have functional effects on the protein. For example, although S to C is a potentially significant amino acid change within the PAS domain, **CLOCK, E7, S(TCT) 208 C(TGT)** occurs at a poorly conserved site in *CLOCK* and *NPAS2* that is populated predominantly by either S or P, two substantially different amino acids. We feel, therefore, that an S to C amino acid transition at this position is unlikely to have a radical effect on protein function.

btCLOCK	178	DPKEPSTY ^E YVKFIGNFKSLNSVSTSAHNGFEG-----TIQ ^R TRH ^R PSYEDRVCF
dogCLOCK	178	DPKEPSTY ^E YVKFIGNFKSLNSVSTSAHNGFEG-----TIQ ^R TRH ^R PSYDDRVCF
hCLOCK	203	DPKEP ^S TYEYVKFIGNFKSLNSVSSSAHNGFEG-----TIQ ^R TRH ^R PSYEDRVCF
mCLOCK	178	DPKEPSTY ^E YVRFIGNFKSLT ^S VSTSTHNGFEG-----TIQ ^R TRH ^R PSYEDRVCF
qCLOCK	178	DPKEQPT ^E Y ^E YVKFIGNFKCLNNVPNSAHNGFEG-----TIQ ^R SRH ^R PSYEDKVCF
xenoCLOCK	178	DPKEPSTY ^E YVKFIGNFKSLNNVPNSTHNGFDG-----ALQ ^R SLR ^P PPY ^E ERVCF
danioCLOCK	178	DPKEPPVY ^E YVKFIGNFKSLNTVPNSTRNGFEG-----VIQ ^R SLR ^H AFEDRVCF
hNPAS2	178	NPKEFPT ^E Y ^E YIKFVGNFRSYNNVPS ^P SCNGFDN-----TL ^S SR ^P CRV ^P LGKEVCF
dogNPAS2	178	NPKEFPT ^E Y ^E YIKFVGNFRSYNNVPS ^P SCNGFDS-----TL ^S SR ^P CRV ^P LGKEVCF
btNPAS2	178	NPKEFPT ^E Y ^E YIKFVGNFRSYNNVPS ^P SCNGFDG-----AL ^S SR ^P CRV ^P LGKEVCF
mNPAS2	178	NPKEFPT ^E Y ^E YIKFVGNFRSYNNVPS ^P SCNGFDN-----TL ^S SR ^P CHV ^P LGKDVCF
danioNPAS2	181	DPKEPPT ^E Y ^E YVKFVGFDFK ^F HNNVPL ^S SCNGYDL-----AFP ^R TL ^Q SSIEEQVCL

CLOCK, E12, L(CTT) 395 I(ATT) is unlikely to be important by virtue of the fact that L to I is a conservative amino acid change, and the L at this position in CLOCK and NPAS2 is poorly conserved.

btCLOCK	364	-----LGIEESL ^L PETAAD---KSQDSGSDNRINTVSLKEALERFDHSPTPSA
dogCLOCK	364	-----LGIEESL ^L PETAAD---KSQDSGSDNRINTVSLKEALERFDHSPTPSA
hCLOCK	389	-----LGIEESL ^L PETAAD---KSQDSGSDNRINTVSLKEALERFDHSPTPSA
mCLOCK	364	-----LGIEESL ^L PETAAD---KSQDSGSDNRINTVSLKEALERFDHSPTPSA
qCLOCK	364	-----LGIEESL ^L PEIKAD---KSQDSGSDNHINTVSLKEALERFDTSPTPSA
xenoCLOCK	364	-----RGNEDSPPAITAE---KNQDSVSDNHMNTVSLKEALERFDDSRTPSP
danioCLOCK	364	-----LGIEESPP ^E ISAD---KSQDSGSE ^S QLNTSSLKEALERFDHSRTPSA
hNPAS2	364	-----LALEDPPSEALHSSALKDKGSSLEPRQHFNTLDVGASGLN ^T SHSPSA
DogNPAS2	364	-----LALEDPPPEAVHASALKDKGSSLDPTQHFNALDAGTLGLN ^T NHSPSV
btNPAS2	364	-----LALEDPLLENVHPSALKEKGSLEPPQHFNALDMGTSGLN ^T SHSPSA
mNPAS2	364	-----LALEDPPTEAMHPSAVKEKDSLEPPQPFNALDMGASGLPSSPSPSA
danioNPAS2	367	-----FGLEES-SSDMATSSIKQ ^E EVFLDMC ^P PLEATRDRIN-----SARSV

NPAS2: Table 3 shows that in 288 study subjects, 15 intronic GVs and 5 exonic GVs were identified in NPAS2. Three of the exonic GVs in NPAS2 were silent: (1) NPAS2, E7, V(GTG) 219 V(GTA) (10.1% frequency), (2) NPAS2, E11, Y(TAC) 354 Y(TAT) (31.6% frequency) and (3) NPAS2, E19, T(ACC) 711 T(ACT) (37.5% frequency). Two of the exonic GVs in NPAS2 were found to produce amino acid changes: (1) NPAS2, E12, T(ACA) 394 A(GCA) (2.43% frequency) and (2) NPAS2, E14, S(TCG) 472 L(TTG) (12.85% frequency). Details of these 2 meaningful exonic GVs in NPAS2 are outlined below.

1. NPAS2, E12, T(ACA) 394 A(GCA)

- **Frequency:** 2.43% (7/288)
- **Diagnoses:** 85.7% (6/7) Mood Disorder (5 with MDD and 1 with Depression NOS)
14.3% (1/7) Schizoaffective Disorder
14.3% (1/7) ADHD
- **Family History:** 57.1% (4/7) family history of Mood Disorder
28.6% (2/7) no family history of psychiatric illness
14.3% (1/7) unknown family history
14.3% (1/7) family history of Anxiety Disorder
- **Ethnicity:** 57.1% (4/7) Caucasian
28.6% (2/7) Hispanic
14.3% (1/7) unknown
- **Sex:** 71.4% (5/7) male, 28.6% (2/7) female

2. **NPAS2, E14, S(TCG) 472 L(TTG)**

- **Frequency:** 12.85% (37/288)
- **Diagnoses:** 45.9% (17/37) Mood Disorder (15 with MDD, 1 with Depression NOS, 1 with Bipolar Disorder).
45.9% (17/37) Unknown.
10.8% (4/37) ADHD
2.7% (1/37) Schizophrenia
- **Family History:** 56.8% (21/37) unknown family history
35.1% (13/37) family history of Mood Disorder
5.4% (2/37) family history of psychiatric illness
2.7% (1/37) family history of ADHD
2.7% (1/37) family history of Anxiety Disorder
- **Ethnicity:** 83.8% (31/37) Caucasian
13.5% (5/37) Native American
2.7% (1/37) Hispanic
- **Sex:** 45.9% (17/37) male, 54.1% (20/37) female

We believe that these two GV's producing amino acid changes in NPAS2 are unlikely to have functional effects on the protein. **NPAS2, E12, T(ACA) 394 A(GCA)** occurs in a poorly conserved region and is a reasonably conservative amino acid change. Furthermore, A is well-conserved at this position in NPAS2 from other species.

btCLOCK	364	-----	LGIEESLPETAAD	---	KSQDSGSDNRINTVSLKEALERFDHSPTPSA
dogCLOCK	364	-----	LGIEESLPETAAD	---	KSQDSGSDNRINTVSLKEALERFDHSPTPSA
hCLOCK	390	-----	LGIEESLPETAAD	---	KSQDSGSDNRINTVSLKEALERFDHSPTPSA
mCLOCK	364	-----	LGIEESLPETAAD	---	KSQDSGSDNRINTVSLKEALERFDHSPTPSA
qCLOCK	364	-----	LGIEESLPEIKAD	---	KSQDSGSDNHINTVSLKEALERFDTSPTPSA
xenoCLOCK	364	-----	RGNEDSPPAITAE	---	KNQDSVSDNHMNTVSLKEALERFDDSRTPSP
hNPAS2	364	-----	LALEDPPSEALHSSALKDKGSSLEPRQHFN	TL	DVGASGLNNTSHSPSA
DogNPAS2	364	-----	LALEDPPPEAVHASALKDKGSSLDPTQHFNALDAGTLGLNNTNHSPSV		
btNPAS2	364	-----	LALEDPLLENVHPSALKEKGSLEPPQHFNALDMGTSGLNNTSHSPSA		
mNPAS2	364	-----	LALEDPPTEAMHPSAVKEKDSLEPPQPFNALDMGASGLPSSPSPSA		
danioNPAS2	367	-----	FGLEES	-SSDMATSSIKQEVFLDMC	PPEATRDRIN-----SARSV

Likewise, **NPAS2, E14, S(TCG) 472 L(TTG)**, which is a fairly substantial amino acid change, occurs at a poorly conserved region of unknown functional importance.

btCLOCK	453	SSFSQS	INSQ	TVGQSLTQP	VMSQSANLPVPHGM	-----
dogCLOCK	453	ASFSSQS	INSQ	SVGQSLTQP	AMSQAANLP	IPQGM-----
hCLOCK	479	SSFSQS	INSQ	SVGSSLTQP	VMSQATNLP	IPQGM-----
mCLOCK	453	SSFSQS	INSQ	SVGPSLTQP	AMSQAANLP	IPQGM-----
qCLOCK	453	SSLSSQSL	SSQSL	GQPVTQPTMSQ	PATLQLQS	-----
xenoCLOCK	451	SSISSQSM	SSQSV	SQPLSQSVMKOTASI	QLQQGMT	-----
danioCLOCK	454	SSISSQSM	SSQT	TGQTMGTSLV	SQPOQPOTLQATV	-----
hNPAS2	456	GLSQAATMP	PAPLPSPS	SCDLTQQLLP	QTVLQS	-----
DogNPAS2	456	GLSQAATMP	PAPLPAPSSCNLT	QQLLPQ	TILQS	-----
btNPAS2	453	GLGQAAAMP	PAPLPAPASCDLT	QQLLPQ	TILQS	-----
mNPAS2	456	GLSQAATMP	TALHSSASCDLT	TKQLLQ	SLPQTGLQS	-----
danioNPAS2	453	MTHTGKTLI	QRQSSSEPPSLSPSCS	QHSAMT		-----

PER2: Table 3 shows that in 288 study subjects, 18 intronic GV's and 7 exonic GV's were identified in PER2. Five of the exonic GV's in PER2 were silent: (1) **PER2, E4, L(CTG) 156 L(CTA)** (49.0% frequency), (2) **PER2, E4, T(ACC) 174 T(ACT)** (0.35% frequency), (3) **PER3, E16, A(GCA) 655 A(GCG)**, (2.08% frequency), (4) **PER3, E16, A(GCG) 664 A(GCA)** (0.35% frequency), and (5) **PER3, E16, S(TCG) 665 S(TCA)** (0.35% frequency). Two of the exonic GV's in PER2 were found to produce amino acid changes: (1) **PER2, E17, R(CGA) 773 Q(CAA)** (0.35% frequency) and (2) **PER2, E18a, V(GTC) 903 I(ATC)** (2.1% frequency). Details of these 2 meaningful exonic GV's in PER2 are outlined below.

1. **PER2, E17, R(CGA) 773 Q(CAA)**

- **Frequency:** 0.35% (1/288) of subjects
- **Diagnoses:** Mood Disorder (MDD)
- **Family History:** Mood Disorder
- **Ethnicity:** Caucasian
- **Sex:** female

2. **PER2, E18, V(GTC) 903 I(ATC)**

- **Frequency:** 2.1% (6/288) of subjects
- **Diagnoses:** 66.7% (4/6) Mood Disorder (all MDD)
16.7% (1/6) Anxiety Disorder
16.7% (1/6) Psychotic Disorder (Schizophrenia)
- **Family History:** 50.0% (3/6) family history of Mood Disorder
33.3%(2/6) no family history of psychiatric illness
16.7% (1/6) unknown family history
- **Ethnicity:** 100% (6/6) Caucasian
- **Sex:** 83.3% (6/7) male, 16.7% (1/7) female

We believe that these two GV's producing amino acid changes in PER2 are unlikely to have functional effects on the protein. Although R to Q is a fairly substantial amino acid change, **PER2, E17, R(CGA) 773 Q(CAA)** occurs in a poorly conserved region of unknown functional significance.

hPER1	809	-----SSSTAPSAL	GERGCHHG	PAPP	SRRH	HCRSKA	KRS--	RHHQN	PRA
mPER1	809	-----TSSVAPSAP	G---	CHHGPI	PPGRR	HCRSKA	KRSRHH	HHQ	T
btPER1	809	-----SSSTAPSAP	GERGCHH	SLAIP	GRR	HCRSKA	KRS--	RHHQ	T
xenoPER1	777	HNQHPQ-----	RGSKPS	RASQ	HHH	ASSCN	PPSP	SKGES	NSGR
cynopsPER1	832	PRHSGQ-----	HADK	GHGR	SRHN	ANGN	GGPG	SSRR	GKS--
danioPER1	842	NAPLSR	GVRC	SRDY	PAAG	SSGR	RRR	GRGG	KRLK
hPER2	765	RSKGQP-----	SE	R	TAP	GLR	NTSG	----	IDSP
mPER2	757	RSRAQA-----	SDR---	GLR	NTSG	----	LESS	WKKT	GKNR
btPER2	771	RSKGHL-----	SNR	TAP	GLR	NT	PG	----	IDSS
podarcisPER2	766	RPKGHP-----	GNR	GVH	GPR	HSG	----	VDQ	SWK
xenoPER2	877	RP-----	GAP	H	T	R	A	Q	G
fPER2	838	QKGQVT-----	SEAV	PAAR	SCKA	G	GGGA	Q	E
danioPER2	838	QKGQVT-----	SEAV	PAAR	SCKA	G	GGGA	Q	E
hPER3	714	KAKYSYF-----	QGD	ST	SKQ	TRS	SAG	CR	GK
mPER3	704	RAQYSCV-----	QAG	ST	A	K	H	S	R
qPER3	665	TNGHSCD-----	QGN	SP	SK	E	M	P	A
btPER3	511	-----	PRG	Q	G	P	T	H	P
fPER1	960	YTFYKE	GLR	L	R	D	A	T	Y
fPER3	615	KEIERN-----	PPP	Q	N	K	R	G	Q

PER2, E18, V(GTC) 903 I(ATC), in addition to being a conservative amino acid substitution, also occurs in a poorly conserved region of no known significance.

hPER1	898	-----LPPAPTSVPPAAFPAPLVTMPVALVLPNYLF
mPER1	897	-----LPPAPTSVSPATFPSPLVTMPVALVLPNYLF
btPER1	898	-----LPPAPTSVPPAAFPAPLVTMPVALVLPNYLF
xenoPER1	871	-----TPPVPRYPPLVTPIVALVMPNYLF
cynopsPER1	943	TF-----GGAQNSPGMRYPLAPPQYPAPMVTMPVALVLPNYIF
DanioPER1	955	-----SMQSGLRFPLQNSQMAPPMPVPPMMALVLPNYMF
hPER2	869	PA-----PPHASFTVPAVPVDLQHQFAVQPPFPAPLAPVMAFMLPSYSF
mPER2	863	PA-----ATHTGFTMPVVPMTQPEFAVQPLPFAAPLAPVMAFMLPSYPF
btPER2	880	-----SGAAHTDLAVPVDAQQVLRVHPPFPASPLAPVMAFMLPSYCF
podarcisPER2	869	PE-----APLSAFSESQDSGNPCHLPLSQFP--NPLMTPVVALVLPNYMY
xenoPER2	977	SANASTSQPF--APLLPPMVALVLPNYVYPASLPTSLYPGPAPQPAFPAQQTSYLPQST
fPER2	950	GFGESQCAPDPRIPMQPIQTPYSAPLVTMPVALVLPNYMFPQVGKRSTPGFLPPQNRDHS
DanioPER2	950	GFGESQCAPDPRIPMQPIQTPYSAPLVTMPVALVLPNYMFPQVGKRSTPGFLPPQNRDHS
hPER3	823	-----GLHGLPLSEGLQPYPAFPFPYLDTFMTVFLPDPPV
mPER3	814	-----GCP--PLSAGPQAVAAFPAYVDTLMTIFLHNAPL
qPER3	776	-----LTSLSQLCCGAPSFALSPNIGMFMAVFLHSFPI
btPER3	582	-----SPAACGPRSHVSRPAPTLGPAGPWPCP----
fPER1	1080	LQDKKAGYGVFDDITKGEKYMGTWQDNQRHGTGVVVTQFGLYYEGTFKENKMMGTGILVS
fPER3	689	-----NGLAGPPMPPLAAGLGEVNLGVAPPLVSG

PER1: Table 4 shows that in 2013 study subjects, 56 intronic GVs and 36 exonic GVs were identified in *PER1*. Eighteen of the exonic GVs in *PER1* were silent: (1) **PER1, E3, R(CGC) 158 R(CGT)** (0.10% frequency), (2) **PER1, E4, T(ACA) 213 T(ACC)** (33.9% frequency), (3) **PER1, E5, G(GGC) 229 G(GGT)** (0.10% frequency), (4) **PER1, E8, R(AGG) 358 R(AGA)** (0.15% frequency), (5) **PER1, E10, T(ACC) 439 T(ACT)** (0.05% frequency), (6) **PER1, E12, T(ACG) 507 T(ACA)** (0.10% frequency), (7) **PER1, E12, T(ACA) 516 T(ACG)** (0.05% frequency), (8) **PER1, E17, G(GGT) 749 G(GGC)**, (24.4% frequency), (9) **PER1, E17, T(ACG) 787 T(ACA)** (24.4% frequency), (10) **PER1, E18, G(GGC) 894 G(GGT)** (0.35% frequency), (11) **PER1, E18, L(CTG) 973 L(CTA)** (2.68% frequency), (12) **PER1, E18, L(CTC) 992 L(CTT)** (2.68% frequency), (13) **PER1, E18, A(GCC) 1008 A(GCT)** (0.05% frequency), (14) **PER1, E19, D(GAC) 1034 D(GAT)** (0.05% frequency), (15) **PER1, E19, H(CAT) 1076 H(CAC)** (0.05% frequency), (16) **PER1, E21, V(GTG) 1184 V(GTC)** (0.05% frequency), (17) **PER1, E22, E(GAA) 1272 E(GAG)** (0.05% frequency), and (18) **PER1, E22, S(TCC) 1278 S(TCT)** (0.15% frequency). Eighteen of the exonic GVs in *PER1* were found to produce amino acid changes: (1) **PER1, E1, P(CCA) 37 S(TCA)** (0.10% frequency), (2) **PER1, E3, R(CGC) 158 C(TGT)** (0.20% frequency), (3) **PER1, E4, E(GAG) 191 C(TGT)** (0.15% frequency), (4) **PER1, E5, V(GTC) 240 I(ATC)** (0.45% frequency), (5) **PER1, E6, S(TCC) 296 C(TGC)** (0.05% frequency), (6) **PER1, E7, R(CGG) 307 Q(CAG)** (0.10% frequency), (7) **PER1, E7, Q(CAG) 314 R(CGG)** (0.05% frequency), (8) **PER1, E15, S(AGC) 640 N(AAC)** (0.05% frequency), (9) **PER1, E17, DEL 758-761 PAPS** (0.05% frequency), (10) **PER1, E18, Q(CAG) 846 R(CGG)** (0.05% frequency), (11) **PER1, E18, P(CCC) 859 S(TCC)** (0.20% frequency), (12) **PER1, E18, P(CCC) 962 A(GCC)** (11.92% frequency), (13) **PER1, E19, V(GTC) 1027 I(ATC)** (0.40% frequency), (14) **PER1, E19, S(TCG) 1060 L(TTG)** (0.05% frequency), (15) **PER1, E20, A(GCT) 1108 S(TCT)** (0.20% frequency), (16) **PER1, E20, V(GTC) 1141 I(ATC)** (0.05% frequency), (17) **PER1, E21, A(GCT) 1196 V(GTT)** (0.89% frequency), and (18) **PER1, E22, T(ACC) 1289 I(ATC)** (0.05% frequency). Details of these 18 meaningful exonic GVs in *PER1* are outlined below.

1. **PER1, E1, P(CCA) 37 S(TCA)**

- **Frequency:** 0.10% (2/2012)
- **Diagnoses:** 50.0% (1/2) Mood Disorder (MDD)
50.0% (1/2) Unknown
- **Family History:** 50.0% (1/2) family history of Mood Disorder.
50.0% (1/2) unknown family history.
- **Ethnicity:** 100% (2/2) Caucasian
- **Sex:** 100% (2/2) female

2. **PER1, E3, R(CGC) 158 C(TGT)**

- **Frequency:** 0.20% (4/2012)
- **Diagnoses:** 100% (4/4) Mood Disorder (MDD)
- **Family History:** 50.0% (2/4) family history of Mood Disorder
25.0% (1/4) family history of psychiatric illness
25.0% (1/4) unknown family history
- **Ethnicity:** 100% (2/2) Caucasian
- **Sex:** 50.0% (2/4) male, 50.0% (2/4) female

3. **PER1, E4, E(GAG) 191 C(TGT)**

- **Frequency:** 0.15% (3/2012)
- **Diagnoses:** 100% (3/3) Mood Disorder (2 with MDD, 1 with Bipolar Disorder)
- **Family History:** 66.7% (2/3) family history of Mood Disorder.
33.3% (1/3) unknown family history.
- **Ethnicity:** 100% (3/3) Caucasian
- **Sex:** 100% (3/3) female

4. **PER1, E5, V(GTC) 240 I(ATC)**

- **Frequency:** 0.45% (9/2012)
- **Diagnoses:** 100% (9/9) Mood Disorder (MDD)
- **Family History:** 66.7% (6/9) family history of Mood Disorder
(4 with MDD, 1 with Bipolar Disorder, 1 with Depression NOS)
11.1% (1/9) family history of ADHD
11.1% (1/9) unknown family history
- **Ethnicity:** 88.9% (8/9) African American
11.1% (1/9) Native American
- **Sex:** 33.3% (3/9) male, 55.6% (5/9) female, 11.1% (1/9) unknown

5. **PER1, E6, S(TCC) 296 C(TGC)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Unknown
- **Family History:** Unknown
- **Ethnicity:** Caucasian
- **Sex:** female

6. **PER1, E7, R(CGG) 307 Q(CAG)**

- **Frequency:** 0.10% (2/2012)
- **Diagnoses:** 100% (2/2) Mood Disorder (MDD)
- **Family History:** 100% (2/2) family history of Mood Disorder
50.0% (1/2) family history of ADHD
50.0% (1/2) family history of Anxiety Disorder (Obsessive-
Compulsive Disorder)
- **Ethnicity:** 100% (2/2) Caucasian
- **Sex:** 100% (2/2) female

7. **PER1, E7, Q(CAG) 314 R(CGG)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Mood Disorder (MDD)
- **Family History:** Mood Disorder
- **Ethnicity:** Caucasian
- **Sex:** female

8. **PERI, E15, S(AGC) 640 N(AAC)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** unknown
 - **Family History:** unknown
 - **Ethnicity:** Caucasian
 - **Sex:** female
9. **PERI, E17, DEL 758 PAPS**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** unknown
 - **Family History:** unknown
 - **Ethnicity:** Caucasian
 - **Sex:** female
10. **PERI, E18, Q(CAG) 846 R(CGG)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** unknown
 - **Family History:** unknown
 - **Ethnicity:** Caucasian
 - **Sex:** male
11. **PERI, E18, P(CCC) 859 S(TCC)**
 - **Frequency:** 0.20% (4/2012)
 - **Diagnoses:** 75.0% (3/4) Mood Disorder (MDD)
 25.0% (1/4) Anxiety Disorder (Obsessive-Compulsive Disorder)
 - **Family History:** 75.0% (3/4) family history of Mood Disorder.
 25.0% (1/4) unknown family history.
 - **Ethnicity:** 100% Caucasian
 - **Sex:** 100% female
12. **PERI, E18, P(CCC) 962 A(GCC)**
 - **Frequency:** 11.92% (240/2012)
 - **Diagnoses:** 72.1% (173/240) Mood Disorder (135 with MDD, 30 with Bipolar Disorder,
 7 with Depression NOS, 1 with Dysthymic Disorder)
 0.83% (2/240) Schizoaffective Disorder
 1.25% (3/240) Anxiety Disorder (all Generalized Anxiety Disorder)
 2.08% (5/240) Psychotic Disorder (3 with Schizophrenia, 2 with Psychosis NOS)
 1.25% (3/240) Substance Related Disorder (2 with Alcohol Dependence,
 1 with Cocaine Dependence)
 1.67% (4/240) ADHD
 0.42% (1/240) Eating Disorders (Anorexia-Nervosa)
 25.0% (60/240) Unknown
 - **Family History:** 41.23% (99/240) family history of Mood Disorder
 48.8% (117/240) unknown family history
 7.5% (18/240) no family history of psychiatric illness
 5.84% (14/240) family history of Anxiety Disorder
 2.92% (7/240) family history of ADHD
 2.08% (5/240) family history of Psychotic Disorder
 2.08% (5/240) family history of Substance Related Disorder
 - **Ethnicity:** 63.8% (154/240) Caucasian
 22.1% (53/240) Native American
 6.25% (15/240) African American
 3.33% (8/240) Hispanic
 2.08% (5/240) Other
 0.42% (1/240) Asian
 0.42% (1/240) Asian / Caucasian

0.42% (1/240) Hispanic / Caucasian

0.42% (1/240) Other / Caucasian

0.42% (1/240) Unknown

- **Sex:** 28.8% (69/240) male, 57.1% (137/240) female, 14.2% (34/240) unknown

13. **PERI, E19, V(GTC) 1027 I(ATC)**

- **Frequency:** 0.40% (8/2012)

- **Diagnoses:** 75.0% (6/8) Mood Disorder (all MDD)
25.0% (2/8) Unknown

- **Family History:** 37.5% (3/8) family history of Mood Disorder
37.5% (3/8) no family history
25.0% (2/8) unknown family history

- **Ethnicity:** 87.5% (7/8) Caucasian
12.5% (1/8) Native American

- **Sex:** 25% (2/8) male, 62.5% (5/8) female, 12.5% unknown

14. **PERI, E19, S(TCG) 1060 L(TTG)**

- **Frequency:** 0.05% (1/2012)

- **Diagnoses:** Mood Disorder (MDD)

- **Family History:** unknown family history

- **Ethnicity:** Native American

- **Sex:** male

15. **PERI, E20, A(GCT) 1108 S(TCT)**

- **Frequency:** 0.20% (4/2012)

- **Diagnoses:** 75.0% (3/4) Mood Disorder (2 with Bipolar Disorder, 1 with MDD)
25.0% (1/4) Unknown

- **Family History:** 50.0% (2/4) family history of Mood Disorder
50.0% (2/4) unknown family history
25.0% (1/4) family history of Psychotic Disorder

- **Ethnicity:** 75.0% (3/4) Caucasian
25.0% (1/4) Native American

- **Sex:** 25.0% (1/4) male, 75.0% female

16. **PERI, E20, V(GTC) 1141 I(ATC)**

- **Frequency:** 0.05% (1/2012)

- **Diagnoses:** Mood Disorder (MDD)

- **Family History:** no family history of psychiatric illness

- **Ethnicity:** Caucasian

- **Sex:** female

17. **PER1, E21, A(GCT) 1196 V(GTT)**

- **Frequency:** 0.89% (18/2012)
- **Diagnoses:** 66.7% (12/18) Mood Disorder (9 with MDD, 2 with Bipolar Disorder, 1 with Depression NOS)
22.2% (4/18) Unknown
5.56% (1/18) with Substance Related Disorder (Alcohol Abuse)
5.56% (1/18) with ADHD
- **Family History:** 38.9% (7/18) family history of Mood Disorder
55.6% (10/18) unknown family history
5.56% (1/18) no family history of psychiatric illness
5.56% (1/18) family history of ADHD
5.56% (1/18) family history of Schizophrenia
5.56% (1/18) family history of Alcohol Abuse
- **Ethnicity:** 88.9% (16/18) Caucasian
11.1% (2/18) Native American
- **Sex:** 38.9% (7/18) male, 50% (9/18) female, 11.1% (2/18) unknown

18. **PER1, E22, T(ACC) 1289 I(ATC)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Mood Disorder (Bipolar Disorder)
- **Family History:** unknown family history
- **Ethnicity:** Caucasian
- **Sex:** female

PER3: Table 5 shows that in 2013 study subjects, 55 intronic GVs, which will not be discussed further, and 47 exonic GVs were identified in *PER3*. 17 of the exonic GVs in *PER3* were silent: (1) **PER3, E2, V(GTC) 59 V(GTG)** (0.05% frequency), (2) **PER3, E2, R(CGC) 71 R(CGT)** (0.05% frequency), (3) **PER3, E4, T(ACC) 195 T(ACG)** (0.05% frequency), (4) **PER3, E5, F(TTT) 210 F(TTC)** (0.05% frequency), (5) **PER3, E6, P(CCC) 233 P(CCG)** (0.05% frequency), (6) **PER3, E6, I(ATT) 259 I(ATA)** (0.05% frequency), (7) **PER3, E12, N(AAT) 498 N(AAC)** (0.05% frequency), (8) **PER3, E16, L(CTC) 658 L(CTG)** (0.05% frequency), (9) **PER3, E17, P(CCA) 753 P(CCG)** (2.39% frequency), (10) **PER3, E17, Y(TAC) 805 Y(TAT)** (0.10% frequency), (11) **PER3, E17, S(TCG) 872 S(TCA)** (3.18% frequency), (12) **PER3, E17, L(TTA) 937 L(TTG)** (0.05% frequency), (13) **PER3, E18, A(GCA) 979 A(GCG)** (0.05% frequency), (14) **PER3, E18, T(ACT) 977 T(ACC)** (11.03% frequency), (15) **PER3, E18, T(ACG) 982 T(ACA)** (0.30% frequency), (16) **PER3, E18, T(ACA) 1000 T(ACG)** (2.49% frequency), and (17) **PER3, E18, T(ACG) 1036 T(ACT)** (0.15% frequency). Thirty of the exonic GVs in *PER3* produced an amino acid change: (1) **PER3, E1, A(GCC) 18 S(TCC)** (0.15% frequency), (2) **PER3, E2, Q(CAG) 45 K(AAG)** (0.05% frequency), (3) **PER3, E2, R(AGA) 50 K(AAA)** (0.05% frequency), (4) **PER3, E2, E(GAA) 61 K(AAA)** (0.05% frequency), (5) **PER3, E2, R(CGC) 71 C(TGC)** (0.05% frequency), (6) **PER3, E2, R(CGC) 85 C(TGC)** (0.05% frequency), (7) **PER3, E3, M(ATG) 112 T(ACG)** (0.05% frequency), (8) **PER3, E3, E(GAG) 116 G(GGG)** (0.05% frequency), (9) **PER3, E9, R(CGG) 365 Q(CAG)** (0.05% frequency), (10) **PER3, E11, P(CCA) 414 A(GCA) and PER3, E11, H(CAC) 416 R(CGC)** (0.20% frequency), (11) **PER3, E12, DEL 422 (G)** (0.05% frequency), (12) **PER3, E13, T(ACT) 519 A(GCT)** (0.65% frequency), (13) **PER3, E13, R(AGA) 545 K(AAA)** (0.05% frequency), (14) **PER3, E15, H(CAT) 638 R(CGT)** (0.05% frequency), (15) **PER3, E15, V(GTC) 639 G(GGC)** (16.00% frequency), (16) **PER3, E16, L(TTG) 664 F(TTC)** (0.05% frequency), (17) **PER3, E16, Q(CAG) 708 L(CTG)** (0.05% frequency), (18) **PER3, E17, S(AGC) 750 N(AAC)** (0.05% frequency), (19) **PER3, E17, INS 804 C** (0.05% frequency), (20) **PER3, E17, P(CCG) 828 L(CTG)** (0.10% frequency), (21) **PER3, E17, P(CCT) 835 S(TCT)** (0.05% frequency), (22) **PER3, E17, D(GAC) 854 H(CAC)** (0.20% frequency), (23) **PER3, E17, P(CCT) 856 A(GCT)** (12.33% frequency), (24) **PER3, E17, L(CTG) 860 M(ATG)** (0.05% frequency), (25) **PER3, E17, INS 917 (T)** (0.05% frequency), (26) **PER3, E18, H(CAT) 984 Y(TAT)** (0.10% frequency), (27) **PER3, E19, Q(CAA) 1086 K(AAA)** (0.05% frequency), (28) **PER3, E19, T(ACA) 1111 I(ATA)** (0.05% frequency), (29) **PER3, E20, T(ACT) 1168 A(GCT)** (0.05% frequency), and (30) **PER3, E21, C(TGT) 1176 S(TCT)** (0.35% frequency). Details of these 30 meaningful exonic GVs in *PER3* are outlined below.

Table 5: GV's in *PER3*.

INTRONIC CHANGES		EXONIC CHANGES (SILENT)			EXONIC CHANGES (MEANINGFUL)		
Exon	Description	Exon	Description	Frequency	Exon	Description	Frequency
1	+22 G→A	2	V(GTC) 59 V(GTG)	0.05%	1	A(GCC) 18 S(TCC)	0.15%
1	+23 A→G	2	R(CGC) 71 R(CGT)	0.05%	2	Q(CAG) 45 K(AAG)	0.05%
1	+25 G→A	4	T(ACC) 195 T(ACG)	0.05%	2	R(AGA) 50 K(AAA)	0.05%
1	+27 C→G	5	F(TTT) 210 F(TTC)	0.05%	2	E(GAA) 61 K(AAA)	0.05%
1	+48 2bp DEL	6	P(CCC) 233 P(CCG)	0.05%	2	R(CGC) 71 C(TGC)	0.05%
2	+49 C→T	6	I(ATT) 259 I(ATA)	0.05%	2	R(CGC) 85 C(TGC)	0.05%
2	-18 1bp INS/DEL	12	N(AAT) 498 N(AAC)	0.05%	3	M(ATG) 112 T(ACG)	0.05%
3	+11 A→G	16	L(CTC) 658 L(CTG)	0.05%	3	E(GAG) 116 G(GGG)	0.05%
3	+53 6bp DEL	17	P(CCA) 753 P(CCG)	2.39%	9	R(CGG) 365 Q(CAG)	0.05%
4	-35 T→C	17	Y(TAC) 805 Y(TAT)	0.10%	11	P(CCA) 414 A(GCA)	0.20%
4	+27 A→G	17	S(TCG) 872 S(TCA)	3.18%		and H(CAC) 416 R(CGC)	
5	-17 G→A	17	L(TTA) 937 L(TTG)	0.05%	12	DEL 422 G	0.05%
5	+27 T→C	18	A(GCA) 979 A(GCG)	0.05%	13	T(ACT) 519 A(GCT)	0.65%
6	-61 1bp INS	18	T(ACT) 977 T(ACC)	11.03%	13	R(AGA) 545 K(AAA)	0.05%
7	-15 T→G	18	T(ACG) 982 T(ACA)	0.30%	15	H(CAT) 638 R(CGT)	0.05%
7	+11 C→T,	18	T(ACA) 1000 T(ACG)	2.49%	15	V(GTC) 639 G(GGC)	16.00%
	or 1bp INS	18	T(ACG) 1036 T(ACT)	0.15%	16	L(TTG) 664 F(TTC)	0.05%
7	-20 2bp DEL				16	Q(CAG) 708 L(CTG)	0.05%
7	+39 A→G				17	S(AGC) 750 N(AAC)	0.05%
7	+42 T→C				17	INS 804 C	0.05%
8	+63 T→C				17	P(CCG) 828 L(CTG)	0.10%
9	+36 T→G				17	P(CCT) 835 S(TCT)	0.05%
9	-14 2bp DEL				17	D(GAC) 854 H(CAC)	0.20%
9	+32 C→T				17	P(CCT) 856 A(GCT)	12.33%
11	-38 C→G				17	L(CTG) 860 M(ATG)	0.05%
11	+63 C→A				17	INS 917 (T)	0.05%
11	+7 G→A				18	H(CAT) 984 Y(TAT)	0.10%
11	+56 G→C				19	Q(CAA) 1086 K(AAA)	0.05%
12	-79 C→T				19	T(ACA) 1111 I(ATA)	0.05%
12	-162 C→A				20	T(ACT) 1168 A(GCT)	0.05%
12	+10 C→T				21	C(TGT) 1176 S(TCT)	0.35%
13	-23 C→T						
13	+4 C→T						
14	+73 A→G						
14	+72 C→T						
14	+81 A→G						
15	+12 G→A						
15	-58 G→A						
15	-48 C→G						
15	-45 G→A						
15	+35 C→T						
15	+51 G→C						
15	+66 2bp DEL						
16	-4 T→G						
16	+36 A→G						
17	+51 A→G						
18	+43 G→A						
18	+16 A→G						
19	+67 T→C						
19	+39 1bp DEL						
19	+70 2bp DEL						
		Intronic (cont)					
		<u>Exon</u> <u>Description</u>					
		20 +58 C→G					
		20 +19 G→A					
		20 +48 G→A					
		21 -49 T→C					
		21 +3 A→G					

1. **PER3, E1, A(GCC) 18 S(TCC)**
 - **Frequency:** 0.15% (3/2012)
 - **Diagnoses:** 66.7% (2/3) Mood Disorder (2 with MDD)
33.3% (1/3) Unknown
 - **Family History:** 33.3% (1/3) family history of Mood Disorder
66.7% (2/3) unknown family history
 - **Ethnicity:** 100% (3/3) Caucasian
 - **Sex:** 33.3% (1/3) male, 66.7% (2/3) female

2. **PER3, E2, Q(CAG) 45 K(AAG)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Mood Disorder (Bipolar Disorder)
 - **Family History:** Unknown
 - **Ethnicity:** Caucasian
 - **Sex:** male

3. **PER3, E2, R(AGA) 50 K(AAA)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Unknown
 - **Family History:** Unknown
 - **Ethnicity:** Native American
 - **Sex:** Unknown

4. **PER3, E2, E(GAA) 61 K(AAA)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Unknown
 - **Family History:** Unknown
 - **Ethnicity:** Native American
 - **Sex:** Unknown

5. **PER3, E2, R(CGC) 71 C(TGC)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Psychotic Disorder (Schizophrenia)
 - **Family History:** Unknown
 - **Ethnicity:** Caucasian
 - **Sex:** female

6. **PER3, E2, R(CGC) 85 C(TGC)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Unknown
 - **Family History:** Unknown
 - **Ethnicity:** Native American
 - **Sex:** Unknown

7. **PER3, E3, M(ATG) 112 T(ACG)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Mood Disorder (MDD)
 - **Family History:** Unknown
 - **Ethnicity:** Caucasian
 - **Sex:** male

8. **PER3, E3, E(GAG) 116 G(GGG)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Mood Disorder (MDD)
 - **Family History:** Mood Disorder
 - **Ethnicity:** Caucasian
 - **Sex:** female
9. **PER3, E9, R(CGG) 365 Q(CAG)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Anxiety Disorder (Panic Disorder)
 - **Family History:** Mood Disorder and Anxiety Disorder
 - **Ethnicity:** Hispanic
 - **Sex:** female
10. **PER3, E11, P(CCA) 414 A(GCA) and PER3, E11, H(CAC) 416 R(CGC)**
 - **Frequency:** 0.20% (4/2012)
 - **Diagnoses:** 75% (3/4) Mood Disorder (2 with MDD, 1 with Depression NOS)
 25% (1/4) Unknown
 - **Family History:** 50% (2/4) unknown family history
 25% (1/4) family history of Schizophrenia
 25% (1/4) family history of Mood Disorder
 - **Ethnicity:** 100% (4/4) Caucasian
 - **Sex:** 100% (4/4) female
11. **PER3, E12, DEL 422 (G)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Mood Disorder (MDD)
 - **Family History:** Unknown
 - **Ethnicity:** Caucasian
 - **Sex:** male
12. **PER3, E13, T(ACT) 519 A(GCT)**
 - **Frequency:** 0.65% (13/2012)
 - **Diagnoses:** 84.6% (11/13) Mood Disorder (10 with MDD, 1 with Depression NOS)
 15.4% (2/13) Unknown
 - **Family History:** 53.8% (7/13) unknown family history
 46.2% (6/13) family history of Mood Disorder
 - **Ethnicity:** 92.3% (12/13) Caucasian
 7.69% (1/13) Native American
 - **Sex:** 53.8% (7/13) male, 46.2% (6/13) female
13. **PER3, E13, R(AGA) 545 K(AAA)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Mood Disorder (MDD)
 - **Family History:** Unknown
 - **Ethnicity:** Caucasian
 - **Sex:** male
14. **PER3, E15, H(CAT) 638 R(CGT)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Mood Disorder (MDD)
 - **Family History:** Mood Disorder
 - **Ethnicity:** African American
 - **Sex:** female

15. **PER3, E15, V(GTC) 639 G(GGC)**

- **Frequency:** 16.0% (322/2012)
- **Diagnoses:** 54.4% (175/322) Mood Disorder (129 with MDD, 33 with Bipolar Disorder, 8 with Depression NOS, 3 with Dysthymic Disorder, 2 with Mood Disorder NOS)
44.4% (143/322) Unknown
4.35% (14/322) with Anxiety Disorder (2 with Generalized Anxiety Disorder, 3 with Panic Disorder, 6 with Obsessive-Compulsive Disorder, 1 with Social Phobia, 2 with Posttraumatic Stress Disorder)
4.35% (14/322) with ADHD
2.48% (8/322) with Substance Related Disorder (5 with Alcohol Dependence, 2 with Opioid Dependence, 1 with Cocaine Dependence)
0.62% (2/322) with Psychotic Disorder (2 with Schizophrenia)
0.62% (2/322) with Eating Disorder (2 with Bulimia Nervosa)
0.31% (1/322) with Schizoaffective Disorder
- **Family History:** 64.9% (209/322) unknown family history
33.9% (109/322) family history of Mood Disorder
6.52% (21/322) no family history of psychiatric illness
3.42% (11/322) family history of ADHD
3.42% (11/322) family history of Anxiety Disorder
5.56% (4/322) family history of Substance Related Disorder
5.56% (4/322) family history of Psychotic Disorder
0.31% (1/322) family history of Personality Disorder
- **Ethnicity:** 62.1% (200/322) Caucasian
33.5% (108/322) Native American
1.55% (5/322) African American
0.93% (3/322) Hispanic
0.93% (3/322) Unknown
0.62% (2/322) Other
0.31% (1/322) Caucasian / Other
- **Sex:** 28.9% (93/322) male, 52.8% (170/322) female, 18.3% (59/322) unknown

16. **PER3, E16, L(TTG) 664 F(TTC)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Mood Disorder (Bipolar Disorder)
- **Family History:** Unknown
- **Ethnicity:** Caucasian
- **Sex:** male

17. **PER3, E16, Q(CAG) 708 L(CTG)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Mood Disorder (MDD)
- **Family History:** Mood Disorder
- **Ethnicity:** Caucasian
- **Sex:** female

18. **PER3, E17, S(AGC) 750 N(AAC)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Mood Disorder (MDD)
- **Family History:** Unknown
- **Ethnicity:** Caucasian
- **Sex:** male

19. **PER3, E17, INS 804 C**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Mood Disorder (MDD)
 - **Family History:** Mood Disorder
 - **Ethnicity:** Caucasian
 - **Sex:** male
20. **PER3, E17, P(CCG) 828 L(CTG)**
 - **Frequency:** 0.10% (2/2012)
 - **Diagnoses:** 50.0% (1/2) Mood Disorder (MDD)
 50.0% (1/2) Unknown
 - **Family History:** 100% (2/2) Mood Disorder
 - **Ethnicity:** 50.0% (1/2) Caucasian
 50.0% (1/2) African American
 - **Sex:** 100% (2/2) female
21. **PER3, E17, P(CCT) 835 S(TCT)**
 - **Frequency:** 0.05% (1/2012)
 - **Diagnoses:** Mood Disorder (MDD)
 - **Family History:** Mood Disorder
 - **Ethnicity:** Caucasian
 - **Sex:** female
22. **PER3, E17, D(GAC) 854 H(CAC)**
 - **Frequency:** 0.20% (4/2012)
 - **Diagnoses:** 100% (4/4) Mood Disorder (2 with MDD, 2 with Dysthymic Disorder)
 - **Family History:** 100% family history of Mood Disorder
 - **Ethnicity:** 75% (3/4) Caucasian
 25% (1/4) Native American
 - **Sex:** 25% (1/4) male, 75% (3/4) female
23. **PER3, E17, P(CCT) 856 A(GCT)**
 - **Frequency:** 12.33% (248/2012)
 - **Diagnoses:** 73.4% (182/248) Mood Disorder (144 with MDD, 27 with Bipolar Disorder,
 8 with Depression NOS, 3 with Dysthymic Disorder)
 16.5% (41/248) Unknown
 4.44% (11/248) Anxiety Disorder (5 with Generalized Anxiety Disorder,
 3 with Obsessive-Compulsive Disorder, 3 with Posttraumatic Stress Disorder)
 2.82% (7/248) ADHD
 2.02% (5/248) Substance Related Disorder (3 with Alcohol Dependence,
 1 with Opioid Dependence, 1 with Polysubstance Abuse)
 2.02% (5/248) Psychotic Disorder (5 with Schizophrenia)
 0.81% (2/248) Schizoaffective Disorder
 - **Family History:** 48.4% (120/248) family history of Mood Disorder
 43.1% (107/248) unknown family history
 6.05% (15/248) family history of Anxiety Disorder
 5.24% (13/248) no family history of psychiatric illness
 2.02% (5/248) family history of Psychotic Disorder
 1.21% (3/248) family history of ADHD
 0.81% (2/248) family history of Substance Related Disorder
 0.81% (2/248) family history of Personality Disorder
 - **Ethnicity:** 80.2% (199/248) Caucasian
 12.9% (32/248) Native American
 2.42% (6/248) African American
 2.42% (6/248) Hispanic
 1.21% (3/248) Other

0.40% (1/248) Caucasian / African American)
0.40% (1/248) Caucasian / Indian
- **Sex:** 33.5% (83/248) male, 59.7% (148/248) female, 6.85% (17/248) unknown

24. **PER3, E17, L(CTG) 860 M(ATG)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Anxiety Disorder (Generalized Anxiety Disorder)
- **Family History:** Unknown
- **Ethnicity:** Caucasian
- **Sex:** male

25. **PER3, E17, INS 917 (T)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Mood Disorder (MDD)
- **Family History:** Mood Disorder and Anxiety Disorder.
- **Ethnicity:** Caucasian
- **Sex:** female

26. **PER3, E18, H(CAT) 984 Y(TAT)**

- **Frequency:** 0.10% (2/2012)
- **Diagnoses:** 50% Mood Disorder (MDD)
50% Unknown
- **Family History:** 100% (2/2) Unknown
- **Ethnicity:** 100% (2/2) Caucasian
- **Sex:** 100% (2/2) female

27. **PER3, E19, Q(CAA) 1086 K(AAA)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Unknown
- **Family History:** Unknown
- **Ethnicity:** Native American
- **Sex:** male

28. **PER3, E19, T(ACA) 1111 I(ATA)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Mood Disorder (MDD)
- **Family History:** Mood Disorder
- **Ethnicity:** Caucasian
- **Sex:** female

29. **PER3, E20, T(ACT) 1168 A(GCT)**

- **Frequency:** 0.05% (1/2012)
- **Diagnoses:** Mood Disorder (MDD)
- **Family History:** Mood Disorder
- **Ethnicity:** Caucasian
- **Sex:** female

30. **PER3, E21, C(TGT) 1176 S(TCT)**
- **Frequency:** 0.35% (7/2012)
 - **Diagnoses:** 71.4% (5/7) Mood Disorder (5 with MDD)
 - 14.3% (1/7) Anxiety Disorder (Generalized Anxiety Disorder)
 - 14.3% (1/7) Unknown
 - **Family History:** 57.1% (4/7) Unknown
 - 28.6% (2/7) Mood Disorder
 - 14.3% (1/7) Anxiety Disorder
 - **Ethnicity:** 71.4% (5/7) African American
 - 14.3% (1/7) Hispanic
 - 14.3% (1/7) Native American
 - **Sex:** 42.9% (3/7) male, 42.9% (3/7) female, 14.3% (1/7) unknown

Figure 1 illustrates the GV's identified in *PER1* and *PER3* in the context of the full amino acid sequences of *PER1*, *PER2* and *PER3* from all species from which *PER1*, *PER2* and *PER3* have all been fully sequenced. Intronic GV's and exonic GV's that did not produce an amino acid change are not shown. Red highlight indicates single nucleotide substitutions that produced amino acid changes. Green highlight indicates a double nucleotide substitution that produced a double amino acid change. Blue highlight indicates deleted amino acid(s). Purple highlight indicates inserted nucleotide base. Yellow highlight indicates inserted amino acid.

Figure 1. *PER1* and *PER3* GV's in the context of the full amino acid sequences of *PER1*, *PER2* and *PER3* from all species from which *PER1*, *PER2* and *PER3* have all been fully sequenced.

RED = single nucleotide substitution producing amino acid change
GREEN = double nucleotide substitution producing double amino acid change
BLUE = deleted amino acid(s)
PURPLE = inserted nucleotide base
YELLOW = inserted amino acid

hPER1	1	M	-----
mPER1	1	M	-----
ratPER1	1	M	-----
DanioPER1	1	M	SDDNSD-----
dogPER1	1	M	A G A G V G S G G R E N E Q G P V S P R L D Q N G R D P G E R R A E E P L S R G R W Q L C F A L G T R V G R W K P D G
hPer2	1	M	-----
mPER2	1	M	-----
ratPER2	1	M	-----
DanioPER2	1	M	-----
dogPER2	1	M	-----
hPER3	1	M	-----
mPER3	1	M	-----
ratPER3	1	M	-----
DanioPER3	1	M	-----
dogPER3	1	M	-----


```

hPER1      2  -----
mPER1      2  -----
ratPER1    2  -----
DanioPER1  8  -----
dogPER1    61 LPFFVWPPGPPGPEGAFEQPLSSAADVGFLGDRGGGGSACQAARPPCVLVVASLPSLFSS
hPer2      2  -----
mPER2      2  -----
ratPER2    2  -----
DanioPER2  2  -----
dogPER2    2  -----
hPER3      2  -----
mPER3      2  -----
ratPER3    2  -----
DanioPER3  2  -----
dogPER3    2  -----

```

```

hPER1      2  -----SGPLEGAD---GGGDPRPGESFCPG-----GVPSPGPPQHR
mPER1      2  -----SGPLEGAD---GGGDPRPGEPFCPG-----GVPSPGAPQHR
ratPER1    2  -----SGPLEGAD---GGGDPRPGEPFCPG-----GVPSPGAPQHR
DanioPER1  8  -----SAPSNDADSGAGGIEKKAGRS-C-----GMSESSPSSNP
dogPER1    121 CPPHGPDMMSGPLEGAD---GGGDGPGGESFCPG-----GAPSPGPLQHP
hPer2      2  -----NGYAEFPP-----SPSNPTKEP
mPER2      2  -----NGYVDFSP-----SPTSPTKEP
ratPER2    2  -----NGYVDFSP-----SPTSPTQEP
DanioPER2  2  -----SEDLDSKPYLFSLEGQDGAIGCSSMATLHRMASFAEGTELGLASEGSDSSQ
dogPER2    2  -----NRYTEYPP-----SPSHPAQEP
hPER3      2  -----
mPER3      2  -----
ratPER3    2  -----
DanioPER3  2  -----PGGD-----GFPDGEQEN
dogPER3    2  -----

```

```

hPER1      35 PCPGPS-----LADDTDA-NSNG--SS-----GNESNGHESRG  PER1 P(37)S
mPER1      35 PCPGPS-----LADDTDA-NSNG--SS-----GNESNGPESRG
ratPER1    35 PCPGPS-----LADDTDA-NSNG--SS-----GNESNGHESRG
DanioPER1  41 ESSGSGGLSGPKGSAGGNRGVNSDDTDG-LSSGND SG-----ERESEGGMQRG
dogPER1    162 SCPGPG-----LADDTDA-NSNG--SS-----GNESNGPESRG
hPer2      19 VEPQPSQVP-----LQEDVDM--SSG--SS-----GHETNENCSTG
mPER2      19 GAPQPTQAV-----LQEDVDM--SSG--SS-----G--NENCSTG
ratPER2    19 GEPQPTQAV-----LQEDVDM--SSG--SS-----G--NENCSTG
DanioPER2  54 DRPTSGHNTRKMSHS-----LHEDVEMKSSSGSSGS-----GTESHGNESHG
dogPER2    19 VEAEPGAP-----LQEDVHM--SSG--SS-----GNEANENHSPG
hPER3      2  -----PRGEAPGPGRGAK-----DEALG  PER3 A(18)S
mPER3      2  -----DPCGDPAVLGG-----DCPQTRG
ratPER3    2  -----DPCGNPAVPGG-----DCPQTRG
DanioPER3  15 SSPGPDIIHTGQTDQTSS----GQDP----GTSGNISASGEEEEAEERIGRRSSGCEESGG
dogPER3    2  -----DPREDLGVSKSLDSRGSEPR-----EPQACCSEALG

```

hPER1 65 A-----SQRSSHSSSSGNGKDSA-LLETTESSKSTNSQSPSPSSSIAYSLLSASSEQD
 mPER1 65 A-----SQRSSHSSSSGNGKDSA-LLETTESSKSTNSQSPSPSSSIAYSLLSASSEQD
 ratPER1 65 A-----SQRSSHSSSSGNGKDSA-LLETTESSKSTNSQSPSPSSSIAYSLLSASSEQD
 DanioPER1 88 SGRGRQSNRSYQSSSSQNGKDSAMGMETTESNKSSNSHSPSPSSSLAYSLLSASSEQD
 dogPER1 192 A-----SQRSSHSSSSGNGKDSA-LLETTESSKSTNSQSPSPSSSIAYSLLSASSEQD
 hPer2 51 R-----DSQGSDCDDSGKELGMLVEPPDAR-----QSP-DTFSLMMAKSEH-
 mPER2 48 R-----DSQGSDCDDNGKELRMLVSSNTH-----PSPDDAFRLMMTEAEH-
 ratPER2 48 R-----DSQGSDCDDSGKELRMLVSSNTH-----PSPDDTFRLMMTEAEH-
 DanioPER2 96 NESHGNEESHGNESSGSSNSRSKDSALLVSSGSNKSSNSHSPSPSSSTNAFSLLSASSEQD
 dogPER2 51 R-----DSQGSE-----ELGMLVGPVVH-----PSP-GAFGLMMAKSEH-
 hPER3 21 E-----ESGERWSPEF
 mPER3 20 P-----GLQGASGQEG
 ratPER3 20 P-----GLQGSSGQEG
 DanioPER3 67 EQTHEDVDMNSTHTSSSGNDSIHHRHHHHHRHHHHHHHSSSNCSPGSTTGSSTKSSKS
 dogPER3 33 K-----GQEEVWSEKS

hPER1 118 NPSTS-----GCSSE----QSARARTQKELMTALRELKLRLPPERRGKG-RSGTLATL **PER1 R(158)C**
 mPER1 118 NPSTS-----GCSSE----QSARARTQKELMTALRELKLRLPPERRGKG-RSGTLATL
 ratPER1 118 NPSTS-----GCSSE----QSARARTQKELMTALRELKLRLPPERRGKG-RSGTLATL
 DanioPER1 148 PPSTS-----GCSSE----QSARVQTQKELMRALNELKIRLPPERKMKG-RSSTLNAL
 dogPER1 245 NPSTS-----GCSSE----QSARARTQKELMTALRELKLRLPPERRGKG-RSGTLATL
 hPer2 91 NPSTS-----GCSSE----QSSKVDTHKELIKTLKELKVHLPADKKAKG-KASTLATL
 mPER2 89 NPSTS-----GCSSE----QSAKADAHKELIRTLKELKVHLPADKKAKG-KASTLATL
 ratPER2 89 NPSTS-----GCSSE----QSAKADAHKELIRTLRELKVHLPADKKAKG-KASTLATL
 DanioPER2 156 NPSTS-----GCSSE----ESAKAKTQKELIKTLKELKLHLPAEKRNKGSKSTTLNNTL
 dogPER2 85 STSAS-----GC-SE----QSAKADAHKELIKTLKELKVHLPVDKKAKG-KASTLATL
 hPER3 32 HLQRK---LADSSHSE----QDNRNVSEELIMVVQEMKKYFPAERHN---KPSTLDAL **PER3 Q(45)K**
 mPER3 31 PLQGT---CVDSSHSE----HEDRNRMSEELIMVVQEMKKYFPAERHT---EPSTLDAL **PER3 R(50)K**
 ratPER3 31 PLOGI---CVDSSHSE----HEDRNRMSEELIMVVQEMKKYFPAERHT---KPSTLDAL **PER3 E(61)K**
 DanioPER3 127 ATGSSSSSFHSTHHTTECGEQTETGREHTHREMMHTVQEMKKRLPSEKRSRS-KASTVEAL **PER3 R(71)C**
 dogPER3 44 QLQSPQLFFFLLSYSE----QDNRNVSEELVMVVQEMKKYFPSGRHS---KPSTLDAL

hPER1 166 QYALACVKQVQANQEYYQQWSLEEGEPSCMDMSTYTLLEELEHITSEYTLQNDTFVAVS **PER1 E(191)C**
 mPER1 166 QYALACVKQVQANQEYYQQWSLEEGEPSCAMDMDSTYTLLEELEHITSEYTLRNQDTFVAVS
 ratPER1 166 QYALACVKQVQANQEYYQQWSLEEGEPSCAMDMDSTYTLLEELEHITSEYTLRNQDTFVAVS
 DanioPER1 196 KYALSCVRQVRANQEYYHQWNVEECHGCSLDLSTFTVEELDNITSEYTLKNTDTFTMAVS
 dogPER1 293 QYALACVKQVQANQEYYQQWSLEEGEPSCAMDMSVYTLLEELEHVTSEYTLRNQDTFVAVS
 hPer2 139 KYALRSVKQVKANEYYQLLMSSEGHPCGADVPSYTVVEEMESVTSEHIVKNADMFAVAVS
 mPER2 137 KYALRSVKQVKANEYYQLLMSSESQPCSVDVPSYSMEQVEGITSEYIVKNADMFAVAVS
 ratPER2 137 KYALRSVKQVKANEYYQLLMSSESQPCSVDVPSYTVVEEGITSEYIVKNSDMFAVAVS
 DanioPER2 205 KYALRCVRQVEANEYYQLLMINDSQPSGLDVSSYVTEEIDSITSEYTLKNTDIFAVAVS
 dogPER2 132 KYALRSVKQVKANEYYQLLMSSENHPCSAVPSYTVVEEIESVTSEFTVKNAGMFAAAVS
 hPER3 81 NYALRCVHVSQANSEFFQIL--SONGAPQADVSMYSLEELATIASEHTSKNTDTFVAVFS **PER3 R(85)C**
 mPER3 80 NYALRCVHVSQANSDFQSL--GPRGARQADVTVYSLEDLTALASEHTSKNTDTFAAVFS **PER3 M(112)T**
 ratPER3 80 NYALRCVHVSQANSEFFQSL--SPRGARQAEATVYNLEELTSLASEHTSKNTDTFVAVFS **PER3 E(116)G**
 DanioPER3 186 HYALNCVKQVQANSEYYNLLM--SSGLDERRDATVCTLEELGFTSEHTLKNTDSFVVVFS
 dogPER3 96 NYALRCVHVSQASSEFFQIL--SQSGTLQTDATVYSLEELATLASGYTSKNTDTFVAVFS

hPER1	226	FLTGRIVYISEQAAVLLRCKRDVFRGTRFSELLAPQDVGVFYGSTAPSRLPTWGTGASAG	PER1 V(240)I
mPER1	226	FLTGRIVYISEQAGVLLRCKRDVFRGARFSELLAPQDVGVFYGSTTPSRLPTWGTGTSAG	
ratPER1	226	FLTGRIVYISEQAGVLLRCKRDVFRGARFSELLAPQDVGVFYGSTTPSRLPTWGTGTSAG	
DanioPER1	256	FLSGKVYIISPQGSLLRCKPERLHGVLFSSELLAPQDVSTFYSENTAPCKLPWASCIGSV	
dogPER1	353	FLTGRIVYISEQAGVLLRCKRDVFRGTRFSELLAPQDVGVFYGSTAPSRLPTWGTGASAG	
hPer2	199	LVSGKILYISDQVASIFHCKRDAFSDAKFVEFLAPHDVGVFHVSFTSPYKLPPLWSMCSGAD	
mPER2	197	LVSGKILYISNQVASIFHCKKDAFSDAKFVEFLAPHDVSFVHVSFTTPYKLPWPWSVCSGLD	
ratPER2	197	LVSGKILYISNQVAPIFHCKKDAFSDAKFVEFLAPHDVSFVHVSFTTPYKLPWPWSVSSGLD	
DanioPER2	265	LITGKIVYISDQAASILNCKRDVFKNAKFVEFLTPQDVSVFYSTTPYRLPSWSMCTGAD	
dogPER2	192	LATGKILYISDQVASIFHCKRDAFYGARFVEFLAPHDVSFVHASTTPYKLPWPWSVGRGAD	
hPER3	139	FLSGRLVHISEQAALILNRKDVLLASHFVDLLAPQDMRVFYAHTARAQLPFWNNWTQRA	
mPER3	138	FLSGRLVHISEQAALILNSKRGFLKSVHFVDLLAPQDVRVAFYAHTAPTQLPFWNNWTQRA	
ratPER3	138	FLSGRLVHISEQAALILNSKKGFLKSLHFVDLLAPRDVRVAFYAHTAPTQLPFWNNTWTQRA	
DanioPER3	245	LASGKVYIASEQASSVLHCKRKFLSAKFVEMLYHQDVNVFYSHTAQPRLPSWNLGTDISA	
dogPER3	154	FLSGRLVHVSEQATLILNCKKDFLESSHFMEELLAPQDVRVFCAPHTAHTQLPLWNNWTQRA	

hPER1	286	SGLRDFQTQEKSVFRCRIRGGPDRDPGPRYQPFRLTPYVTKIRV----SDGA--PAQPCCLL	PER1 S(296)C
mPER1	286	SGLKDFQTQEKSVFRCRIRGGPDRDPGPRYQPFRLTPYVTKIRV----SDGA--PAQPCCLL	PER1 R(307)Q
ratPER1	286	SGLKDFQTQEKSVFRCRIRGGPDRDPGPRYQPFRLTPYVTKIRV----SDGA--PAQPCCLL	PER1 Q(314)R
DanioPER1	316	SPPMECTQEKSMFCRISGDVSSSSDVRYYPFRLTPYLIILRD----SDMA--FPQPCCLL	
dogPER1	413	SGLKDFQTQEKSVFRCRIRGGPDRDSGPRYQPFRLTPYVTKIRV----SDGA--PAQPCCLL	
hPer2	259	SFTQECMEEKSFFCRVSVRKSHENEIRYHPFRMTPYLKVRD----QQGA--ESQLCCLL	
mPER2	257	SFTQECMEEKSFFCRVSVGKHHENEIRYQPFMTPYLKVQE----QQGA--ESQLCCLL	
ratPER2	257	SFTQECMEEKSFFCRVSVGKHHENEIRYQPFMTPYLKVQE----QKGA--ASQLCCLL	
DanioPER2	325	SSPSDCMQEKSFFCRISGGKECEADLQYYPFRMTPSYLDEGSGCGAFRRIS--SAAFCCPL	
dogPER2	252	SFTQECMEEKSFFCRVSVGKNHENEIGYHAFSMTPYLVKVRD----QQCA--GSQLCCVL	
hPER3	199	A-RYECAPVKPFRCRIRGGEDRKQEKCHSPFRIPYLIHVHH----PAQPELESEPCCLT	
mPER3	198	S-QYECAPAKPFFCRICGGGDRE-KRHYSPPFRILPYLVHVHS----SAQP--EPEPCCLT	
ratPER3	198	S-QYECAPVKPFFCRICGGGDREQKRHYSPPFRILPYLVHVHS----PAQP--EPEPCCLT	
DanioPER3	305	AVLFECAQVKPFFCRIRGGKDRDGMRYSPFRITPYLIKVQG----SSG---EPEPCCLA	
dogPER3	214	S-QYEFAPVKSFFCRIRGGKDAEQEKHYYPFRIPYLIHVHR----AAQP--EPEPCCLT	

hPER1	340	IAERIHSGYEAPRIPDPDKRIFTTRHTPSCLFQDVDERAAP--LLGYLPQDLIGAPVLLFL	
mPER1	340	IAERIHSGYEAPRIPDPDKRIFTTRHTPSCLFQDVDERAAP--LLGYLPQDLIGAPVLLFL	
ratPER1	340	IAERIHSGYEAPRIPDPDKRIFTTRHTPSCLFQDVDERAAP--LLGYLPQDLIGAPVLLFL	
DanioPER1	370	IAERVHSGYEAPRIPDKRIFTTSHTPSCVFQEVDERAVP--LLGYLPQDLVGTPTVLLCI	
dogPER1	467	IAERIHSGYEAPRIPDPDKRIFTTRHTPSCLFQDVDERAAP--LLGYLPQDLIGAPVLLFL	
hPer2	313	LAERVHSGYEAPRIPPEKRIFTTHTPNCLFQDVDERAVP--LLGYLPQDLIETPVLVQL	
mPER2	311	LAERVHSGYEAPRIPPEKRIFTTHTPNCLFQAVDERAVP--LLGYLPQDLIETPVLVQL	
ratPER2	311	LAERVHSGYEAPRIPPEKRIFTTHTPNCLFQDVDERAVP--LLGYLPQDLIETPVLVQL	
DanioPER2	383	LAERVHSGYEAPRIPDKRIFTTHTPSCVFQDVDERAVPLQLLGYLPQDLIGTPVLLIHL	
dogPER2	306	LAERVHSAYEAPRIPPEKRIFTTHTPNCLFQDVDERAVP--LLGYLPQDLIETPVLVRL	
hPER3	254	VVEKIHSGYEAPRIPVNRKIFTTHTPGCVFLEVDEKAVP--LLGYLPQDLIGTSILSYL	
mPER3	250	LVEKIHSGYEAPRIPVDKRIFTTHTPGCVFLEADERAVP--LLGYLPQDLIGTSILTLYL	
ratPER3	251	LVEKIHSGYEAPRIPVDKRVFTTHTPGCVFLEVDERAVP--LLGFLPQDLIGTSILTLYL	
DanioPER3	358	LAERIIHSGYEAPRIPMDKRIFSTTHSPGCVFLEVDDRVP--LLGYLPQDLIGTSVLTCL	
dogPER3	267	LVEKIHSGYEAPRIPVDKRIFTTHTPGCVFLEIDERAVP--LLGYLPQDLMGRSVLTYL	

hPER1	398	HPEDRPLMLAIHKKILQLAGQ-PFDHSPIRFCARNGEYVTMDTSWAGFVHPWSRKVAFVL	
mPER1	398	HPEDRPLMLAIHKKILQLAGQ-PFDHSPIRFCARNGEYVTMDTSWAGFVHPWSRKVAFVL	
ratPER1	398	HPEDRPLMLAIHKKILQLAGQ-PFDHSPIRFCARNGEYVTMDTSWAGFVHPWSRKVAFVL	
DanioPER1	428	HPDDRHMVAIHKKILQFAGQ-PFEHSPIRMCARNGEYMTIDTSWSSFINPWSRKVAFIV	
dogPER1	525	HPEDRPLMLAIHKKILQLAGQ-PFDHSPIRFCARNGEYVTMDTSWAGFVHPWSRKVAFVL	
hPer2	371	HPSDRPLMLAIHKKILQSGGQ-PFDYSPIRFRARNGEYITLDTSWSSFINPWSRKISFII	
mPER2	369	HPSDRPLMLAIHKKILQAGGQ-PFDYSPIRFRTRNGEYITLDTSWSSFINPWSRKISFII	
ratPER2	369	HPSDRPLMLAIHKKILQASGQ-PFDYSPIRFRTRNGEYITLDTSWSSFINPWSRKISFII	
DanioPER2	443	HPNDRPTMLGIHRKIC--AGQ-PFDHS-IRFCARNGEYITIDTSWSSFVNPWSRKVSFVI	
dogPER2	364	HPGDRPLMVTVHKKIVQSGGQ-PFDYSPIRFRARNGEYVTLDTSWSSFINPWSRKISFII	
hPER3	312	HPEDRSLMVAIHQKVLKYAGHPPFEHSPIRFCTQNGDYIILDSSWSSFVNPWSRKISFII	PER3 R(365)Q
mPER3	308	HPEDRPLMVAIHQKVLKYAGHPPFEHSPVRFCTQNGEYVILDDSSWSSFVNPWSRKVSFII	
ratPER3	309	HPEDRPLMVAIVHQKVLKYAGHPPFEHSPIRFCTQNGDYVILDDSSWSSFVNPWSRKVSFII	
DanioPER3	416	HPDDRLLMLAMHRKIVKYAGQPPFEHSPIRFRCQNGDYVTLDDSSWSSFINPWSRKVAFII	
dogPER3	325	HPEDRSLMLTVHQKVLKYAGHPPFEHSPIRFCTQNGDYIILDSSWSSFVNPWSRKVSFII	
hPER1	457	GRHKVRTAPLNEDVFTPPAPSPAPSLDIDIQELSEQIHRLLLQPVHSPSPTGLCGVGAVT	
mPER1	457	GRHKVRTAPLNEDVFTPPAPSPAPSLDSDIQELSEQIHRLLLQPVHSSSPTGLCGVGPLM	
ratPER1	457	GRHKVRTAPLNEDVFTPPVPSPAPSLDSDIQELSEQIHRLLLQPVHSSSTTGLCGVGPLM	
DanioPER1	487	GRHKVRTSPLNEDVFTPPRGLERALTDPDIVQLSEQIHRLLVQPVHCGSSQGYGSLPSNG	
dogPER1	584	GRHKVRTAPLNEDVFTPPAPSPALSIDSDIQELSEQIHRLLLQPVHSPSPSGLCGVGPIT	
hPer2	430	GRHKVRVGPLNEDVFAAHPCTEEKALHPSIQELTEQIHRLLLQVPVPHSGSSGYGSLGSNG	
mPER2	428	GRHKVRVGPLNEDVFAAPPCEEKTPHPSVQELTEQIHRLLMQVPVPHSGSSGYGSLGSNG	
ratPER2	428	GRHKVRVGPLNEDVFAASPCPEEKTPHPSVQELTEQIHRLLMQVPVPHSGSSGYGSLGSNG	
DanioPER2	499	GRHKVRMGVFNEDVFAAPATAEGKCVDSIDIQDITEQIHRLLLQPVHNNGSSGYGSLGSN-	PER3 P(414)A
dogPER2	423	GRHRVRVGPLNEDVFSAPSLVEEKDQHPISIQELTEQIHRLLLQVPVPHSGSSGYGSLGSNG	and
hPER3	372	GRHKVRTSPLNEDVFATKIK-KMNDNDKIDITELQEIQYKLLLPVHVSVSSCYGSLGSSG	PER3 H(416)R
mPER3	368	GRHKVQTSPLNEDVFATRIK-KAASNKDKIAELQEIQIHKLLLQPVHASASSGYGSLGSSG	
ratPER3	369	GRHKVRTSPLNEDVFATRIK-KATSHDEDITELQEIQIHRLLLQPVHASASSGYGSLGSSG	PER3 DEL422 G
DanioPER3	476	GRHKVRTPLNEDVFAARSKADQPMCEDVKELQAMIHKLFLQPVHNNGSSGYGSLGSNG	
dogPER3	385	GRHKVRMSPLNEDVFATRIK-KMNSNDKDVTELQEIQIHKLLLQVPVHASASSGFGSLGSGD	
hPER1	517	SPGPLHSPGSSSDSNGGD-----AEGPGPPAPVTFQQICKDVHLVKHQGQQLFIESRAR	
mPER1	517	SPGPLHSPGSSSDSNGGD-----AEGPGPPAPVTFQQICKDVHLVKHQGQQLFIESRAK	
ratPER1	517	SPGPLHSPGSSSDSNGGD-----AEGPGPPAPVTFQQICKDVHLVKHQGQQLFIESRAK	
DanioPER1	547	SHEHQPSAASSSDSSGPG-----LEDPSQLHKPMTFQQICKDVHVMKTNGQQVFIDSRNR	
dogPER1	644	SPGPLLSPGSSSDSNGGD-----AEGPGPPAPVTFQQICKDVHLVKHQGQQLFIESRAR	
hPer2	490	SHEHLMSQTSSSDSNGH-----EDSRRRR-----AEICKNGNKTKNRSHY-----SH	
mPER2	488	SHEHLMSQTSSSDSNGQ-----EESHRRR-----SGIFKTSGKIQTSHV-----SH	
ratPER2	488	SHEHLMSQTSSSDSNGQ-----EESHWRR-----SGIFKTSGKSQKSHF-----SP	
DanioPER2	558	--DHLLSVASSSESNNGNTRQRHEEDIRKAKPRSFQEICKGVHMQKNQELQ-----SK	
dogPER2	483	SHEHLMSQTSSSDSNGH-----EDSRRRR-----TEICKNGSSVKNKSH-----PG	
hPER3	431	SQEQLVSIASSSEASGHR-----VEETKAEQ--MTLQQVYASVNKIKNLGQQLYIES-MT	
mPER3	427	SQEQHVSITSSSESSGHC-----PEEQHEQ--MTLQQVYASVNKIKNVGQQLYIES-MA	
ratPER3	428	SQEQHISVTSSSESSGHC-----VEEAQQEQ--MTLQQVYASVNKIKNVGQQLYIES-MA	
DanioPER3	536	SHEHYISVASSSDSNGNL-----WEDSHRET--MTLQQFCADVNVKKNWGQOAYLESRKK	
dogPER3	444	SQEPRASLASSRESGGPR-----GEAARRAP--TALQRVCASVNKMKKLGQQLHIESAAA	

hPER1 571 PQSRPRLPATGTFKAKALPCQSPDPELEAGSAPVQAPLALVPEEAERKEASSCSYQQINC
 mPER1 571 PPPRPLLATGTFKAKVLPQSPNPELEVAPVPDQASLALAPEEPERKETS GC SYQQINC
 ratPER1 571 PPPRPLLATGTFKAKVLPQSPNPELEVAPAPDQASLALAPEEPERKESSGCSYQQINC
 DanioPER1 602 PPPKKHSTAGALKAGQSAEVCRLVPCAAPPKSSAPS LIVQKEP----PTTF SYQQINC
 dogPER1 698 PMPRPLPATGMFKAKTL SGQFPDPELEMVPAPGPAPLTLTPEEAERKEASSCSYQQINC
 hPer2 532 ESGEQKKKSVTEMQTNPPAEKKAVPAMEKDSL G-----VSFPEELACKNQPTCSYQQISC
 mPER2 530 ESGGQKEASVAEMQSSPPAQVKAVTTIERDSSGASLPKASFPEELAYKNQPPCSYQQISC
 ratPER2 530 ESGGQKEASVAEMQSSPPAQVRSVTTMERDSSGASLPKASFPEELTYKSQPPCSYQQISC
 DanioPER2 610 KSPTKFVQKSPVVRPKDSAYPVNWRESQEEQR-----AAVQEELAFKDQTVYSYQQISC
 dogPER2 524 ESGEQKEKSAEMHSSSPAQMKA VP-VEKDSSGTS LPA GSSPEELGCKNPPAGSYQQISC
 hPER3 483 KSSFKPVTGTR-TEPNGGGECKTFTSFHQTLKNNS-VYTEPCEDL-RNDEHSPSYQQINC **PER3 T(519)A**
 mPER3 479 RSSVKPVAETC-VEPQGGDEQKDLSS-SQTLKNKSTTDTGSGGNL-QQE QPSSSYQQMNC
 ratPER3 480 RSSVKPVMETC-TEPQGSDEQKDFSS-SQTLKNKS-TDTGSGGDL-RPEQHSSSYQQMNC
 DanioPER3 589 LTALGPATAVA-----GAGVHASSSHDLGIRDHL---KQSLQKA-RKQPHIPSYQQINC
 dogPER3 497 RSPDKHAMGTHPARP--GGEQKASSP-LQTLKNNS-VHMESCEGW-RKDQHSPSYQQINC

 hPER1 631 LDSILRYLES CNLPSTTKRKCAS---SSSYTTSSASDDDRQRTGPVSVGTTKDKPPSAALS **PER1 S(640)N**
 mPER1 631 LDSILRYLES CNIPSTTKRKCAS---SSSYTASSASDDDKQ RAGPVPVGA KKDPSSAMLS
 ratPER1 631 LDSILRYLES CNIPNTTKRKCAS---SSCTASSASDDDKQ RAGPVPVGA KKDTSSAVLS
 DanioPER1 658 LDSIIRYLES CNVPNTV KRKCGS---SSCTASSTSDDDKQ QEAP---GNAKGPSVSLVD
 dogPER1 758 LDSILRYLES CNIPSTTKRKCAS---SSSCTTSSASDDDKQ RTGPVPLGT KDKPP-AVLS
 hPer2 587 LDSVIRYLES CN EAATLKRKCEF---PANVPALRSSDKRKATVSPGPHAGEA EPPSRVNS
 mPER2 590 LDSVIRYLES CNSEAATLKRKCEF---PANIPS-----RKATVSPGLHSGEAARPSKVTS
 ratPER2 590 LDSVIRYLES CN EAATLKRKCEF---PANIPS-----RKATVSPGLHSGEAARSSKVTS
 DanioPER2 664 LDSVIRYLES CNVPIITV KRKQCS---SSNTTSSNSDEDKQRNADSSMQVSEE--PAHLKE
 dogPER2 583 LDSVIRYLES CNSEAATLKRKCEF---LGNMATQKASDKRKAVAS PGLHSTDTTLPTKVNS
 hPER3 540 IDSVIRYLKSYNIPA-LKRKCIS---CTNTTSSSSEEDKQNHKADDVQALQAGLQIPAI P **PER3 R(545)K**
 mPER3 536 IDSVIRYLTSYSLPA-LKRKCIS---CTN-TSSSSEEAKPIPEVDSSQ----RDTEQLLD
 ratPER3 536 IDSVIRYLTSYFPA-LKRKCIS---CTN-TSSSSEEAKPNPEADGSL----RDTEQLLD
 DanioPER3 639 VDSIIRYLES CATSA-LKRKCESLSITSSSSSTSEEDKPTAAAHENTDEAALDAARALD
 dogPER3 552 IDSVIRYLKSYNIPA-LKRKCIS---CTNTTSSSSEEDGQNHKAHHAQALQ-GNTNALLT

 hPER1 688 GEG---ATPRKEP----VVGGLSPLALANKAESVVS VTSQCSFSSTIVHVGDKKPPESD
 mPER1 688 GEG---ATPRKEP----VVGGLSPLALANKAESVVS VTSQCSFSSTIVHVGDKKPPESD
 ratPER1 687 GEG---ATPRKEP----VVGGLSPLALANKAESVVS VTSQCSFSSTIVHVGDKKPPESD
 DanioPER1 711 DSA-----LPLALHNKAESVASVTSQCSFSSTIVHVGDKKPPESD
 dogPER1 814 GEG---ASLQKEP----VVGGLSPLALANKAESVVS VTSQCSFSSTIVHVGDKKPPESD
 hPer2 644 RTG-----VGTHTLSLALPGKAESVASLTSQCSYSSTIVHVGDKKPPQPEL
 mPER2 641 HTE-----VSAHLSSLTLPGKAESVSLTSQCSYSSTIVHVGDKKPPQPEL
 ratPER2 641 HTE-----VSAHLSSLALPGKAESVSLTSQCSYSSTIVHVGDKKPPQPEL
 DanioPER2 719 QSGLSTLEVSKKPPGSGVSPSLTPLALPSKPESVVSITSQCSYSSTIVHVGDKKEI---
 dogPER2 640 HAE-----VSAHLPLTLPCKAESVSLTSQCSYSSTIVHVGDKKPPQPEL
 hPER3 596 KSEMP TNGRSIDT-----GGGAPQILSTAMLSLGSGISQCGYSSTIVHV---PPPET- **PER3 H(638)R**
 mPER3 587 IRKQETTGPSTDI-----EGGAARTLSTAALSVASGISQCSCSSTSGHA---PPLQ-- **PER3 V(639)G**
 ratPER3 587 IPEQETTTPSADA-----EGGVARTLSTAALSMASGVSQCSCSSTTDHV---PPLQ--
 DanioPER3 698 -SQVSAGSATTAA---VVGAPLTDITISTEAMSVVS VTSQCSYSSTIVHV---PQPESE
 dogPER3 607 NLEIPTAWQSTHA-----TEGTPRTLAPAALSLGSGMSQCSYSSTMVLA---PPPE--

hPER1	741	IIMMEDLPGLAPGPA-----PS P APSPTVAP-DPAPDAYR-----PVGLT	PER1 DEL758 PAPS
mPER1	741	IIMMEDLPGLAPGPA-----PSPAPSPTVAP-DPTPDAYR-----PVGLT	
ratPER1	740	IIMMEDLPGLAPGPA-----PSPAPSPTVAP-DPAPDAYR-----PVGLT	
DanioPER1	753	IV-MEEAPP-TPNTALPVTQPQFPMATPSLPLSP-APDRDAGRRGGPGASAGGERLGLT	
dogPER1	867	IIMMEDLPGLAPGPA-----PSPAPSPTVAP-DPAPDAYR-----PVGLT	
hPer2	689	EM-VEDAAS-GPESLD-----CLAGPALACGL-SQEKEPFK-----KLGLT	
mPER2	686	ET-VEDMAS-GPESLD-----GAAG-----GL-SQEKGPLQ-----KLGLT	
ratPER2	686	ET-VEDVAS-GPESQD-----DAAG-----GL-SQEKGSLQ-----KLGLT	
DanioPER2	776	---IEDVPS-AEGTDVQ-----GLAVPPAAVSPQNQEREAYK-----KLGLT	
dogPER2	685	EL-VEDAVS-GPEPD-----GRPC-----SL-GPEKEPLR-----TLGLT	
hPER3	645	---ARDAFL-FCPEW-----TLNMQPAP L TS-----EEFK-----HVGLT	PER3 L(664)F
mPER3	635	---SESVAV-ACKPW-----ALRTKASHLAA-----GGFK-----HVGLT	
ratPER3	635	---SESVAG-ACEPW-----ALRTK-AHVTA-----EGFK-----PVGLT	
DanioPER3	750	VTAL E DAPM-GSEPADSAPAPASPAHDSGSASTSQ-----EELL-----VLGLT	
dogPER3	655	---SEDAAP-VCEPW-----TLSTSPAPLMS-----EEFK-----HIGLT	
hPER1	780	KAVLSLHTQKEEQAFLSRFRDLGRLRGLDSSSTA---PSALGERGCHHGPPAPSRRH---	
mPER1	780	KAVLSLHTQKEEQAFLNFRFDLGRRLGLDTSSVA---PSAP---GCHHGPIPPGRRH---	
ratPER1	779	KAVLSLHTQKEEQAFLSRFRDLGRLRGLDTSSVA---PSAP---GCHHGPIPSGRRH---	
DanioPER1	810	KEVLSAHTQKEEQNFMCFRGDLKLRVFDPTSAVRRRPNAPLSRGVRCRSDYPAAGS---	
dogPER1	906	KAVLSLHTQKEEQAFLSRFRDLGRLRAFDSSSPA---PLAPGERGCHHGPPAPGRRH---	
hPer2	727	KEVLAHAHTQKEEQSFLQKFKEIRKLSIFQSHCHY---YLQERSKGQPSERTAPGLRN---	
mPER2	719	KEVLAHAHTQKEEQGFLQRFREVSRLSALQAHCQN---YLQERSRAQASDR---GLRN---	
ratPER2	719	KEVLAHAHTQREEQGFLQRFREVSRLGALQAHCQN---YLQERSRAPASDR---GLRN---	
DanioPER2	814	KQVLAHAHTQKEEQAFLSRFRELRGVHAFKADCSL---YL-ERQKGQVTSEAVPAARSCKA	
dogPER2	718	KEVLAHAHTQKEEQSFLRFKEMRKLSTFQSRCHH---YLQEKSKGQLSERTTPGLRN---	
hPER3	676	AAVLSAHTQKEEQNYVDKFRF---KILSSPYSS---YL Q QESRSKAKYSY-FQGDS---	PER3 Q(708)L
mPER3	666	AAVLSAHTQKEEQNYVDRFRF---KILTSPTYGC---YLQEQSRNRAQYSC-VQAGS---	
ratPER3	665	AAVLSAHTQKEEQNYVDRFRF---KILTSPTYGC---YLQEQGRNHAKYACVVGAGA---	
DanioPER3	793	KEVLSAHTQKEEQQFVDRFRH---RIVQSPYSS---YLQQDNSSNA-----	
dogPER3	686	KAVLSAHTQKEEQNYVDKLRF---KIFLSPYRS---CLQEQESRSRAKHLY-VQGDC---	
hPER1	834	-----HCRSKAKRSR--HH Q NPRAEAPCYVSH P -----	PER1 Q(846)R
mPER1	831	-----HCRSKAKRSRHHHHQTPRPETPCYVSH P -----	PER1 P(859)S
ratPER1	830	-----HCRSKAKRSR--HHQTPRPETPCYVSH P -----	
DanioPER1	867	-----SGRRRGRGGKRLK--HQESSEQTGSCSPAGPIRGLLPGVLPALGRPSNP	
dogPER1	960	-----HCRSKAKRSR--HHQTPRAEAPCYGSH P -----	
hPer2	781	--TSGIDSPWKKKTGKNRKLKSKRVK--PRDSSESTGSGGPVSA-----	
mPER2	770	--TSGLESSWKKKTGKNRKLKSKRVK--TRDSSESTGSGGPVSH-----	
ratPER2	770	--ASGISSWKKKTGKNRKLKSKRVK--TRDSSESTGSGGPVSH-----	
DanioPER2	870	GGGGAQETTTTTRRGRNKKTKSKRVK--PNESSDSTPSGRRPAH-----	
dogPER2	772	--ASGIDSSWKKKTGKNRKLKSKRAK--PRDSSESTGSGGPAPL-----	
hPER3	725	-----TSKQTRSAGCRKGKHKRKK--LPEPPD S SSSNTGSG P -----	PER3 S(750)N
mPER3	715	-----TAKHSRCAGSERQKHKRKK--LPAPVDTSSPGAHLCP-----	
ratPER3	715	-----TPKHSRCAGSERRKHKRKK--LPTPVDSSSSSAHLCP-----	
DanioPER3	833	-----HSHHRGDVVRQPNKHKRPK--PEDSSDSYECSQPGNYW-----	
dogPER3	735	-----AGKQTRSTGCKKSKQK--LPVLSDSRGTQDTFC P -----	

hPER1	860	----SPVPPSTPWPTPPAT-----TPFPVAV-----VQPYPLPVF-----SP	
mPER1	859	----SPVPSSGPWPPPPAT-----TPFPAM-----VQPYPLPVF-----SP	
ratPER1	856	----SPVPSSGPWPPPPAT-----TPFPVAV-----VQPYPLPVF-----SP	
DanioPER1	913	SIPMGPTASSSSW-PTSQSASVQVYPT-----PTVLPVLPVYPPISHPVSDPSM	
dogPER1	986	----PPVSPSAPWPPPAT-----TPFPVAV-----VQPYPLPVF-----SP	
hPer2	820	-RPPLVGLNATAWSPSDTSQSSCPAVFPAP--VPAAYS--LPVFPA-----PGTVAAP	
mPER2	809	-RPPLMGLNATAWSPSDTSQSSCPSAFPFTA--VP-AYP--LPVFQAPGIVSTPGTVVAP	
ratPER2	809	-RPPLVGLNATAWSPSDTSQSSCPSAFPAP--VP-AYP--LPVFPAPGIVSTPGTVVAP	
DanioPER2	911	-RPQLQGLNQTWSWSPSDTSQSTFP-IAYPAV--MP-AYP--LQMYPGAGGMQPRVDPMP	
dogPER2	811	-RPPLLGLNATAWSPSDTSQSSCPTTFPAS--VP-AYP--LPVFPAGILPTPGAVAAA	
hPER3	760	-R-RGAHQNAQPCCPSAASSPHTSSPTFPPAAMVPSQAPYLVPAPFLPAATSPGREYAAP	PER3 INS804 C
mPER3	750	-HVTGLLPDEQHWGSPASPSPLGAGLAFPSALVVPSQTPYLLPSFPLQDMASQGVGSAA	
ratPER3	750	-HVRGLLPDVQHWASVTS-PCATGLALPSALVVPNQTPYLLSSFPLQDMAPHGVGDSAP	
DanioPER3	869	SLPGPTAAPHSSWSPSESSQPPPSNIGFVPPMAVPMQTP---PYFNIIGADQQ-----	
dogPER3	770	-HFGGESESRQPWGPALSSCLQAPGLSFPAAAMVPSLAPYFVPALRIPALPSVQREPGAS	
hPER1	892	RGGPQPLPPAPT-----SVPP--AAFPAPLVTPMVALVLPNYL-----FP--	
mPER1	891	RGGPQPLPPAPT-----SVSP--ATFPSPLVTPMVALVLPNYL-----FP--	
ratPER1	888	RGGPQPLPPAPT-----SVSP--ATFPSPLVTPMVALVLPNYL-----FP--	
DanioPER1	963	QSGL-----RFPLQN--SQMAPPMVPPMMALVLPNYM-----FPQP	
dogPER1	1018	RGGSQSLASAPT-----AGPP--AAFPAPLVTPMVALVLPNYL-----FP--	
hPer2	869	PAPPHASFTVPVAVPVDLQHQFAVQP--PPFPAPLA-PVMAFMLPSYS-----FPSG	
mPER2	863	PAATHGFTMPVVPVPMGTQPEFAVQP--LPFAAPLA-PVMAFMLPSYP-----FPPA	
ratPER2	863	PAAAHTGFTMPVVPVPMGTQPEFAVQP--LPFAAPLA-PVMAFMLPSYP-----FPPA	
DanioPER2	964	GFGESQCAPDP-----RIPMQPIQTTPYSAPLVTPMVALVLPNYM-----FPQV	
dogPER2	865	PVAPHASFAVPPPLPVDARHEFGLQP--SPFAVPLA-PVMALVLPNYP-----LPAV	
hPER3	818	GTAPEGLHGLPL-----SEGLQPY-PAFFFPYLDTFMTVFLPDPV-----CPLL	PER3 P(828)L
mPER3	809	WGAAAGC--PPL-----SAGQAV-AAFPSAYVDTLMTIFLHNAPL-----FPLW	PER3 P(835)S
ratPER3	808	WGAAAECC--PPL-----SAGPHPV-STFPSAYMGTFTMTVLLHNSPL-----FPLW	PER3 D(854)H
DanioPER3	919	---PVMLQPDPG-----VQNLQPM-TP-----MMVVLLPSFPMYPPNNGMYFMA	PER3 P(856)A
dogPER3	829	LTTLDYLLKPPL-----LNGLHSF-PALSPSSDVTMTTFLPDPTG-----CPLL	PER3 L(860)M
hPER1	930	-----TPSSYPYGA--LQTPAEGPPTPASHSPSPSLP---	
mPER1	929	-----TPSSYPYGV--SQAPVEGPPTPASHSPSPSLP---	
ratPER1	926	-----SPTSYPYGV--SQAPVEGPPTPASHSPSPSLP---	
DanioPER1	997	SVGMA-----QPFYSPNSAFPFAAAANMGSPAPCQIQTPIQRA---	
dogPER1	1056	-----TPSGYPYGV--PQTPAEGPPTPASHSPSPSLP---	
hPer2	917	-----TPNL-PQAFFPSQPQFPSHPTLTSEMASASQPEF-	
mPER2	911	-----TPNL-PQAFLLPSQPHFPAHPTLASEITPASQAEF-	
ratPER2	911	-----TPNL-PQAFFPSQPHFPAHPTLASEITPASQAEF-	
DanioPER2	1007	GKRSTPGFLPPQNRDHSPPSPFRLQPGFTPQASFPPQSTFTTIQTQFTSQNPFSQPTFQ	
dogPER2	913	-----PPGL-PQAFFPGQPDFLSH-----VIPASQPEL-	
hPER3	862	-----SPSFLPCPFLGATASSAISPSMSSAMSPTLDP---	
mPER3	851	-----PPSFSYPYSLGAAGSSELAP-LVPAMAPNPEP---	
ratPER3	850	-----PASFSYPYFLGATGPSQMAP-LVPAMAPDLEP---	
DanioPER3	960	-----APGVVYNYIGGFVPPGTMPMAEAPLQGHNLESAGV	
dogPER3	873	-----SPSFCPYAFLGAAGSSGTPP-FVSAVAPHLEQ---	

hPER1	960	--ALPPSPPHR-----PDSPLFNSRCSSPLQLNL	PER1 P(962)A
mPER1	959	--PPPLSPPHR-----PDSPLFNSRCSSPLQLNL	
ratPER1	956	--PPPPSPPHR-----PDSPLFNSRCSSPLQLNL	
DanioPER1	1034	--HSRSSTPHSYSQRENGAEREG-----AESPLFQSRCSSP--LNL	
dogPER1	1086	--PPPPSPPRR-----SDSPLFNSRCSSPLQLNL	
hPer2	950	--PSRTSIPRQPCACP-----ATRATPPSA---MGRASPPLFQSRSSSPLQLNL	
mPER2	944	--PSRTSTLRQPCACP-----VTPPAGTVA---LGRASPPLFQSRGSSPLQLNL	
ratPER2	944	--PSRTSMLRQPCACP-----VTPPAGTVA---LGRASPPLFQSRGSSPLQLNL	
DanioPER2	1067	PQPFPPACPEDPPKAPEPELREEQSRSPTPQSMGGG---GPPSPPLFQSRCSLPLQLNL	
dogPER2	940	--AGRTPSPKQPCACQPAERGPAASRAATPASPAPASGPTGRASPPLFQSRGSSPLQLNL	
hPER3	894	----PPSVTSQRREEEKWEAQS-----EGHPFITSRSSSPLQLNL	PER3 INS917(T)
mPER3	882	----TTSGHSPRRVEENWEAHS-----EELPFISSRSSSPLQLNL	
ratPER3	881	----TPSDHGPRRVEENWETHSE-----EEHPFISSRSSSPLQLNL	
DanioPER3	995	GVPAEPDSIPEPWFGEDLDAAQ-----PTALFSSSRSSSPIQLNL	
dogPER3	904	----LSSVLSQRQAEGRWEMPH-----GEHHCINRSRSSSPLQLNL	
hPER1	987	LQLEELPRAEG-----A--AVAGGPGSSAGPP-----	
mPER1	986	LQLEESPRTEG-----G--AAAGGPGSSAGPL-----	
ratPER1	983	LQLEESPRTEG-----G--AAAGGPGSSAGPL-----	
DanioPER1	1071	LQLEESPSNRFEVASGQQTTSMPV--GQGGGAGGQASSN-----	
dogPER1	1113	LQLEEPPRVEG-----G--ATAGGPGSSAGPP-----	
hPer2	994	LQLEEAPEGGT---GAMGTTGATE--TAAVGADCKPGTS-----	
mPER2	988	LQLEEAPEGST---GAAGTLGTTG--TAASGLDCTSGTS-----	
ratPER2	988	LQLEEAPESST---GAAGTLGTTG--TAASGLDCTSGAS-----	
DanioPER2	1123	LQLEETQRSADRQENTAPSAVPLN--NCSTGVEKAGSVT-----	
dogPER2	998	LQLEEAPEGSS---AAAATAGSSG--TA--GPDCKPGTS-----	
hPER3	930	LQEEMPRPSESPDQMRNRCPQTEY-CVTGNNGSESSPATTGALSTGSPPRENPSHPTAS	PER3 H(984)Y
mPER3	918	LQEEMPAPSEYADALRRGACPDQAKHHCVTGPSGSRSRHC-----	
ratPER3	918	LQEEMPAPSEYADALRRGACPDQAKLQCVTGNNSGSRSPPC-----	
DanioPER3	1035	LQEELTKPSEAQTSTNADSLHEHH--TKTDDARSEC-----	
dogPER3	940	LQEDMLRSCSSDQ-----GVLGRSGSKKNPF-----	
hPER1	1012	-----PPSAEAAPEARLAEVTESSNQDALSGSSDLLLELL	PER1 V(1027)I
mPER1	1011	-----PPSEETAPEARLVEVTESSNQDALSGSSDLLLELL	
ratPER1	1008	-----PPSEESAPEPRLVEVTESSNQDALSGSSDLLLELL	
DanioPER1	1108	-----QRGSAVDSKTNENGETNESNQDAMSTSSDLLDLL	
dogPER1	1138	-----PPSEKTAPEASLVEVTESSNQDALSGSSDLLLELL	
hPer2	1028	-----RDQQPKAPLTRDE--PSDTQNSDALSTSSGLLNLL	
mPER2	1022	-----RDRQPKAPPTCNE--PSDTQNSDAISTSSDLLNLL	
ratPER2	1022	-----RDRQPKAPPTCSE--PSDTQNSDAISTSSDLLNLL	
DanioPER2	1160	-----AQSKPVKDVVQDEGSPVDGQHSDALSSSSDLLDIL	
dogPER2	1030	-----WDRQPKTAPIRED--PADAQNSDALSTSSGLLDLL	
hPER3	989	ALSTGSPPMKNPSHPTASALSTGSPPMKNPSHPTASTLSMGLPPSRTPSHPTATVLTSGS	
mPER3	957	-----TSGELATAT	
ratPER3	957	-----ATGELATAS	
DanioPER3	1070	-----HQDAHS--SSEMLDQL	
dogPER3	967	-----TASELSMAL	

hPER1 1047 LQEDSRSGTGSAA**S**GLGSLGLS-----GSGSGSHEGGSTASITRSSQSSHTSKYFGS **PER1 S(1060)L**
 mPER1 1046 LQEDSRSGTGSAA**S**GLGSLGLS-----GSGSGSHEGGSTASITRSSQSSHTSKYFGS
 ratPER1 1043 LQEDSRSGTGSAA**S**GLGSLGLS-----GSGSGSHEGGSTASITRSSQSSHTSKYFGS
 DanioPER1 1142 LQEDSRSGTGSAA**S**GSSGTGSSGSGSGSSGSGSN-GCSSSGSGTRSSQSSNTSKYFGS
 dogPER1 1173 LQEDSRSGTGSAA**S**GLGSLGLS-----GSGSGSHEGGSTASITRSSQSSHTSKYFGS
 hPer2 1061 L**N**EDLCSASGSAAS-----E-----SLGSGSL-GCDASPSGAGSSDTSHSTKYFGS
 mPER2 1055 L**G**EDLCSATGSALSRSGASATSD-----SLGSSSL-GFGTSQSGAGSSDTSHSTKYFGS
 ratPER2 1055 L**G**EDLCSATGSALSRSGASATSD-----SLGSSSL-GCDTSRSGAGSSDTSHSTKYFGS
 DanioPER2 1195 -**P**EDSRSGTGSATSGSMGSGS-N-----RCGTSA**A**EG--S**A**SRTESSNKSNNSSNYFGS
 dogPER2 1063 L**H**EDLCSATGSALSRSGASATSD-----SLGSGSL-GCDTSRSGTGSSTSHSTKYFGS
 hPER3 1049 **P**PSESPSRTGSAASGS-----SDSSIIYLTS
 mPER3 966 **A**Q**Q**ECPS---AAASGS-----SASSIYFSS
 ratPER3 966 **V**Q**Q**ESPS---AAASGS-----SASSVHGSG
 DanioPER3 1085 L**Q**EDARSGTGSNASGSGSGESGG-----SLGSGS--**G**LG**S**NGTSTSHSTGSSNSKYFAS
 dogPER3 976 L**P**EE**S**PSGAGSTASGS-----SDSSIIYLAS

hPER1 1101 ID-SSEAE**A**GAARGGA-----EPGDQ**V**IKYVLQDP**I**WLLMANADQ**R**VMMTYQVPSRDMTS **PER1 A(1108)S**
 mPER1 1100 ID-SSEAEAGAA**R**ART-----EPGDQ**V**IKCVLQDP**I**WLLMANADQ**R**VMMTYQVPSRDAAS **PER1 V(1141)I**
 ratPER1 1097 ID-SSEAEAGAA**Q**ART-----EPGDQ**V**IKYVLQDP**I**WLLMANADQ**H**VMMTYQVPSRDAAS
 DanioPER1 1201 **V**D-SSENSHSR**K**QT**A**E----GDGEA**Q**FIKCVLQDP**I**WLLMANTDEKTM**M**TYQ**L**P**I**RD**R**DS
 dogPER1 1227 ID-SSEAEAGAA**Q**ARA-----EPGDQ**V**IKYVLQDP**I**WLLMANADQ**R**VMMTYQVPSRDMAT
 hPer2 1106 ID-SSENNHKAKMNTG----MEESE**H**FIKCVLQDP**I**WLLMADADSSVM**M**TYQ**L**PSRN**L**EA
 mPER2 1108 ID-SSENNHKAKMIPD----TEESE**Q**FIKYVLQDP**I**WLLMANTDDSIM**M**TYQ**L**PSRDL**Q**A
 ratPER2 1108 ID-SSENNHKAKMITD----TEESE**Q**FIKYVLQDP**I**WLLMANTDDNIM**M**TYQ**L**PSRDL**Q**A
 DanioPER2 1245 **V**D-SS**Q**KSHKAKA**Q**GSGV**L**ALDRSE**N**L**I**KYVLQDP**L**WLLMAN**V**DE**D**VMM**S**YQ**L**PSRDI**Q**K
 dogPER2 1116 ID-SSENNHQAKMKAD----MEES**K**HFIKYVLQDP**V**WLLMADTDDSVMM**M**TYQ**M**PSRN**L**ET
 hPER3 1074 SVYSSK**I**SQNG**Q**Q**S**QD-----VQK**K**ETFPN**V**A**E**EP**I**WR**M**IR**Q**T**P**ER**I**L**M**TYQ**V**PER**V**KEV **PER3 Q(1086)K**
 mPER3 988 TDY**A**SEVSE**N**RQ**R**PQD-----RQ**R**DE**A**PPG**A**EE**S**IWR**M**IER**T**PE**C**VL**M**TYQ**V**PER**G**REE **PER3 T(1111)I**
 ratPER3 988 SDY**T**SEVSE**N**Q**R**SQD-----TH**R**D**R**AF**S**G**A**EE**S**IWR**M**IER**T**P**Q**CV**L**MTYQ**V**PER**G**RD**T**
 DanioPER3 1137 **N**D-SS**D**TSR**K**ARK**S**AE---AQ**E**RE**R**SG**F**KK**H**V**D**DP**L**WS**M**IK**Q**T**P**EP**V**ML**T**YQ**I**SS**R**D**Q**A**Q**
 dogPER3 1001 SDY**S**SE**I**TS**N**G**Q**Q**F**Q**G**-----VQ**K**ETFP**P**GL**A**EE**S**M**W**R**M**IK**Q**T**P**EC**I**L**M**TYQ**V**PER**V**TE**A**

hPER1 1155 VL**K**QDRERLRAMQ**K**Q**Q**PRF**S**EDQ**R**REL**G**AVHSWVR**K**Q**L**PR**A**LD**V**M---AC**V**DC**G**S**S**T**Q**D **PER1 A(1196)V**
 mPER1 1154 VL**K**QDRERLRAMQ**K**Q**Q**PRF**S**EDQ**R**REL**G**AVHSWVR**K**Q**L**PR**A**LD**V**T---AC**V**DC**G**S**S**V**Q**D
 ratPER1 1151 VL**K**QDRERLRAMQ**K**Q**Q**PRF**S**EDQ**R**REL**G**AVHSWVR**K**Q**L**P**Q**ALD**V**T---AC**V**DC**G**S**S**V**Q**D
 DanioPER1 1256 VL**K**EDRAALRAMQ**K**H**Q**PRF**T**EE**Q**SE**L**SQ**V**HP**I**RT**G**RL**P**RA**I**N**I**S---AC**A**G**C**R**S**PP**S**V
 dogPER1 1281 VL**K**QDRERLRAMQ**K**Q**Q**PRF**S**EDQ**R**REL**G**AVHSWVR**K**Q**L**PR**A**LD**V**M---AC**V**DC**G**S**S**T**Q**D
 hPer2 1161 VL**K**EDREKL**K**L**L**Q**L**Q**P**RF**T**ES**Q**K**Q**EL**R**EV**H**Q**W**M**Q**T**G**GL**P**AA**I**D**V**A---EC**V**Y**C**EN**K**E**K**G
 mPER2 1163 VL**K**ED**Q**E**K**L**K**L**L**Q**R**S**Q**PRF**T**EG**Q**RREL**R**EV**H**P**V**W**H**T**G**GL**P**TA**I**D**V**T---GC**V**Y**C**E**S**E**E**K**G**
 ratPER2 1163 VL**K**ED**Q**E**K**L**K**L**L**Q**R**S**Q**PH**F**T**E**G**Q**RREL**R**EV**H**P**V**W**H**T**G**GL**P**TA**I**D**V**T---GC**V**Y**C**E**S**E**E**K**G**
 DanioPER2 1304 VL**R**EDREKL**R**Q**M**Q**K**S**Q**PRF**T**DE**Q**K**R**EL**A**D**V**HP**M**RR**G**GL**P**KA**I**D**I**K---AC**M**G**C**E**E**L**S**E**A**
 dogPER2 1171 VL**K**EDREKL**K**AM**Q**K**S**Q**P**RF**T**EG**Q**R**Q**EL**Q**D**V**HP**W**L**R**AG**L**P**T**AL**D**LT---EC**V**Y**C**EN**Q**G**P**D
 hPER3 1129 VL**K**EDLEK**L**ES**M**R**Q**Q**P**Q**F**SH**G**Q**K**E**L**AK**V**Y**N**W**I**Q**S**Q**T**V**T**Q**E**I**D**I**Q**---AC**V**T**C**----- **PER3 T(1168)A**
 mPER3 1043 VL**K**Q**D**LE**K**L**Q**S**M**E**Q**Q**P**L**F**SPA**Q**RE**L**AK**V**RS**W**I**H**S**H**T**A**P**Q**E**G**H**L**Q---SC**V**A**C**----- **PER3 C(1176)S**
 ratPER3 1043 VL**R**EDLE**K**L**H**S**M**ER**Q**R**P**Q**F**SS**A**Q**K**E**L**AK**V**RS**W**I**H**SH**P**AP**E**ER**Q**L**R**AM**S**P**V**K**T**-----
 DanioPER3 1193 VL**Q**EDREKL**L**IM**Q**PM**Q**P**W**F**T**SD**Q**K**K**EL**A**EV**H**P**W**I**Q**Q**N**T**V**P**Q**E**I**N**T**Q---GC**V**SC**N**T**I**E**P**N
 dogPER3 1056 VL**R**EDLE**K**L**A**S**M**Q**G**Q**Q**P**W**F**S**R**G**Q**R**Q**E**L**A**SV**H**SW**I**Q**S**Q**T**V**Q**G**I**D**I**Q---DC**V**T**C**-----

hPER1 1212 PGH-PDDPLFSELDGLG-LPEMEEGGGEGQSS-----GGGSGEGEGCEEAQG----CAKA
 mPER1 1211 PGH-SDDPLFSELDGLG-LPEMEEGGGEGGGC-----GVGGGGGDDGEEAQTQI--GAKG
 ratPER1 1208 PGH-SDDPLFSELDGLG-LPEMEEGGGEGGGVGGGGGGVGGGGGGGEEAQTQI--GTKG
 DanioPER1 1313 PSATPFDVEIHMEFCSVLAVAAEEKQTPDTV--MEKSETDGQNETCKENNGTV--TTAQ
 dogPER1 1338 PGH-PNDPLFSELDGLG-LPEMEEGGGEGGGE--GGGEGGGEGEGGEEAQAQA--GARV
 hPer2 1218 NICIPY-----EEDIPSL--GLSE
 mPER2 1220 NICLPY-----EEDSPSP--GLCD
 ratPER2 1220 NLCLPY-----EEDSPSL--GLCD
 DanioPER2 1361 LN-----EDDPPDLHMGEAE
 dogPER2 1228 SICVPY-----EEDSPTL--GPSE
 hPER3 1180 -----E-NEDSA--DGAA
 mPER3 1094 -----E-DRGSV--GDTA
 ratPER3 1097 -----EVQLVTL--QRPV
 DanioPER3 1250 EKL-----NLQTDSP--NPPD
 dogPER3 1107 -----E-SKESV--RVFA

hPER1 1261 SSSQDLAMEEEEEGRSSSSPALPTAGNCIS
 mPER1 1262 SSSQDSAMEEEEEQGGSSSPALPAEENSTIS
 ratPER1 1264 SSSQDSAMEEEEEQGGSSSPALPAEENGTS
 DanioPER1 1369 INDQEMLTTEEQEMTSQIEEEMGASHTQMTHT
 dogPER1 1392 SSSQDLAMEEEEEQGGSSSPALPATENGTS
 hPer2 1235 VSDTK-----EDENGSPLNHRIEEQT-
 mPER2 1237 TSEAK-----EEEGEQLTGPRIEAQT-
 ratPER2 1237 TSEAK-----EEESGQLANPRKEAQT-
 DanioPER2 1376 NSDVTAAPNSQELQEPNNSPTHSCPGPDT-
 dogPER2 1245 AIDTQ-----EKERGAPSGCSREERT-
 hPER3 1190 TSCGQ-----VLVEDSC
 mPER3 1104 EVLEQ-----HPAEDTS
 ratPER3 1108 NSVQQ-----KTPVEQL
 DanioPER3 1264 ISCPQ-----DCPPQENRPDTDT-
 dogPER3 1117 ESCGH-----TPAANSS

PER1 T(1289)I

Table 6: Classification of GVs in *PER1* and *PER3*

- CLASS 1:** 1. *PER3* INS 917 (T)
2. *PER3* DEL 422 G
3. *PER3* P(414)A and H(416)R
- CLASS 2:** 4. *PER3* E(61)K
5. *PER3* R(365)Q
6. *PER3* H(638)R
7. *PER3* E(116)G
8. *PER3* R(85)C
9. *PER1* S(640)N
10. *PER1* R(158)C
11. *PER3* R(71)C
12. *PER3* C(1176)S
13. *PER3* Q(45)K
14. *PER1* S(1060)L
15. *PER3* P(828)L
16. *PER3* P(835)S
17. *PER3* INS 804 C
- CLASS 3:** 18. *PER3* V(639)G
19. *PER3* S(750)N
20. *PER1* S(296)C
21. *PER3* Q(708)L
22. *PER3* D(854)H
23. *PER1* R(307)Q
24. *PER3* R(545)K
25. *PER3* R(50)K
26. *PER3* M(112)T
- CLASS 4:** 27. *PER1* DEL 758-761 PAPS
28. *PER3* H(984)Y
29. *PER3* P(856)A
30. *PER3* T(1111)I
31. *PER1* E(191)C
32. *PER1* P(962)A
33. *PER1* Q(314)R
34. *PER1* P(859)S
35. *PER1* Q(846)R
36. *PER3* T(1168)A
37. *PER1* A(1108)S
38. *PER1* V(240)I
39. *PER1* A(1196)V
40. *PER3* T(519)A
41. *PER1* V(1027)I
42. *PER3* Q(1086)K
43. *PER3* L(664)F
44. *PER3* L(860)M
45. *PER1* T(1289)I
46. *PER1* V(1141)I
47. *PER3* A(18)S
48. *PER1* P(37)S

Table 6 illustrates our classification of all potentially meaningful exonic changes that were discovered in *PER1* and *PER3*. These GVs were broadly divided into 4 classes, and then further ranked within these classes. Class 1 is composed of truncations and radical amino acid changes having, or very likely having, functional consequences on protein function. Class 2 is composed of GVs in which the amino acid change is radical, or otherwise located within a highly conserved region likely to have functional importance. Class 3 is composed of amino acid changes that are less radical or that occur at a less well-conserved amino acid site still located within a larger conserved region. Class 4 is composed of amino acid changes that are either not radical or not located at a conserved amino acid site or within a larger conserved region.

Class 1 is composed of 3 GVs: (1) *PER3* INS 917 (T), (2) *PER3* DEL 422 G, and (3) *PER3* P(414)A and H(416)R. *PER3* INS 917 (T) inserts a T nucleotide within exon 17 that causes a frameshift mutation. *PER3* DEL 422 G is a deletion of the amino acid G at a perfectly conserved G in all PER proteins across all species from which the PER proteins have been fully sequenced. This G closely follows the conserved nuclear export sequence (NES) (*PER3* 528 ITELQEIQYKLLLQPVH), which is highly conserved in all PER proteins across all species from which the *PER* genes have all been fully sequenced. Deletion of this perfectly conserved G within a very highly conserved region of *PER3* is likely to have serious consequences on proper protein functioning. The double mutation *PER3* P(414)A and H(416)R also occurs on the immediate C-terminal side of the NES. As shown in **Figure 1**, these two amino acids are perfectly conserved in all *PER3* proteins from which *PER3* has been fully sequenced, and is almost perfectly conserved in all PER proteins from all species from which the *PER* genes have all been fully sequenced. Within proteins, proline often functions to terminate α -helical domains, and a mutation that

substitutes alanine for proline might disrupt the normal α -helical structure of the NES. We have more fully analyzed the *in vitro* consequences of this double mutation, and shown that it effectively disrupts nuclear export function of *PER3*.

The *PER3* P(414)A and H(416)R double mutation affects nuclear localization of *PER3*: Nuclear entry of mammalian clock gene products is an essential step in assuring 24 hour rhythmicity of the core circadian clock (35,36). Subcellular localization of the murine clock Period proteins (mPeriod 1, 2, and 3) is thought to be controlled by a number of mechanisms including dimerization (37,38), phosphorylation by CKI ϵ (39), and intrinsic localization signals (38,39,40). It was first recognized in *Drosophila* that the dPeriod protein contained a clear nuclear localization signal (NLS) and cytoplasmic localization domain (CLD) (35,36). A few years later a series of papers was published describing similar domains in mPeriod 1 (mPer1), mPeriod 2 (mPer2), and mPeriod 3 (mPer3) (38). Furthermore, Vielhaber and colleagues demonstrated a conserved, functional nuclear export signal (NES) in the mPer proteins (40). In efforts to understand the specific residues required for a functional NES of human Per3 (hPER3), alanine scanning mutagenesis was performed in which sequential triple alanines were substituted for residues within the NES or surrounding sequences (**Figure 2**). These were generated in the context of a construct containing residues 1-454 of hPer3 fused to EGFP (**Figure 3**). The various constructs were transfected in HEK 293 cells, and localization visualized by fluorescence microscopy. The results are described in **Figure 4** and shown in **Figure 5**. Mutant constructs containing triple alanine substitutions in residues 400-417 failed to be excluded from the nucleus. These results demonstrate that residues 400-417 are critical for functionality of the Per3 NES.

* * *

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DITELQEIQYKLLLQPVHVS SVSSGYGSLGSSGS
AAAEIQYKLLLQPVHVS SVSSGYGSLGSSGS
DITAAAEIQYKLLLQPVHVS SVSSGYGSLGSSGS
DITELQAAAYKLLLQPVHVS SVSSGYGSLGSSGS
DITELQEIQIAAALLQPVHVS SVSSGYGSLGSSGS
DITELQEIQIYKLAAPVHVS SVSSGYGSLGSSGS
DITELQEIQYKLLLQAAAVS SVSSGYGSLGSSGS
DITELQEIQYKLLLQPVHAAASSGYGSLGSSGS
DITELQEIQYKLLLQPVHVSVAAYGSLGSSGS
DITELQEIQYKLLLQPVHVS SVSSGAAALGSSGS
DITELQEIQYKLLLQPVHVS SVSSGYGSAASGS
DITELQEIQYKLLLQPVHVS SVSSGYGSLGSAAA

```

Figure 2. Triple alanine scanning mutagenesis of residues 400-432 of hPer3. The NES is highlighted in yellow while the various positions of the substituted alanines are in red. Single asterisks indicate the site of the *PER3* P(414)A and H(416)R double mutation. Double asterisks indicate the site of *PER3* DEL 422 G.

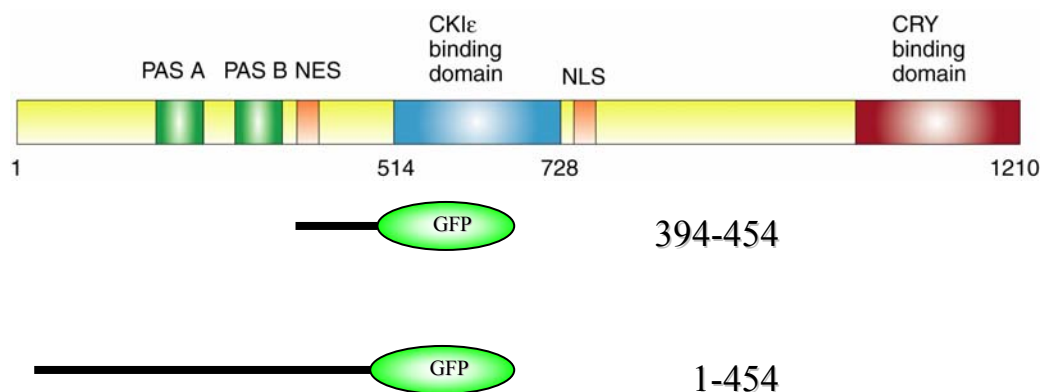


Figure 3. Truncated Per3 GFP fusion constructs. C-terminal Per3 truncation constructs were generated with either residues 394-454 (consisting of the NES and surrounding conserved regions) or 1-454 (includes both PAS domains and the NES) fused to an enhanced GFP to investigate the role of various mutations on nuclear/cytoplasmic localization.

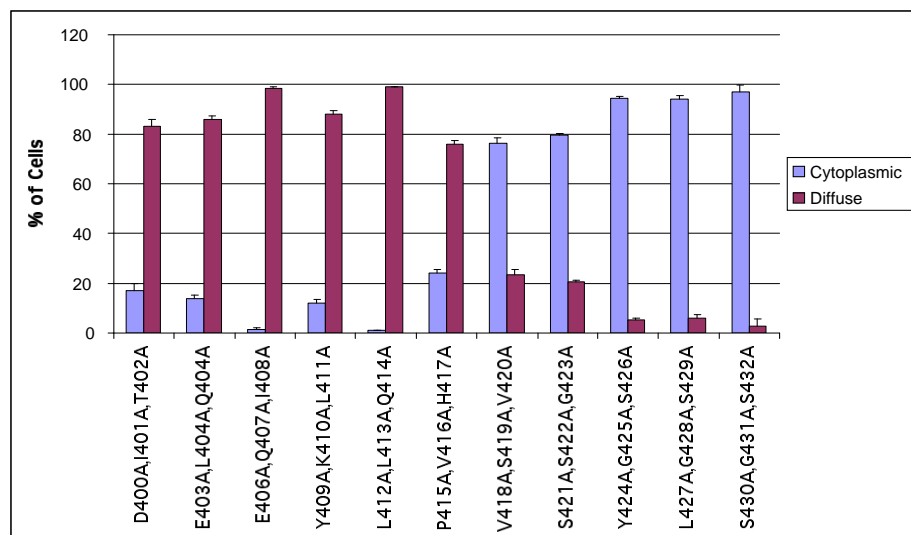


Figure 4. Subcellular localization of NES triple alanine mutants. Following transfection of the various mPer3 (1-454)-GFP constructs, cells were stained with DAPI and scored based on the exclusion of GFP from the nucleus.

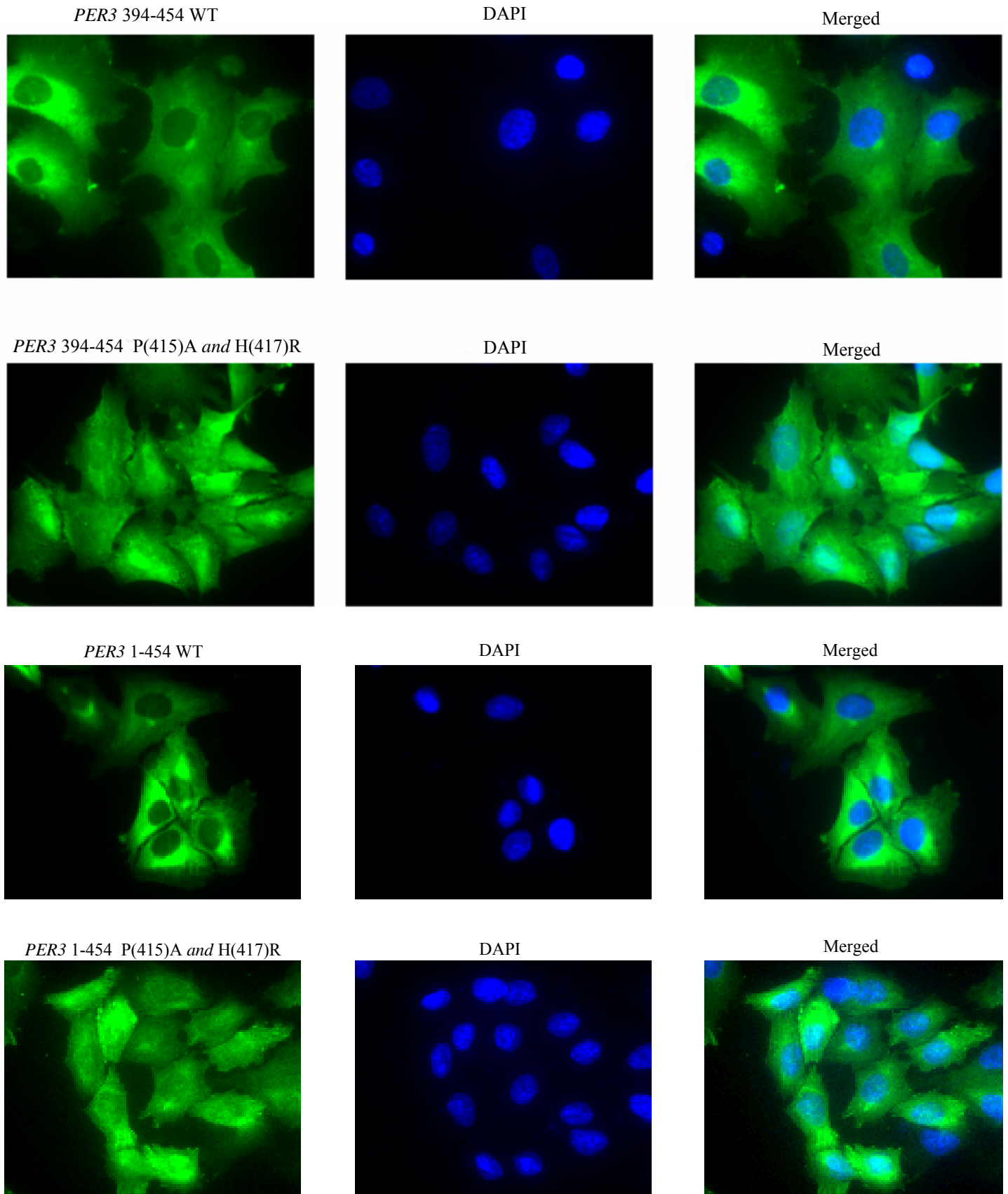


Figure 5. *PER3* P(415)A and H(417)R lesions affect cytoplasmic shuttling of Per3. *PER3* P(415)A and H(417)R-GFP fusions displayed diffuse fluorescence whereas the wildtype distribution is confined to the cytoplasm. Nuclei were stained with DAPI.

As demonstrated in **Figure 4**, P415 and H417 are essential for nuclear export of PER3 constructs. P(415)A and H(417)R Per3 mutations were generated in the context of the truncated GFP fusion constructs illustrated in **Figure 3**. These constructs have previously been shown to be an effective means for assessing subcellular localization of mutant Per constructs. HEK 293 cells were stably transfected with wildtype *PER3* constructs or *PER3* P(415)A and H(417)R constructs, and subcellular localization was visualized by fluorescence microscopy. In both truncated constructs, introduction of the double mutation *PER3* P(415)A and H(417)R resulted in GFP signal diffusely present in both nucleus and cytoplasm, whereas the wildtype counterparts produced signal that was confined to the cytoplasm (**Figure 5**). This demonstrates that the *PER3* P415A and H(417)R double mutation identified in study subjects affects nuclear localization of PER3. Irregular PER3 subcellular localization might lead to altered circadian rhythms that, in combination with other environmental or genetic factors, might yield susceptibility to mental illness. It is also notable that this double amino acid GV might be capable of acting in a dominant manner. Premature entry of the product of only one of the two alleles of PER3 might disrupt normal functioning of the circadian system. This may be of importance given the identification of this GV only in the heterozygous state in the four study subjects carrying this GV.

Within the *PER1* and *PER3* GVs, Class 2 is composed of 14 GVs: (1) *PER3* E(61)K, (2) *PER3* R(365)Q, (3) *PER3* H(638)R, (4) *PER3* E(116)G, (5) *PER3* R(85)C, (6) *PER1* S(640)N, (7) *PER1* R(158)C, (8) *PER3* R(71)C, (9) *PER3* C(1176)S, (10) *PER3* Q(45)K, (11) *PER1* S(1060)L, (12) *PER3* P(828)L, (13) *PER3* P(835)S, and (14) *PER3* INS 804 C. According to our classification scheme, all of these amino acid changes are classified as either radical, located at a highly conserved site, or located within a larger highly conserved region. For example, as shown in **Figure 1**, *PER3* E(61)K, *PER3* R(365)Q, and *PER1* S(640)N all occur at amino acid sites that are perfectly conserved and located within larger domains of high conservation in all PER proteins from all species from which all PER proteins have been fully sequenced. *PER3* E(116)G (located within the PAS domain), *PER3* R(85)C (located within the PAS domain), *PER1* R(158)C, *PER3* R(71)C (located within the PAS domain), *PER3* H(638)R (located within the CKIε binding domain), *PER3* C(1176)S, *PER3* Q(45)K, *PER1* S(1060)L, *PER3* P(828)L, and *PER3* P(835)S are all located at relatively highly conserved amino acid sites that are within larger highly conserved regions. *PER3* INS 804 C occurs directly adjacent to a highly conserved region, and could alter the spacing between this conserved domain and a relatively well-conserved APXGA penta-amino acid sequence located 12 amino acids downstream.

Class 3 is composed of 9 GVs: (1) *PER3* V(639)G, (2) *PER3* S(750)N, (3) *PER1* S(296)C, (4) *PER3* Q(708)L, (5) *PER3* D(854)H, (6) *PER1* R(307)Q, (7) *PER3* R(545)K, (8) *PER3* R(50)K, and (9) *PER3* M(112)T. *PER3* S(750)N,

PER1 S(296)C, *PER3* Q(708)L, *PER3* D(854)H, *PER1* R(307)Q, *PER3* R(50)K, and *PER3* M(112)T all occur at poorly-conserved amino acid sites, yet these sites are located within a larger conserved region. *PER3* R(545)K is a conservative amino acid change that occurs at a perfectly conserved R in a highly conserved region in all PER proteins from all species from which the PER proteins have all been fully sequenced. Of particular interest is the fact that *PER3* V(639)G, which is located within the CKIε binding domain, was found in 16% of study subjects. 18% of individuals carrying *PER3* V(639)G carried a diagnosis of bipolar disorder, which is significantly higher than the 9.4% rate of bipolar disorder found in the overall study population. However, *PER3* V(639)G has also been discovered in a separate general population study to be similarly present in 17% of study subjects (EntrezSNP accession# rs10462020). Another subject with mood disorder (major depressive disorder) was found to have the neighboring conservative GV *PER3* H(638)R.

Class 4 is composed of 22 GVs, all of which produce amino acid changes that are either not radical or not located at a conserved amino acid site or within a larger conserved region: (1) *PER1* DEL 758 PAPS (2) *PER3* H(984)Y, (3) *PER3* P(856)A, (4) *PER3* T(1111)I, (5) *PER1* E(191)C, (6) *PER1* P(962)A, (7) *PER1* Q(314)R, (8) *PER1* P(859)S, (9) *PER1* Q(846)R, (10) *PER3* T(1168)A, (11) *PER1* A(1108)S, (12) *PER1* V(240)I, (13) *PER1* A(1196)V, (14) *PER3* T(519)A, (15) *PER1* V(1027)I, (16) *PER3* Q(1086)K, (17) *PER3* L(644)F, (18) *PER3* L(860)M, (19) *PER1* T(1289)I, (20) *PER1* V(1141)I, (21) *PER3* A(18)S, and (22) *PER1* P(37)S. *PER1* DEL 758 PAPS produces a deleted sequence in a poorly conserved region, and is thus likely to have little consequence on protein function. The PAPS sequence is immediately preceded by an identical amino acid sequence encoded by an identical nucleotide sequence, and thus is likely to result from unequal chromosome crossover. *PER1* T(1289)I was assigned to Class 4 despite the fairly good conservation of T1289 because it is located within a non-conserved region at the end of the protein, and thus unlikely to be critical to protein function

DISCUSSION

Analysis of the data collected in this study raises the possibility that genetic variation in *PER3* may be more likely to be involved in mental illness than GVs in the *PER1* gene. For example, almost twice as many meaningful GVs were discovered in *PER3* compared to *PER1*. This finding correlates with our observation that *PER3* is significantly less conserved across species than *PER1* and *PER2*. This difference in conservation among the three classes of PER proteins fully sequenced from 5 species is illustrated in **Figure 6**. Calculated pairwise distances from sequences shown in alignment (**Figure 1**), using the JTT matrix (Jones, Taylor, Thornton) (41) of the PHYLIP software package, were used to generate a phylogenetic tree using the FITCH program with global rearrangements, according to established methods (42).

The phylogenetic tree was plotted with the drawgram feature of the PHYLIP package such that branch length is inversely related to similarity of amino acid sequence. **Figure 6** shows that PER3 is considerably more divergent among the species examined than PER1 and PER2. The reasons for this difference in divergence are not clear. PER3 may in some manner be predisposed to genetic variation, or its increased divergence relative to PER1 and PER2 may reflect a higher degree of species-specific function. Alternatively, increased divergence might simply have resulted from a lower degree of evolutionary constraint, which could indicate that PER3 function is less critical to survival of the organism than PER1 and PER2.

The possibility that mutations in *PER3* may be more relevant to mental illness than mutations in *PER1* may also be predicted from the fact that 82% of the GVs in Classes 1 and 2 were found in *PER3*, whereas GVs in *PER3* and *PER1* were roughly equally represented within Classes 3 and 4 (52% and 48% respectively). As articulated above, Classes 1 and 2 are judged to comprise GVs with a greater likelihood of functional significance. Not surprisingly, the Class 1 and 2 GVs were more rare (1.39% of the overall study population) than the GVs in Classes 3 and 4 (45% of the overall study population). Of potential importance, the incidence of mood disorder was

71% in study subjects carrying Classes 1 and 2 GVs, which is somewhat greater than the incidence of mood disorder in study subjects carrying Classes 3 and 4 GVs (66%) or the overall study population (63%). More specifically, 64% of study subjects carrying Class 1 and 2 GVs had a diagnosis of major depressive disorder, which is greater than that seen in study subjects carrying Class 3 and 4 GVs (52%) and also in the overall study population (48%). No meaningful differences in other forms of mental illness, or in reported family history of mental illness, emerged among these three groups.

It is important to close with proper acknowledgement of the weaknesses of our study design. Psychiatric diagnosis was not standardized between study subjects and genetic analysis was not performed on matched controls. Thus, we are unable to draw firm conclusions from our data with regards to any link between these GVs and mental illness. We present here a descriptive study in which we have identified and stratified a large number of genetic variations in circadian rhythm genes from a large study population. Despite these shortcomings, we hope to contribute to the field of psychiatric genetics by posting these GVs on www.mcknightlab.com so that other investigators might utilize our findings in their own future studies on the genetic basis of psychiatric disease

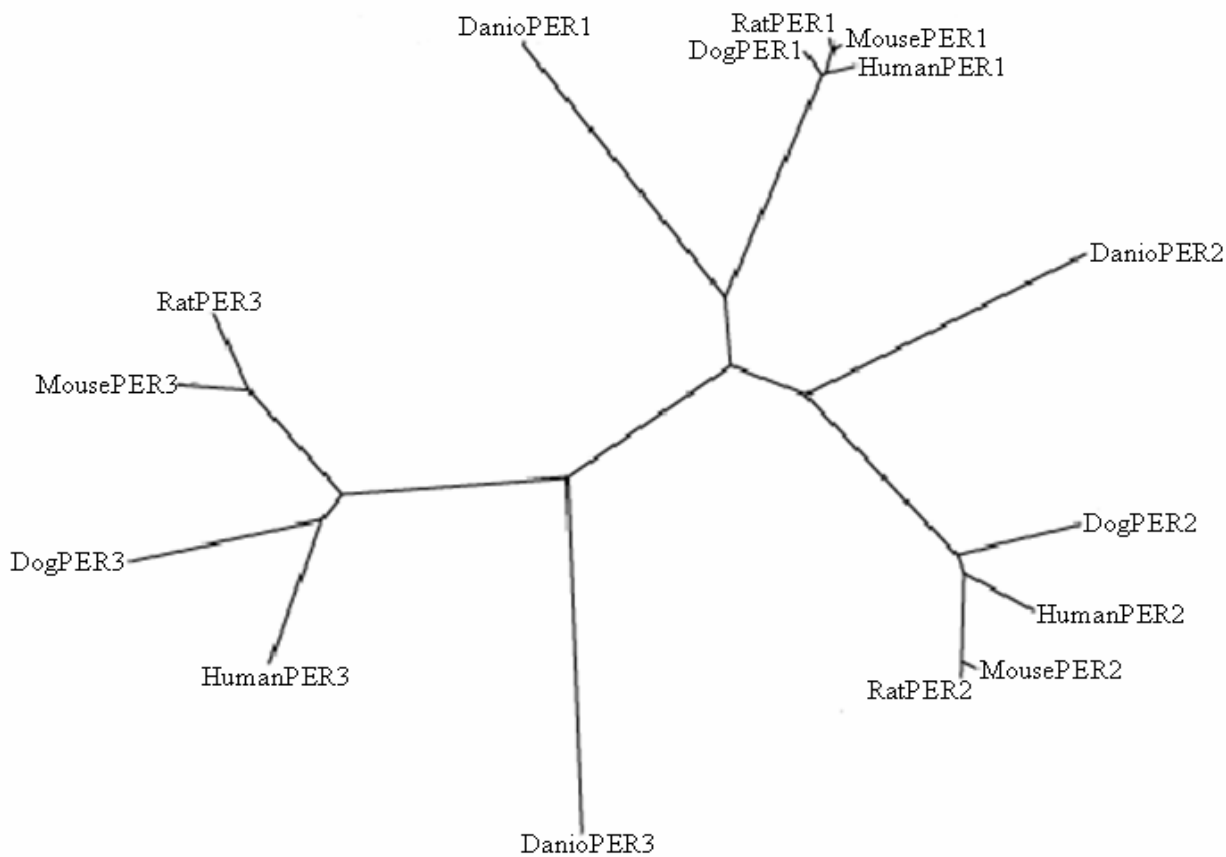


Figure 6. Phylogenetic tree of PER1, PER2 and PER3 proteins from all species from their genes have been fully sequenced. The line distance is inversely proportional to similarity in amino acid sequence.

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Appendix 1. Primer sequences used for PCR amplification of genes controlling circadian rhythm.

Exon sequences are displayed in upper case with yellow highlight. Flanking intron sequences are displayed in lower case. Primer sequences, located within flanking introns, are displayed in lower case bold with red highlight. Green highlight indicates areas in which primer sequences overlapped with exonic sequences.

BMAL1

Exon1: **gggttctccaccacttttg**agagctcatcgaaataaacacacctttgtgcctctgtaacaattccag**ATCATCCAATGGCAGACCAGAGAATGGACATTCTTCAACCATCAGTGATTTTCATGTCCCCGGGCCACCCGACCTGCTTCCAGCTCTCTTGGTACCAGTGGTGTGGATTGCAACCGAAACGGAAAGGCAGCTCCACTGACTACCA**gtaagccttggggcatgtctctctgttga**aacttgggtcagttctcgg**

Exon2: **gtctttattaacatgcagtcac**attctctttgtttttcag**AGAAAGCATGGACACAGACAAAGATGACCCTCATGGAAG**gtaccatgaacctagtaattgaa**cttcagcatccttatagcc**

Exon3: **aacttggccattcatctccag**agaattatgttttatcttttgcctttctccccag**GTTAGAATATACAGAACACCAAGGAAGGATAAAAAATGCAAG**gtaagccttggaccttattgtctacaaagcatcctagt**ctgggtgcttagagagcag**

Exon4: **gatgcttggttacattttataag**aaatcgttttcatattgtgttcag**GGAAGCTCACAGTCAGATTGAAAAGCGGCGTCGGGATAAAAATGAAACAGTTTTATAGATGAATTGGCTTCTTTGGTACCAACATGCAACGCAATGTCCAGGAAATTAGATAAACTTACTGTGCTAAGGATGGCTGTTTCAGCACATGAAAACATTAAGAG**gtgagacctgggctctattgtcctttatgtccttggccac**aaatgttaccaccttgc**

Exon5: **gaggcagcaagtagaatga**gacattttctgaatcaagataccaattctttcttttgccttaag**GTGCCACCAATCCATACACAGAAGCAAACCTACAAACCAACTTTTCTATCAGACGATGAATTGAAACACCTCATTCTCAGG**gtatgtcaattatggattgttttacaacgtttgtttataaattt**caagtaa****gtaccagcatgtgg**

Exon6: **agaaagcacatcctctattt**gtatcagggtgattacaattatgttctacagatgagaaattgattatcatttctctgattag**GCAGCAGATGGATTTTTGTTTGTGTAGTAGGATGTGACCCGAGGGAAGATACTCTTTGTCTCAGAGTCTGTCTTCAAGATCCTCAACTACAGCCAG**gtattgtcatgctcctgttgatgtgggcagcctcac**agcagtcagaagtgcactc**

Exon7: **gactgtgcatgcttactgt**gcataattgattttctgcatgcaattgactgtcatgttaacatttcatctcccag**AATGATCTGATTGGTCAGAGTTTGTGTTGACTACCTGCATCCTAAAGATATTGCCAAAGTCAAGGAGCAGCTCTCCTCCTCTGACACCCGACCCCGGGAGCGGCTCATA**GATGCAAAAA**gtgagtaccagagaggctcgcatttctcagcagccactcacaggcagcc****aacctgagtgagcagagg**

Exon8: **aggctttgctcaaggtcac**actccccctctgacagacaacactgctctcagttatcacatttgtgtattgattgag**CTGGACTTCCAGTTAAAGCAGATATAACCCCTGGGCCATCTCGATTATGTTCTGGAGCACGACGTTCTTTCTTCTGTAGGATGAAGTGTAACAGGCCTTCAGTAAAGTTGAAGACAAGGACTTCCCCTCTACCTGCTCAAAGAAAAAAG**gtaccaatftaacagtcattaaacctgtgacaggtgaagcatgctttctgtagcggactctcagctgggc**gttggttccatggtttctg**

Exon9: **ctccatggcccaaacctagt**gctgacactaaccagcaacttgettctag**CAGATCGAAAAAGCTTCTGCACAATCCACAGCACAGGCTATTTGAAAAGCTGGCCACCCACAAAGATGGGGCTGGATGAAGACAACGAACCAGACAATGAGGGGTGTAACCTCAGCTGCC**TCGTCGCAATTGGACGACTGCATTCTCATGTAGTTCCACAACCAGTGAACGGGGAAATCAGGGTGAAATCTATGGAATATGTTTCTCGGCACGCATAGATGGAAAGTTTGTGTTTGTAGACCAGAG**gtaagagtctacatactacctttagcaatgat****ggtagaggatttcaaccct**

Exon10: **gcaattaatcatctgaatggct**tttctctttaaattattctttattcccttttag**GGCAACAGCTATTTTGGCATAATTTACCACAAGAACTTCTAGGCACATCGTGTTATGAATATTTTACCAAGATGACATAGGACATCTTGCAGAATGTCAATAGGCAAG**gtaagcttaggatgtatgaaagatcttaagttaaagtgc**cccttctcttagactagtc**

Exon11: **ctgtttaatactttggtctgaga**aaacaacaatgccaatgtttctttacattttag**TTTTACAGACGAGAGAAAAAATTACAATAATTGCTATAAATTTAAAATCAAAGATGGTTCTTTTATCACACTACGGAGTCGATGGTTTCAGTTTCATGAACCTTGGACCAAGGAAGTAAATATATTGTCTCAACTAACACTGTTGTTT**gtaagtactttctatatctgaagctcccctt**cttcaaacagatgcctagg**

Exon12: **gaatgggtgcacagttctgag**caggcctgactcacgtttctattgtctggatgttcag**AGCCAACGTCCTGGAAGGCGGGACCCAACCTTCCCACAGCTCACAGCATCCCCCACAGCATGGACAGCATGCTGCCCTCTGGAGAAG**gtaactatgtgctgctgggcccctgggcttggccgtg**gga****aggtgcttgggtcaaa**

Exon13: **tcccccttctactctcaga**ttccctttgttagGTGGCCCAAAGAGGACCCACCCCCTGTTCCAGGGATTCCAGGGGAACCCGGGCTGGGGCAGGAAAAATAGGCCGAATGATTGCTGAGGAAATCATGAAAT**CCACAG**gcaagtaacaccttctagtctctgtta**aaccagt**
ggttctcaacca

Exon14: **caaagcacatacactccact**gaaaaagaaaaggcagtgtaattctctttctgacagGATAAGAGGGTCATCGCCTTCTAGCTGTGGCTCCAGCCATTGAACATCACGAGTACGCCTCCCCCTGATGCCTCTTCTCCAGGAGGCA**AGAAG**gtaagactgatgattcttagcctaagctagag**aacct**
ctgccaagatctg

Exon15: **ggcattgctcataaactgatt**caaaactcacttccctctttgttagATTTTAAATGGAGGGACTCCAGACATTCTTCCAGTGGCCTACTATCAGGCCAGGCTCAGGAGAACCCAGGTTATCCATATTCTGATAGTTCTTCTATTCTTGgtaagtggcatcattatctgttccattgcaatgagctgcaaaaacatcttacataaagcaattttaagaa**actgaactgtgtaacaagc**

Exon16: **ggaattgcttacttaactgaa**gatcgttataaaagaatacactgaccagctttatctctcccacagGTGAGAACCCCCACATAGGTATAGACATGATTGACAACGACCAAGGATCAAGTAGTCCCAGTAATGATGAGGCAGCAATGGCTGTCATCATGAGCCTCTTGGAAAGCAGATGCTGGACTGGGTGGCCCTGTTGACTTTAGTGACTTGCCATGGCCGCTGTAAacactacatgttcttggcaacagctatagatcaaaagtgcaat**ctggtggagtfttacagtc**

BMAL2

Exon1: **ttgtgtactctgctgccca**taggtaaaagtgtgagagaggagaaccagtgcatgCTCCTGTGGTTTCCAGCCGCGTGAGTCCAGGGACAAGACC AACAGCTATGGGGTCTTTCAGCTCACACATGACAGAGTTTCCACGAAAACGCAAAGGAAGTGATTCAGACCCATCCCA GTaagtgaattggctcttaaccagtgagatcttgactttaggagaaagaggaaaatactcttttaaaatcattaattttccaagttcatggtaacattggagatggagagacttatccacca tctgctacc**ttgctgggactgacttgg**

Exon2: **tctccacttgaggacaggct**gtgtgtcattcccagaacatctggtaggggtgaccaaggcctccttccaggtCAGGAATCATGACAGAAAAAGTGG TGGAAAAGCTTTCTCAGAATCCCCTTACCTATCTTCTTCAACAAGGATAGAAATATCAGCCTCCAGTGGCAGCaggttaagtc ctgactgtctttgacatactctcccacttgaagaggcatagagtgggagtgaaacatgatacacg**tccactgatttgcctatca**

Exon3: **agaacagtgctgctgctg**ggctcagcatctgtccagtgagcaacacgggggtgactgggggtctgctgaatgttaaataaaaggaagttcctttcccttAGAGAAGCT CATAGCCAAACTGAAAAGCGGAGGAGAGATAAAATGAATAACCTGATTGAAGAACTGTCTGCAATGATCCCTCAGTGC AACCCCATGGCGCGTAAACTGGACAAACTTACAGTTTTAAGAATGGCTGTTCAACACTTGAGATCTTTAAAAAGgtgagttga cgat**ggcttccacacttcgtaag**

Exon4: **gccaagagcaaataccagc**agcagcagcattgctaattgtaagcattttgccctctctactataattccaataactcttgatgcctttcttttagGCTTGACAAATTCTT ATGTGGGAAGTAATTATAGACCATCATTCTTTCAGGATAATGAGCTCAGACATTTAATCCTTAaggttaactaaagatattgtctaagt gtga**gtgctttcattgtcttftga**

Exon5: **tgccacagtaatttctcagaa**ctgaatgtgtgtgtgtgtgctgtgtataagagacagacaatattttaaataattcactttttttaaactctAGACTGCAGAAGGCTTC TTATTTGTGGTTGGATGTGAAAGAGGAAAAATCTCTTCGTTTCTAAGTCAGTCTCCAAAATACTTAATTATGATCaggtatc caaaaatgaggatattttccatacaatgtttaatttttgaacaaacacatattttaagctcttttctgaaca**cttctccccactgggatal**

Exon6: **ctggacatactttgagctt**gaaaaaatcaatcaaaaatcaaaaagaacattattgtatgcatcaagaaatgtagaaaagcatggactgattttaaataatgctacctatgaat AGGCTAGTTTACTGGACAAAGCTTATTTGACTTCTTACATCCAAAAGATGTTGCCAAAAGTAAAGGAACAACCTTTCTTC TTTTGATATTTACCAAGAGAAAAGCTAATAGATGCCAAAAGtaagtgtccattccgcatgcttattttatgtaaagta**atgatcacctaaaagtttagc**
taca

Exon7: **ctattctctegcccctct**gcacgaaagCTGGTTTGCAAGTTCACAGTAATCTCCACGCTGGAAGGACACGTGTGTATTCTGGCT CAAGACGATCTTTTTTCTGTGCGATAAAGAGTTGTAATAATCTCTGTCAAAGAAGAGCATGGATGCTTACCCAACCTCAA GAAGAAaggtatcattttgaaatgct**agtgatgcaaacatggc**

Exon8: **ggaatacattcccccttca**tattttagcatattaaagacattttatagcacaattataactattatagatgcaataataagaaatgaactatttataatgatccaatgctcttttaaaat ctttgaattAGAGCACAGAAAATTCTATACTATCCATTGCACTGGTTACTTGAGAAGCTGGCCTCCAAATATTGTTGGAATGG AAGAAGAAAGGAACAGTAAGAAAGACAACAGTAATTTACCTGCCTTGTGGCCATTGGAAGATTACAGCCATATATTG TTCCACAGAACAGTGGAGAGATTAATGTGAAACCAACTGAATTTATAACCCGGTTTGCAGTGAATGGAAAATTTGTCTA TGTAGATCAAAGGtaaacatttacatgttataatgattagaat**tcaatgggatattgagctattaaa**

Exon9: **gtgggctacagctctctgg**gaggagtagactcaccactctgaagttattttcaatttgaaccagg**GCAACAGCGATTTTAGGATATCTGCCTCAGGA**
ACTTTGGGAACTTCTTGTTATGAATATTTTCATCAAGATGACCACAATAATTTGACTGACAAGCACAAAGCaggtaggtatgc
att**gagcagaatacatttggggg**

Exon10: **cttaattfcccattctctgga**aatttgaagttgaattaatctcacaacattgattttatagtcattgactattatgctgataattatctttctcgta**AGTTCTACAGAGTAAG**
GAGAAAATACTTACAGATTCCTACAAATTCAGAGCAAAAGATGGCTCTTTTGTAACCTTTAAAAAGCCAATGGTTTAGTT
TCACAAATCCTTGGACAAAAGAACTGGAATATATTGTATCTGTCAACACTTTAGTTTTGtaagtaattttatgtaagacctttatattgattc
aatgagctctttgcttt**ctcctctcatcttgctaaacca**

Exon11: **cttccacttagaaagtaaatcacc**atggtgttttaattctagg**GGACATAGTGAGCCTGGAGAAGCATCATTTTTACCTTGTAGCTCTC**
AATCATCAGAAGgtaagcttacttttagatgatggaagacttattactaagacatattattaagactattactat**ttttctgctctggagagg**

Exon12: **AAAGTCCTCAACTGAATTTCTCC**tttctgttactt**AGAATCCTCTAGACAGTCCTGTATGAGTGTACCTGGAATGTCT**
ACTGGAACAGTACTTGGTGCTGGTAGTATTGGAACAGATATTGCAAATGAAATTCTGGATTTACAGaggtaatgtttattgctgcaaa
tattttcaaaagtaaaaatcatattataaaat**caatatacaaaaatcagtagccttcc**

Exon13: **cagttfcaagttctcactgta**tttagtagattattatgatttagaggagaaaatttctcttaaaatgtaaaatataaaatgtttatgtatcacttttaa**AGGTTACAGTC**
TTCTTCATACCTTGTAGATTTCGAGTCCAACAGGTTTAAATGAAAGATACTACTGTAACCTGCAGGAGTgtaagtatactgttaa
atgataatattcatgaaataaa**gaaacaataaaattgcccc**

Exon14: **cacagcgagcctccatc**caaaaaataaaaaataaaaagtaaaaaataaaataaagagtgcttattctagtaggaacctcactgtttgtactctgctgtctttcag**ATGTC**
AAATAAGGAGTTGTTCCACCAAGTCCTTCTGAAATGGGGGAGCTAGAGGCTACCAGGCAAACCAGAGTACTGTTGC
TGTCCACAGCCATGAGCCACTCCTCAgtaagttt**cttgggaactgctgacct**

Exon15: **ctcctcaaatgtgtgaaatgatga**cttactgacaccttacttacacaggcctgtattttaaattcatag**GTGATGGTGCACAGTTGGATTTTCGATGCCCTA**
TGTGACAATGATGACACAGCCATGGCTGCATTTATGAATTACTIONTAGAAGCAGAGGGGGGCTGGGAGACCCTGGGGAC
TTCAGTGACATCCAGTGGACCCTCTAGcctttgat**tttaactccaaaatgagaaaca**

CRY1

Exon1: **ggaagcgaaggtgctgg**ctatgagccggagcctcctctgaatttccctggaggaccgcccgcgccccggc**ATGGGGGTGAACGCCGTGCACTGGT**
TCCGAAAGGGGCTCCGGCTCCACGACAACCCCGCCCTGAAGGAGTGCATTCAGGGCGCCGACACCATCCGCTGCGTCT
ACATCCTGGACCCCTGGTTCGCCGGCTCCTCCAATGTGGGCATCAACAGGTGGCGgtgagtcacaagcccggtggaaatgatttgggtgttta
atgagctgatgtaataaatt**catgcatccgccaatctg**

Exon2: **gatggttttggaaaaagtatatafc**aataggaggtataagatagatggtgacattcaactttagaataacatgacttgaataattatgcttctaaatgatttttaataattaaat
aatactttctctctta**GATTTTTGCTTCAGTGTCTTGAGGATCTTGATGCCAATCTACGAAAAATAAACTCCCCTCTGTTTGTGATT**
CGTGGACAACCAGCAGATGTGTTCCAGGCTTTCAAGgtaatttgaataatattgcataaaacaatctttctcagataattacataattgtaataaaagtttt
tgactaatt**gaaaatgtagcgaatataagattttcaag**

Exon3: **ctttgctagattgtgcttagc**ataatgcctagaatctaattggttatgcttacttattatgatttttaattgataaattgttacttttctgcatattcaagtttgattatgtataatcctttga
tatgtagattttcagctttttcacttttctgtataatagaaaaataactattacaattggtgtacattgtcccttctctacttttag**GAATGGAACATTACTAACTTTCAATTGA**
GTATGATTCTGAGCCCTTTGGAAAGGAACGAGACGCAGCTATTAAGAAACTGGCAACTGAAGCTGGAGTAGAAGTCAT
TGTAAGAATTTACATACATTA**TATGACCTAGACAA**gtgagtc

Exon4: **cacctcaagactcagtg**attaatttttttctgcttttaagccttttggagccttattagccaaaatgattgtcttttaataactaactacatttactaactcttattatag**GATCATA**
GAACTCAATGGTGGACAACCGCTCTAACTTATAAAAGATTCCAGACTCTCATCAGCAAAATGGAACCACTAGAGATA
CCAGTAGAGACAATTACTTCAGAAGTGATAGAAAAGTGCACAACCTCTGTCTGATGACCATGATGAGAAATATGGA
GTCCCTTCACTGGAAGAGCTAGgtgagtg**gtaaacgtgtagctgagtgagg**

Exon5: **gtctcccagttatfgggg**taataaaaatagtttgcgaagaatgatgtttttctttctttctgtag**GTTTTGATACAGATGGCTTATCCTCTGCAGTGTG**
GCCAGGTGGAGAACTGAAGCACTTACTCGTTTGGAAAGGCATTTGGAAGAAAAgtatgataatgtagattatagctat**gcttgtatttcca**
aactgcc

Exon6: **gacaatagtaataataatfttctctgtgtg**ttttcagGCTTGGGTGGCAAATTTTGAAGACCTCGAATGAATGCGAATTCTCTGCTTG
CAAGCCCTACTGGACTTAGTCCTTATCTCCGATTTGGTTGTTTGTGCATGTCGACTGTTTTACTTCAAACCTAACAGATCTCT
ACAAAAAGgtattctctaaatagagcttattgttaataactttaaaaaaaattctgataactctttg**ctftttaacataggtaaagaagaacag**

Exon7: **gactgtttacttcaaaactaacagatc**ctacaaaaaggattctctaaaatagagcttattgttaataactttaaaaaaaattctgataactctttgcttttaacatagGTAAAGA
AGAACAGTTCCCTCCCTTTCCCTTTATGGGCAACTGTATGGCGTGAATTTTTCTATACAGCAGCAACAAATAATCCAC
GCTTTGATAAAATGGAAGGAAACCCTATCTGTGTTCAATTCCTGGGATAAAAAATCCTGAGGCTTAGCCAAATGGGGC
GAAGGCCGGACAGGCTTTCCATGGATTGATGCCATATGACACAGCTTCGTCAGGAGGGTTGGATTTCATCATCTAGCCAG
GCATGCAGTTGCTTCTCTGACACGAGGGGACTGTGGATTAGTTGGGAAGAAGGAATGAAGgtaagtgttctaa**ctgatatagcat**
gcctattttg

Exon8: **tgctctgactttg**gctctactgtgaccttgaatgcttctggaattatgtgtgcaactaattggtactgttactctgaagGTATTTGAAGAAATTATTGCTTG
ATGCAGATTGGAGCATAAATGCTGGAAGTTGGATGTGGCTGTCTTGTAGTTCCCTTTTTCAACAGTTTTTCACTGCTAT
TGCCCTGTTGGTTTTGGTAGGAGAACAGATCCAATGGAGACTATATCAGgtaaatcaagggtgattactactcagtttggaatagtaattcaagaag
agcttttcatgtttaat**caatgcttaaagtattccccac**

Exon9: **gatgggcagcagagatgag**aagggtaaacagatcattaaatgcttctgattgattttgctgtctcatagctagtagttagttgcttagagtgcatfttattagtaatctttctttctcca
aagGCGTTATTTGCCTGTCTTAAGAGGCTTCCCTGCAAAATATATCTATGATCCCTGGAATGCACCAGAAGGTATCCAAA
AGGTAGCCAAATGTTTGTAGGAGTTAATTATCCTAAACCAATGGTGAACCATGCTGAGGCAAGCCGTTTGAATATCGA
AAGGATGAAACAGATCTATCAGCAGCTTTCACGATATAGAGGACTAGgtaatgtaagaactgctttgttctttggcagctgttatgtacttactttgaatt
ttacttctgatcataatttaaagaaaattttt**ctcttttaggtctctgtgc**

Exon10: **gaggactaggtatgtaagaactgtc**ttgtttctttggcagctgtttatgtacttactttgaatttacttctgatcataatttaaagaaaattttgtgcttttagGTCTTCTGGCAT
CAGTACCTTCTAATCCTAATGGGAATGGAGGCTTCATGGGATATTCTGCAGAAAATATCCAGGTTGTAGCAGCAGTGG
AAgtaagtgaagaaatttctgcacttagtaacatgaagaggttataaacaataatattgttattgatctcactaacatattttataaaaaat**ctgtctttgaaatagcttaaatag**

Exon11: **tggttcacataggaagattgagatttagt**cttaaaagcatataatgaccttaagtacaagcgtaaaagtggatttgtagacttaataataacatacacttggatttgatttaagtaattttact
gtgttttaataactaacagGTTGCTCTCAAGGGAGTGGTATTTTACACTATGCTCATGGCGACAGTCAGCAAACCTCACCTGTTGAAG
CAAGgtaagaatgaagcattggagcactactgttcttttctcttctacttaaacatacatttttaaatgtgca**ggaagaagctccat**

Exon12: **gctcatggcagcagctcag**caaaactcacctgttgaagcaaggtaagaatgaagcattggagcactactgttcttttcttctctacttaaacatacatttttaaatgtgagGAAGAA
GCTCCATGGGCACTGGTCTCAGTGGTGGGAAACGTCTAGTCAGGAAGAGGACACACAGAGTATTGGTCCATAAAGTCC
AGAGACAGAGCACTAATTAGgtaaatatttagagctgtatttctgtttagaagagtataataaacataaaatgaataatttcaaaaatggagcaaatctctatttt**caaacagaga**
aaatcttgaggc

CRY2

Exon1: **tggtctggagcagctctg**acagtcATGGCGGCGACTGTGGCGACGGCGGCGAGCTGTGGCCCCGGCGCCAGCGCCCCGGCACGG
ACAGCGCCTTTCGGTGCAGCTGGTTCCGCAAAGGGCTGCGACTCCACGACAACCCGGCGTTGCTGGCGGCCGTGCGCG
GGGCGCGCTGCGTGCCTGCGTTTACATTCTCGACCCGTGGTTCGCGGCCCTCCTCAGTCGGGATCAACCGATGGAG
gtgaggggaccggggctgggtggcggggacgcagc**caggacctgacctg**

Exon2: **cagcgaaccagtttctccct**gctttgtagaaagagagccactcttcatgatgttatcactaacaaggcctgtgtggactccacagGTTCTACTTTCAGTCTCTGGAA
GATTTGGACACAAGTTTAAAGGAAACTGAACTCCCGCTGTTTGTAGTCCGGGGACAGCCAGCCGACGTGTTCCCAAGGC
TGTTCAAGgtaagcgtgcagagcccagagaagacagtgagattctgtcctgacggtttcc**ccacagcctgagtgatag**

Exon3: **cccaaacacagtggtgagc**ataacagatcctctccccacagGAATGGGGAGTGACCCGCTTGACCTTTGAATATGACTCTGAACCCTTTG
GGAAAGAACGGGATGCAGCCATCATGAAGATGGCCAAGGAGGCTGGTGTGGAAGTAGTGACGGAGAATTCTCATACC
CTCTATGACCTGGACAGgtaagagatggggcccaggatcaggittaccaattgtgagagttagtaattt**ggccccctgctgagcggaac**

Exon4: **gcatgtgggtaaacactagc**tatgctttgggctccccagGATCATTGAGCTGAATGGGCAGAAGCCACCCCTTACATACAAGCGCTTTC
AGGCCATCATCAGCCGCATGGAGCTGCCAAGAAGCCAGTGGGCTTGGTGACCAGCCAGCAGATGGAGAGCTGCAGG
GCCGAGATCCAGGAGAACCACGACGAGACCTACGGCGTGCCCTCCCTGGAGGAGCTGGgtgcgtacttctg**ccagagccactgtgtc**
gg

Exon5: **cagaacagccgtgccggg**ctatcactgaatgtcaaacctctgtcttgaccttctctctctcag **GGTCCCCACTGAAGGACTTGGTCCAGCTGTCT**
GGCAGGGAGGAGAGACAGAAGCTCTGGCCCGCTGGATAAGCACTTGGAACGGAAGGtatgggccgttctgagacacagagctgcagat
actgatatccacaca**gcaggagatacaggctcatg**

Exon6: **ggctgtctgtgaccgtagg**cagattcctaaccaccaatgcctccattttctctctgttacatccaagccttctcttggcaccctctcttctgctgtag **GCCTGGGTTGCCAA**
CTATGAGAGACCCCGAATGAACGCCAACTCCCTCCTGGCCAGCCCCACAGGCCTCAGCCCCCTACCTGCGCTTTGGTTGT
CTCTCCTGCCGCTTCTACTACCGCCTGTGGGACCTGTATAAAAAAGgtaagggggacatacctgccacattgca **ctaaggcctgcagccag**

Exon7: **cctttgtagaagagacctgag**aggccacatgctaagagctgggcgagtggtttgatccatgtgccaccctacctctcag **GTGAAGCGGAACAGCACACCTCCC**
CTCTCCCTATTTGGGCAACTCCTATGGCGAGAGTTCTTCTACACGGCAGCTACCAACAACCCAGGTTTGACCCGCATGG
AGGGGAACCCCATCTGCATCCAGATCCCCTGGGACCGCAATCCTGAGGCCCTGGCCAAGTGGGCTGAGGGCAAGACAG
GCTTCCCTTGGATTGATGCCATCATGACCCAACCTGAGGCAGGAGGGCTGGATCCACCACCTGGCCCCGCATGCCGTGGC
CTGCTTCTGACCCGCGGGGACCTCTGGGTCAGCTGGGAGAGCGGGGTCCGGgtgagtctctctcaacgaaaagctggcctgtaccctctgctca
ggcccgtcaagggcagccc **cctttggtgctgaggatg**

Exon8: **gggcaactgtggtgacttg**ggaaaaaacatggctgcatgtcccaaggaggetgatccctccctctctag **GTATTTGATGAGCTGCTCCTGGATGCAG**
ATTTACAGCGTGAACGCAGGCAGCTGGATGTGGCTGTCTGCAGTGCTTTCTTCCAGCAGTTCTTCCACTGCTACTGCCCT
GTGGGCTTTGGCCGTCGCACGGACCCAGTGGGGACTACATCAGgtgagatacagaccaggctctctggcctctgaccactgtg **gctcctactagga**
tggg

Exon9: **gaccactgtgacctctact**taggatgggataccctggccttttgaaggaggctggtgatgctgatggctcatctggtgatcttatttcag **GCGATACCTGCCAAAT**
TGAAAGCGTTCCCCTCTCGATACATCTATGAGCCCTGGAATGCCCCAGAGTCAATTCAGAAGGCAGCCAAGTGCATCAT
TGGTGTGGACTACCCACGGCCCATCGTCAACCATGCCGAGACCAGCCGGCTTAACATTGAACGAATGAAGCAGATTA
CCAGCAGCTTTCGCGCTACCGGGGACTCTgtaaggagacaaacacctagctcactgaaggaagga **cagcacctacaggctcagg**

Exon10: **cctctgcaactctgcgag**acggcactctgattactcctgcctctctccag **GTCTACTGGCATCTGTCCCTTCTGTGTGGAAGACCTCAGTC**
ACCCTGTGGCAGAGCCCAGCTCGAGCCAGGCTGGCAGCATGAGCAGTGCAGgtgagcagcagcaaccaacctctgtggcctctctgtg **gacctgt**
gccaccacttcag

Exon11: **gacaegcttccctacagg**CCCAAGACCACTACCCAGTGGCCAGCATCCCCCAAACGCAAGCTGGAAGCAGCCGAGGAA
CCACCTGGTGAAGAACTCAGCAAACGGGCCCGGGTGGCAGAGTTGCCAACCCAGAGCTGCCGAGCAAGGATGCCTG
AGagtgagtacagcagcctgattcaacctcaggaaggaagtgggagtggggggctactgccctgccagctgcaggtgaaacatagcaaaactagatgaaatctggtgg **gaccacca**
atgctcagcc

CLOCK

Exon1: **ctcaagataagttgtggaag**taacattttagaaaactaatgaccattttttctttcacctaaaggagaagtacaatgtctactacaagacgaaaacgtagatgtt **ATGTTGTT**
TACCGTAAGCTGTAGTAAAATGAGCTCGATTGTTGACAGgtatgttttgaagactattttaagttatataaatttttaaaa **gcactattagaataatggtct**

Exon2: **ctgagtgattfacatgctac**ttagtattgctgtgcttagtgagctgctcttacttctctatccgctttcttttag **AGATGACAGTAGTATTTTTGATGGGTTGGT**
GGAAGAAGATGACAAGGACAAAGCGAAAAGgtagttgattagatataaaatgtaaatgaataatagataaataatgtaaaataatgtaaaatgatt
tccaaaagctatgctttag

Exon3: **gtatattggttaacctgggag**atattgttaccatctatgttgatagaagtacatgctgtgcatgctctaaattaacattgtatataactactgtgtaataaatggattgttaaaaaatgcattttt
tcatttcacag **AGTATCTAGAAACAAATCTGAAAAGAAACGTAGAGATCAATTTAATGTTCTCATTAAAGAACTGGGATCCAT**
GCTTCTGGTAATGCTAGAAAGATGGACAAATCTACTGTTCTGCAGAAAAGCATTGATTTTTTACGAAAACATAAAGgta
aatttttaactctgtaaaatggaacagactctcaagcattagt **agaactctggcagagatgc**

Exon4: **gtagggtctttgactcctc**cggtggtggagatgccactaatgtcaatctgtttacag **AAATCACTGCACAGTCAGATGCTAGTGAAATTCGACA**
GGACTGGAAACCTACATTCCTTAGTAATGAAGAGTTTACACAATTAATGTTAGAGgtatgtccagatthaattttgaaagttttttctcaaaaa
agaaatcacagggtgacttaatatccaggtgtacctggcgatattgcgagttgagttccagaccactgcaataaagctaatatttca **gtaaaatgagtcacatgaattg**

Exon5: **tattctgtctgcaaaatac**ttttctttcatttaacatattatgtttaatttcagGCTCTTGATGGTTTTTTTTTAGCAATCATGACAGATGGAAG
CATAATATATGTGTCTGAGAGTGTAACCTCATTACTTGAACATTTACCAgtaagtataaagatcctacaatctactcgtattaaatgcctttaaataat
tctaaag**cactgggaagtggacttga**

Exon6: **gcaattgtctcttgaatcattg**aagtattttacttttaacaattttcttcagTCTGATCTTGTGGATCAAAGTATATTTAATTTTATCCCAGAAGG
GGAACATTGAGAGGTTTATAAAATACTCTCTACTCATCTGCTGGAAAGTGATTCATTAACCCAGAATATTTAAAATgtaa
gtagtagctgtaagcaaaaaagcaaatgtgtattcag**tagcactatcctttgcaag**

Exon7: **gatctactttatgtggtatatac**aatcattgtttatatacagaatattgatttttaaaatctctttatttcagCAAAAAATCAGTTAGAATTCTGTTGTACATG
CTGCGAGGAACAATAGACCCAAAGGAGCCATCTACCTATGAATATGTAATAATTTATAGGAAATTTCAAATCTTTAAAC
AGTGgtgagttaaaatgctctctcacaatgtgtttaactgttatttt**ctgtgctcttaagacatag**

Exon8: **ctgtgctcttaagacataga**gtttgaatatcagtgacaattaggtttgctggcataactgatgatacatatttccctattgttttagTATCCTCTTCAGCACACAATGG
TTTTGAAGGAACTATACAACGCACACATAGGCCATCTTATGAAGATAGAGTTTGTGTTTGTAGCTACTGTCAGGTTAGCT
ACACCTCAGTTCATCAAGgtatgttttaattttatttcccaaggggatttcagttcatatgctgagagctgcctgaa**acttctgagacattgagg**

Exon9: **gattacaggtgtgagccact**gcacctggccatgactttttatattgtagcaatatttaattcttaagacacaaagtattataaatttaattatttttagGAAATGTGCAC
TGTTGAAGAACCCAATGAAGAGTTTACATCTAGACATAGTTTAGAATGGAAGTTTCTGTTTCTAGATCACAGgtaattccatttt
aaattccatgaaaaggtaatgcatgttatataattctgaa**attaatggatcaagggcaaac**

Exon10: **gactttgaaacctgttccca**tttttgaaaaataagcccccccccaagttatttctagtgaatatttcttattatgaaaaactataataatgatttttctgttaatttagGGCA
CCACCCATAATAGGGTATTTGCCATTTGAAGTTCTGGGAACATCAGGCTATGATTACTATCATGTGGATGACCTAGAAA
ATTTGGCAAAATGTCATGAGCACTgtaagtagatttaacattctgtgataataactgtttataagcagaagctcctgcctgaa**atgataggtagtaagacacag**

Exon11: **atgtaaatgatagcttttggta**aaaaacaactttatataatgaattaaagaaaaaatatttctctattttcccttagTAATGCAATATGGGAAAGGCAAATCA
TGTTATTATAGGTTCTGACTAAGGGGCAACAGTGGATTTGGCTTCAGACTCATTATTATATCACTTACCATCAGTGGAA
TTCAAGGCCAGAGTTTATTGTTTGTACTCACACTGTAGTAAGgtaataattcttttagagaatttctgaattagggtaacatcctatgatattttgacattgtaact
tt**atgcgtaagttgtaagagc**

Exon12: **gaatagttacagctgtgcact**attttaaacgaatgaccagacactaaaatttgattattttccattgtagTTATGCAGAAGTTAGGGCTGAAAGACGACG
AGAACTTGGCATTGAAGAGTCTCTTCTGAGACAGCTGCTGACAAAgtatgtttcttataaataaaaaaatttttaatttctcccaataaaagatgaaa
ctcaataaataaggaactattttcaaaaatactttattt**ctcacttataacagggatgtg**

Exon13: **ttgtgaatttgagatctctg**aactgaaccacaagaaacatttttactctgtctccatagaGCCAAGATTCTGGGTCAGATAATCGTATAAACACA
GTCAGTCTCAAGGAAGCATTGGAAAGGTTTGTATCACAGCCCAACCCCTTCTGCCTCTTCTCGGAGTTCAAGAAAACCAT
CTCACACGGCCGTCTCAGACCCTTCTTgtgagtaccctgtctcaagcagactcctttaaagtaactaactaaacttttagttacttata**acagacttctcatcaaacgc**

Exon14: **cactttcaattgaatggtttggaa**aaaaataatcaaaagccatttttactgaaatacattttgagattaacttttaaaaactatattttataaagtactaatgctctctgattttgtgactcag
CAACACCAACCAAGATCCCCGACGGATACGAGCACTCCACCCAGGCAGCATTACCAGCTCATGAGAAGATGGTGCAAA
GAAGGTCATCATTTAGTAGTCAGgtaagctcttttagtgatattctctgaataaagattttaagaggggaaaaatgatctaatctcagaat**catctatttgcacccctc**

Exon15: **ctgetggaagtactcatgta**tggaatgagaatcacttcagtgatttttttttctctagTCCATAAATCCCAGTCTGTTGGTTCATCATTAAACAC
AGCCAGTGATGTCTCAAGCTACAAATTTACCAATTCACAAGGCATGTCCCAGgtactttttggttttctcagttgcgtatttgaatgataaattg
cttttaagctaattgtaatttttaaaaatccaggctgtctggca**agcaccgtagccacagcta**

Exon16: **gttgtgcaattataaggagtaa**gtaattctaaaatataattacttttccgtacatggtactcagTTTCAGTTTTTCAGCTCAATTAGGAGCCATGCAAC
ATCTGAAAGACCAATTGGAAACAACGGACACGCATGATAGAAGCAAATATTCATCGGCAACAAGAAGAACTAAGAAAA
ATTCAAGAACAACCTCAGATGGTCCATGGTCAGGGGCTGCAGgtaattgttatattgaaat**caaacaaagcatcccattcac**

Exon17: **cttttagactgattttgctt**cttttaaatgctcattctcttttcaactcaaaagctcatttaacataatctttatttttaagATGTTTTTGCAACAATCAAATCCTGG
GTTGAATTTTGGTTCCGTTCAACTTTCTTCTGGAAATTCATCTAACATCCAGCAACTTGCACCTATAAATATGCAAGGCC
AAGTTGTTCTACTAACCAGATTCAAAGTGGAAATGAATACTGGACACATTGGCACAACCTCAGCACATGATACAACAAC
AGACTTTACAGAGTACATCAACTCAGgtaattgtactgagcagcagggctatggagtgatcagtggttggagg**cacactattgctgaagcaga**

Exon18: **gaatftagcactactcccaa**ataattatttcagttaatctgtctataaaaatctctttatttttaacagAGTCAACAAAATGTACTGAGTGGGCACAGTCAG
CAAACATCTCTACCCAGTCAGACACAGAGCACTCTTACAGCCCCACTGTATAAACTATGGTGATTTCTCAGCCTGCAG
CCGGAAGCATGGTCCAGATTCCATCTAGTATGCCACAAAACAGCACCCAGAGTGCTGCAGTAACTACATTCACTCAGG
ACAGGCAGATAAGgtagttgcatatttcattgtatttttaaattgtaaaccgattgattagaaaacaataatttgatttcttaataatgtgattttaa**fgagatgctcactgcagc**
c

Exon19: **actccactgcgttttatgatg**tataacctgtacttggactccaatttttctcttcttctaacagATTCTCAAGGTCAACAACTTGTGACCAAATTAGT
GACTGCTCCTGTAGCTTGTGGGGCAGTCATGGTACCTAGTACTATGCTTATGGGCCAGGTGGTGACTGCATATCCTACTT
TTGCTACACAACAGCAACAGTCACAGACATTGTCAGTAAACGCAGCAGCAGCAGCAGCAGAGCTCCCAGGAGCAGCAG
CTCACTTCAGTTCAGCAACCATCTCAGGCTCAGCTGACCCAGCCACCGCAACAATTTTACAGgtaattctccccatggggaagctgctt
caaacctacttacttcatgtaatgaaattaagcatt**aagfgaacagattfgtgagtga**

Exon20: **gacaggggagagtgtgagta**actattatgtgggtgccataaaggagtaaagcaatgctgcataatccattgttttttagCTTCTAGGTTGCTCCATGGGAATC
CCTCAACTCAACTCATTCTCTCTGCTGCATTTCTCTACAACAGAGCACCTTCCCTCAGTCACATCACCAGCAACATCAG
TCTCAGCAACAGCAGCAACTCAGCCGGCACAGGACTGACAGCTTGCCCGACCCTTCCAAGGTTCAACCACAGTAGCAC
ACGTGCTTCTCTCTTGACATCAAGGGAGGAAGGGGATGGCCCATTA**agagtactcagatgactg**

NPAS2

Exon1: **caggaaaaactgcatagaaaatc**taATGGATGAAGATGAGAAAGACAGAGCCAAGAGgtaagatgcagctgtccccctgctcagcagagctctctgg
ccccggggg**ctgctcggcagaatctcg**

Exon2: **ctttgtgacgtggaatgttc**cagtaacctgctcgtttgtgttcagagCTTCTCGAAACAAGTCTGAGAAGAAGCGTCGGGACCAGTTCAAT
GTTCTCATCAAAGAGCTCAGTTCATGCTCCCTGGCAACACGCGGAAAATGGACAAAACCACCGTGTGGAAAAGGTC
ATCGGATTTTGCAGAAACACAATGgtaaaggtcaccttctct**gtttttttccacctgccc**

Exon3: **catagaagtaaacatgtgc**ttcatttgaattccaatttagtgccattgaatataaaggcttattgtgtctctttctagAAGTCTCAGCGCAAACGGAAATCTGT
GACATTACAGCAAGACTGGAAGCCTTCACTTCCCTCAGTAATGAAGAATCACCCAGCTGATGTTGGAGGgtaaatgcactttcaaaaata
gcttaaacagttgccagttaaatggtag**ctactgtgtcagataagtc**

Exon4: **aacgcattgctaaggagct**ttcaaatgttcattttccacaggCATTAGATGGCTTCAATTATCGCAGTGACAACAGACGGCAGCATCATCT
ATGTCTCTGACAGTATCACGCCTCTCCTTGGGCATTTACCGgtgagtttccactccaatggccttt**accggttcacgttaccatg**

Exon5: **ttcatcttcgttgagggtg**facctttgctcttattttcttttcagTCGGATGTCATGGATCAGAATTTGTTAAATTTCTCCAGAACAAAGAAC
ATTGAGAAGTTTATAAAATCCTTTCTTCCCATATGCTTGTGACGGATTCCCCCTCCCAGAAATACTTAAATgtaagttaatttttc
tggtttacaagctagaagataagaatt**tgcttttgaaggagggttag**

Exon6: **agtcigtgcaatgctcacga**cccctttctctctcttcttcttaacggcccagCTGACAGCGATTTAGAGTTTTATTGCCATCTTCTCAGAGGCA
GCTTGAACCCAAAGGAATTTCCAACCTTATGAATACATAAAATTTGTAGGAAATTTTCGCTCTTACAACAATGgtaagctttaatt
gtcatataattgtgacagtgcttt**ctcatgcaaacgtgcacag**

Exon7: **gagacagggtaacetatgt**gtcctctcttcccaacccccagTGCCTAGCCCCCTCCTGTAATGGTTTTGACAACACCCTTTCAAGACCTT
GCCGGGTGCCACTAGGAAAGGAGGTTTGTCTTCAATTGCCACCGTTCGTCTGGCAACACCACAATTTCTTAAAGGcaagtacctga
gaggcagttcattgtgcg**gagctgttatgattgactcac**

Exon8: **agcatctggcaccgaagcaa**ctttttttttctgcttccaatacaggAAATGTGCATAGTTGACGAACCTTTAGAGGAATTCATTCAAGGC
ATAGCTTGAATGGAAATTTTATTCTGGATCACAGgtttgagaaaagaaaacatattgggtgggccc**ttctcaagctctgtttgctg**

Exon9: **gttgatcattatgaaaggcat**ggccaccaggtgagccctgcaggggtctctcctgatgacaagctctctgtctctgtgcagAGCACCTCCAATCATAGGAT
ACCTGCCCTTTGAAGTGTGGGAACCTCAGGCTATGACTACTACCACATTGATGACCTGGAGCTCCTGGCCAGGTGTCA
CCAGCACCgtgagtaccactgccagcccagcatgggggccc**tgctgtcactcactggg**

Exon10: **caagccatgtttggtattgtc**tttttttgaagccttcttacaataactcttggggaaaagatcatttcatataaacattggtatgctggatccattttaccgacagTGATGC
AGTTTGGCAAAGGGAAGTTCGTGTTGCTACCGTTTCTGACCAAAGGTCAGCAGTGGATCTGGCTGCAGACTCACTACTA
CATCACCTACCATCAGTGAACCTCAAGCCCGAGTTCATCGTGTGCACACACTCGGTGGTTCAGGtaccgpcacggggcaggggtgc
ggctgctcctgtctgcacctgggggaggggtgcagatggcgtggcccc**tgatggccaaggcagatcag**

Exon2: **agacattagctccagagtg**ggcctgggccccagacctctctccagctcaccgacgtacCTGCAGCCACTGGTGGACGGGTTGTCTGTCTGCTAGCTGGCACTCAGGAGGCTGTAGGCAATGGAAGTCTGGGTGGGGATGGGCTCTGAGAGTTTGTgctaggagacagcaacaggcccagttacagtagggccagcagtgctgaggctgtcaccagc**ctgctgctcaagaac**

Exon3: **gtgaggcattcagtaagga**ggctgcctctctcgggagcccaggcccaggcattccctcttgggacacaccacttaCCTGCACCTGCTTGACACAGGCCAGTGCGTACTGCAGCGTGGCCAGGGTCCCAGARCGGCCCTTGCCCCGGCGCTCTGGCGGCAGTCAAGCTTGAGCTCTCGAAGTGCTGTATGAGTTCCTTCTGAGTCTTGCCCCGGCTGACTGTTCACTGctgctggggccacaggaagaa**agagataaagacattagctcag**

Exon4: **agctgtgggagaaggagta**gggatagggtgcgtcgggatgcagaggccaggccgcccgtgacCTGGTTCTGAAGTGTGTACTCAGACGTGATGTGCTCCAGCTCCTCCAGGGTATAGGTGGACATGTCCATGGAGCAAGGCTCGCCCTCCTCCAGGCTCCACTGCTGGTAGTATTCCTGGTTGGctgcagagtgaggcagtgaggcattcag**aaggagctgctcaaac**

Exon5: **ctcacagcaggaatttct**gggactgctatgctccccacagcgttgggacctcacCTGCTGAGGCCCTGTGCCCCAGGTGGGCAGGCGAGATGGAGCAGTGGAAACCATAGAAGACTCCCACATCCTGGGGAGCCAGGAGCTCAGAGAAGCGGGTACCCCGAACACAGTCCCGCTTGAACGCAGCAGGACGGCTGCCTGTCCGAAATGTAGACGATTCGGCCCCGTAGGAAGGAGACAGCCACTGAGAAGGTATCctggcaggagggggagagcaagagcagattcaagagctgtgggagaaggagtaggggtgct**fcgggatgcagaggccag**

Exon6: **ggcagaggtcttctccagt**cccctcacctacCTGATACGGCAGAAGACGGACTTCTCCTGGGTAAAGTCCCTGAGGCCTGAACctgggacagacaggagaggtgagcacagcttctgcccctccctagctgcaagaatccactaagggaagctctgggttccccggcccct**cacagcaggaatttctg**

Exon7: **ttgaaagctccatgctct**ctctctttgctagAGGAGTCTGACCGGGATCCAGGGCCTCGGTACCAGCCATTCCGCCTAACCCCGTATGTGACCAAGATCCGGGTCTCAGATGGGGCCCCTGCACAGCCGTGCTGCCTGCTGATTGCAGAGCGCATCCATTCCGGTTACGAAGgtgggcagttcaggccctggcctgtggggctgggagaaagg**acatttctcatggccaga**

Exon8: **gttgggcttctggagcaaaa**cccagtgaccacactctctgtgctcagCTCCCCGGATACCCCTGACAAGAGGATTTTCACTACGCGGCACACACCCAGCTGCCTCTTCCAGGATGTGGATGAAAAGgtgaggataggacctagaggagacagggcagccagggtgagccacggccact**gatgctctctccgtcag**

Exon9: **tgaggccacggcactctg**atgcctccttcccgtcagGGCTGCCCCCTGCTGGGCTACCTGCCCCAGGACCTCCTGGGGGCCCCAGTGCTCCTGTTCTGCATCCTGAGGACCGACCCCTCATGCTGGCTATCCACAAGAAGAgtgagttcctctgcctgctgccttcccactgtctggcctttg**agtggtgctccttgggt**

Exon10: **tggcatggcctccctctta**ctcagctctcctcctttgaccgctcctccttcccacttccatcagttCTGCAGTTGGCGGGCCAGCCCTTTGACCACTCCCTATCCGCTTCTGTGCCCGCAACGGGGAGTATGTCACCATGGACACCAGCTGGGCTGGCTTTGTGCACCCCTGGAGCCGCAAGGTAGCCTTCGTGTTGGGCCGCCACAAAGTACGCACgtaagtgggcatgccccagctggcgttggggataggcagtgccgtgggggacagaccgggcccagg**ctggattcactctcactc**

Exon11: **gagctggcgttggggata**gggcagtgccgtgggggacaggaccgggcccaggcgtgattcactcttactctacagGGCCCCCTGAATGAGGACGTGTTCACTCCCCGGCCCCAGCCAGCTCCCTGGACTGATATCCAGGAGCTGTCAGAGCAGATCCACCGGCTGCTGCTGCAGgtgagagtagcggagaggagcctgggag**gtgagaaaaggtgtgggaag**

Exon12: **gtgagaaaaggtgtgggaag**cgggtcaagccatctaactgccctctcctgctgagCCCCTCCACAGCCCCAGCCCCACGGGACTCTGTGGAATCGGCGCCGTGACATCCCCAGGCCCTTCCACAGCCCTGGGTCTCCAGTGATAGCAACGGGGGTGATGCAGAGGGGCTGGGCCTCCTGCGCCAgtgagtacctgcttctacctaccccttaategcccttcccctctctt**cttggaaaccagcacttgag**

Exon13: **cttctcaagctcacatgga**aaaaaacagcaaatgggtgggggtgaaggtcaggggacccccaggtctgtctcttaccacacatcatcatcaactcacCAGGGAGGGGGGCCGGGACTGAGGCCGGGCCGAGACTCAATAAAAAGCTGCTGGCCCTGGTGCTTACCAGATGCACATCCTTACAGATCTGCTGAAAAGTACctgtgggacacagcaccacagtgagcagaaccagggggtgctgccagtgtcagggccaaggccacaataaacaagaaggtaccagtggggagacagagcct**gatgggagcaggacaagaag**

Exon14: **tgtgttttttccatgtgag**ctttagaaggctatttctcttctcttcttggcccagCTACAGGCACGTTCAAGGCCAAGGCCCTTCCCTGCCAATCCCCAGACCCAGAGCTGGAGGCGGGTCTGCTCCCGTCCAGGCCCACTAGCCTTGGTCCCTGAGGAGGCCGAGAGGAAAGAAGCCTCCAGCTGCTCCTACCAGCAGATCAACTGCCTGGACAGCATCCTCAGgtaaggcctgcccagcattcttccactcgggcttaaccctgcccccacagcctgct**ctgatgctctgtgctgtg**

Exon15: **atgccctgtgctgtgtccat**ccccagGTACCTGGAGAGCTGCAACCTCCCCAGCACCCTAAGCGTAAATGTGCTCCTCCTCC
TCCTATACCACCTCCTCAGCCTCTGACGACGACAGGCAGAGGACAGGTCCAGTCTCTGTGGGGACCAAGAAAGgtaaagatc
caatgaccctgctcccactgccccctctgctgctggtggccctgtgctctttccctctgctctgggccc**cttgcctgcctcctc**

Exon16: **gatcctctcctgacttcc**cagtgggggtggggatggaactggcaccatctctgcacagATCCGCCGTCAGCAGCGCTGTCTGGGGAGGGGGC
CACCCACGGAAGGAGCCAGTGGTGGGAGGCACCCTGAGCCCCGCTCGCCCTGGCCAATAAGGCGGAGAGTGTGGTGTCT
CGTACCAGTCAGTGTAGCTTCAGCTCCACCATCGTCCATGTGGGAGACAAGAAGCCCCCGAGTCGGgatatgggtggaattg
ggggcag**gcttgggctccaccggtct**

Exon17: **caacaatccagtcctagact**gggcagagggcaggctccaggaggeccccaggtggtctacCTCGCTCGCCAAGGGCTGAGGGAGCTGTGGAAGA
GCTGTCGAGTCCACGCAGCCTGCCAGGTCTCGGAAGCGGCTGAGGAAGGCTTGCTCTTCTTCTGYGTGTGCAGGGAC
AGCACGGCCTTGGTGAGCCCCACTGGACGGTAGGCGTCTGGGGCTGGGTGAGGGGCTACTGTGGGGCTGGGGGCTGGG
CTGGGGGCTGGGCCTGGGGCTAGGCCAGGCAGGTCTCCATCATGATGATGTctgaggagagtgataggaaaggtcatcagaaccactca
ggggtcaacacatccataccacacc**ccctgtctgatagcctag**

Exon18a: **factaaccccagggtgagg**cttgtaaacctagtctctccccacagGCTGCCACCACGGCCCCGCACCCCCAAGCCGCCGACACCCTG
CCGATCCAAAGCCAAGCGCTCACGCCACCACCAGAACCCCTCGGGCTGAAGCGCCCTGCTATGTCTCACACCCTCACCC
GTGCCACCCTCCACCCCTGGCCACCCACCAGCCACTACCCCTTCCCAGCGGTTGTCCAGCCCTACCCTCTCCAGT
GTTCTCTCTCGAGGAGGCCCCAGCCTCTTCCCCCTGCTCCACATCTGTGCCCCAGCTGCTTCCCCGCCCTTTGG
TGACCCCAATGGTGGCCTTGGTGTCTCCCTAACTATCTGTTCCCAACCCCATCCAGCtatccttatgggcaactccagaccctgctgaaggcc
tcc**caactctgctcgaactc**

Exon18b: **tggtgctccctaaactatctgttcc**caaccccatccagcTATCCTTATGGGGCACTCCAGACCCCTGCTGAAGGGCTCCCACTCCTGC
CTCGCACTCCCCTTCTCCATCCTTGGCCGCCCTCCCCCGAGGTCTCTCACCGCCCGGACTCTCCACTATTCAACTCG
AGATGCAGCTCTCCACTCCAGCTCAATCTGCTGCAGCTGGAGGAGCTTCCCCGTGCTGAGGGGACTGCTGTTGCAGGAG
GCCCTGGGAGCAGTGCCGGGCCCCACCTCCAGTGCGGAGGCTGCTGAGCCAGAGGCCAGACTGGtgagcactgaccctgct
ctgctgcccagccccaccagccccgcccctctgcccacc**tggtgctgctgctctctc**

Exon19: **agcagtggaagggaggccta**gggtgctgaccctccatcctctctgccccctccccctctccagcCGGAGGTCAGTACTCCAATCAGGACGC
ACTTCCGGCTCCAGTGACCTGCTCGAACTTCTGCTGCAAGAGGACTCGCGCTCCGGCACAGGCTCCGCAGCCTCGGGC
TCCTTGGGCTCTGGCTTGGGCTCTGGGTCTGGTTCAGGCTCCCATGAAGGGGGCAGCACCTCAGCCAGCATCACTCgtgag
taccgcctccagcatctcccaggtagggcagtgattggggagccgggagcccaggccccg**cttggcggagcttctaag**

Exon20: **cttgtgaggteccaggagt**gggcatgeagcggcctgactcccattggtctgcccccaacttcaagGCAGCAGCCAGAGCAGCCACACAAGCAAAT
ACTTTGGCAGCATCGACTCTTCCGAGGCTGAGGCTGGGGCTGCTCGGGGCGGGGCTGAGCCTGGGGACCAGGTGATTA
AGTACGTGCTCCAGGATCCCAATTTGGCTGCTCATGGCCAATGCTGACCAGCGCGTCATGATGACCTACCAGGTGCCCTC
CAGgtgaggcatttcagaggcctcttggcc**ctcttfcagaggtagtagtg**

Exon21: **aaagctgtgtagagaaaagga**tgccagctcatggtagtgccccgggtctctgatccagcctctgcttctgaacccctcttgggagGGACATGACCTCTGTG
CTGAAGCAGGATCGGGAGCGGCTCCGAGCCATGCAGAAGCAGCAGCCTCGGTTTTCTGAGGACCAGCGCGGGAAGT
GGTGTGTGCACTCCTGGTCCGAAGGGCCAAGTGCCTCGGGCTCTTGATGTGATGgtgagagaagcctgggagccgggagaaaaagaa
ttgagctcaagttcaagggg

Exon22: **agttctgagaattgggacata**GgagaagaaagcctctcatggactcctggagatgggtcccagaatggagtCTAGCTGGTGCAAGTTTCTGCTGTAGGTA
AGGCTGGACTGGATGAGCTCCTGCCTTCTTCTCCTCCTCCATAGCCAAGTCTGAGAGCTTGAAGCCTTGGCCCCGCC
TGGGCCTCCTCGCAGCCCTCTCCCTCAACCTGCCGCCACCCTGCTGCCCTGCTCGCCTCCACCCTCTTCCATGGGCTC
CAGCCCCAGTCCATCCAGCTCTGAGAAGAGTGGGTATCAGGGTGACCAGGATCTTGGGTGCTGCTCCACAGTCCAC
ACAGGCcttggtagagaaatggacatgagagag**tcagacagggctcactg**

PER2

Exon1: **ccttgcgtgtgcttgtta**atgcgtgacagcatccctctgtttgccagcttcgtccagagcccagc**ATGAATGGATACGCGGAATTTCCGCCAGCCCC**
AGTAACCCACCAAGGAGCCCGTGGAGCCCCAGCCCAGCCAGGTCCCCTGCAGGAAGATGTGGACATGAGCAGTGG
CTCCAGTGGACATGAGACCAACGAAAACGCTCCACGGGGCGGGACTCGCAGGGCAGTGACTGTGACGACAGTGGGA
AGGAGCTGGGGATGCTGGTGGAGCCACCGGATGCCCGCCAGAGgtgagttcagcctctggccagatggaggctggcaggtgttttctcagtgctcatt
tctgctgtgattgattgcttttgaactttaaa**catgattaccaagttttcaag**

Exon2: **ttttctgatgtctgaaggt**tttatattccagtttatcttaacctgtatttttaaaaaattgtcttaccatggtattatctagcctgttatcagtgtaggatggcagggggaagatgtgtctggagc
atacaattgtctaaatgttctttttttttttttttttcatag**TCCAGATACCTTTAGCCTGATGATGGCAAAATCTGAACACAACCCATCTACAAGTGG**
CTGCAGgtaaggcaattagaactcacaatagagggttttagaгааaattgaaagacttctattggagggttagtttctgggagtgacgtggccttttaagctgtctaaaacccatctgtgtggct
atgtgggtacgaaccagcc**caactctggcctttcagacac**

Exon3: **gggcaagaggcagcttct**tcaggaaaggacacctaggaagctaactttggctgctcttttgaatcctgcag**TAGCGACCAGTCTTCGAAAAGTGGACAC**
ACACAAAGAAGTATAAAAACACTAAAGGAGCTGAAGGTCCACCTCCCTGCAGACAAGAAGGCCAAGGGCAAGGCCA
GTACGCTGGCCACCTTGAAGTACGCCCTCAGGAGCGTGAAGCAGGTGAAAGgtacgtcggcctcgacatctgtccaacctatagaatattgtt
taaattcccccaattatagcttgattgtgttgaacttc**taaaactcagaggtcatcgc**

Exon4: **gtaagagctagtgactgtct**ccggccaagcgtgggtctgccactgagtgaaactgtctctcctgcag**CCAATGAAGAGTATTACCAGCTGCTGATGT**
CCAGCGAGGGTCAACCCCTGTGGAGCAGACGTGCCCTCTACACCGTGGAGGAGATGGAGAGCGTTACCTCTGAGCACA
TTGTGAAGAATGCCgtaagcctcttccgcaaagtttcttc**taaaatggcaggagttctctc**

Exon5: **gtccgacaccatctgactct**gtcatcagagcccgactctctcttttcag**GATATGTTTGCGGTGGCCGTGTCCTGGTGTCTGGGAAGATCCTG**
TACATCTCTGACCAGGTTGCATCCATATTTCACTGTAAGAGAGATGCCTTCAGCGATGCCAAGTTTGTGGAGTTCTTG
CGCCTCACGATGTGGGCGTGTCCACAGTTTACCTCCCCGTACAAGCTTCCCTTGTGGAGCATGTGCAGTGGAGCAGgt
gagtgaggagcaggtgagtatacagaggtgtgcttcttccctctgggctcgggaaagggccaggagctgggccaaccagatgtgtgcagggcgc**tgccctcactttcagagcc**

Exon6: **gtttcacttgaattctgtct**gattctgtctctctcttttgttgagaaatgaggaacactgtatttagttgttggttgatgaatgactttgggctctctcttttag**ATTCTTTTACT**
CAAGAATGCATGGAGGAGAAATCTTTCTTTTGCCGTGTCAgtaagcctggttccagtttcttaaatagaaaaccgtata**aacatttcaecccagcactgg**
tc

Exon7: **aggaacagaacaggggact**gttctctgtgtcacagttccaactagagcagagctctcaccgcag**TGTCCGAAAAGCCACGAGAATGAAATCCCG**
TACCACCCCTTCCGCATGACGCCCTACCTGGTCAAGGTGCGGGACCAACAAGGTGCTGAGAGTCAGCTTTGCTGCCTTC
TGCTGGCAGAGAGAGTGCACCTCTGGTTATGAAGgtaacagccaagcccagggcgagggcagatgtgtctctgctctcc**ctcagttactctgtggttc**

Exon8: **facagggtgtttctggttagt**tttaataatacatcaaatatgcatttcttagatcacaaatgtgtcaatattctgttctttcag**CCCCTAGAATTCCTCCTGAAAAGAG**
AATTTTACAACCACCCATACACCAAAATTGTTTGTCCAGGATGTGGATGAAAGgtacgtgtcttgaccaccccttttcatgtttttgatataaa
agctatttagccaagccaagactgcatcttggtttataaatt**catgataatggacaaaaaatg**

Exon9: **ggttcttagtgacaatctctct**catctgtttgatgccaatcctagcgtgtgtctgcttgcctccag**GGCGGTCCCTCTCCTGGGCTACCTACCTCAGGACC**
TGATTGAAACCCAGTGCTCGTGCAGTCCACCTAGTGACAGGCCCTTGATGCTGGCCATCCACAAAAGAgtaggtcccctt
ttcatgtacatcctgaagtgttggcgaagttctgtgtccttgggctgct**cttgggaccagctagctc**

Exon10: **ctgagtgaactcttgaacttgt**ctctctactataaatctgtttgctccccctttcccctgaatgctggcttttctctctcag**TCCTGCAGTCAGGCGGGCAGCCTTT**
GACTATTCTCCCATTCGGTTTCGCGCCCGGAACGGAGAGTACATCACGTTGGACACCAGCTGGTCCAGCTTCATCAACC
CATGGAGCAGGAAAATCTCCTTCATCATTGGGAGGCACAAAGTCAGGGTgtgagtgctccaagggcccaggtgctcaggggtcttggcggg
ggtctcgggctgtctcactccc**agcaacagatggcatagggga**

Exon11: **gctatacagtcacgccagagaggt**ctctctgtgggcccactcaacaagatgaattaaaccacgcag**GGGCCCTTTGAATGAGGACGTGTTTGCAGC**
CCACCCCTGCACAGAGGAGAAGGCCCTGCACCCACGATTTCAGGAGCTCACAGAGCAGATCCACCGGCTCCTGCTGCA
Ggtgggtgtgtgctgctcat**atgtctctctccaggttagc**

Exon12: **cgaaacaggtgtgtgtggca**gggggccacatgcatagctcagcag**CCCGTCCCCACAGCGGCTCCAGTGGCTACGGGAGTCTGGGCAG**
CAACGGGTCCCACGAGCACCTTATGAGCCAGACCTCCTCCAGCGACAGCAACGGCCATGAGGACTCACGCCGGAGGAG
AGCCgtacgtctctccattctccctgagaaaatgagttgtgagtgctccctcagagttaaaaa**gcacactcaagacaactttt**

Exon13: **ctctctgttctcactttgcc**ggacagactgaaggaggtctcctagaatgaataatgttctatttgttttctcaag **GAAATTTGTAAAAATGGTAACAAGACC**
AAAAATAGAAGTCATTATTCTCATGAATCTGGAGAACAAAAGAAAAAATCCGTTACAGgtaaaaaaaaaataattcaacatttcttactgaa
actagatgatgccacatgagaagagggaacctgggttaaatgctgactctggctggcaggg**agctctacctttagccgtg**

Exon14: **ctctcttccaggtagaacga**aaatgctttgtaatacacacagcgtttctgtgggagaaaaatgaatgaaagaacaatttgcattcctcag **AAATGCAAATAATCCC**
CCAGCTGAGAAGAAAGCTGTCCCTGCCATGGAAAAGGACAGCCTGGGGGTTCAGCTTCCCCGAGGAGTTGGCCTGCAAG
AACCAGCCCACCTGCTCTACCAGCAGATCAGCTGCTTGGACAGCGTCATCAGgtatgccggcattccagcggagctccaccatctcacacac
cttccctctgcatgttgtgtggccttaccagtggt**catgcttccacacaggfac**

Exon15: **ccatctcacacaccttccc**ctctcatgttgtgtggcctcaccagtggttcatgcctttcacacag **GTACTTGGAGAGCTGCAATGAGGCTGCCACCCT**
GAAGAGGAAATGCGAGTTCCCAGCAAACGTCCCAGCGCTAAGGTCCAGTGATAAGCGGAAGGCCACAGTCAGCCCAG
GGCCACACGCTGGAGgtatctaactgtgtagagccatgatcatgtgaaataatgaaatcctctggagtagagtcagagctccc**catggcttctgtggacacag**

Exon16: **gggtgtcggtttctcatctg**cacagtgcatgtaatgacacactaatgtttgttcccccttctctcatgaa **AGGCAGAGCCGCCCTCCAGGGTGAACAGCC**
GCACGGGAGTAGGTACGCACCTGACCTCGCTGGCACTGCCGGCAAGGCAGAGAGTGTGGCGTTCGCTCACCAGCCAGT
GCAGCTACAGCAGCACCATCGTCCATGTGGGAGACAAGAAGCCGCAGCCGGAGTTAGgtatgactatgggctcttggatcagagagcagttt
gattttaacatgaaacaagaagtttccatcttaatttt**ctaaagtgcagaagaactcc**

Exon17: **gaatgattgtctgttctgctg**aatatagtgtggcctaaataataaacagggcagctgtggaccagagccctgggttctgtgttac **AGATGGTGGAAAGATGCTGCG**
AGTGGCCAGAATCCCTGGACTGCCTGGCGGGCCCTGCCCTGGCCTGTGGTCTCAGCCAAGAGAAGGAGCCCTTCAAG
AAGCTGGCCCTACCAAGGAGTACTCGCTGCACACACAGAAGGAGGAGCAGAGCTTCTGCAGAAGTTCAAAGA
AATAAGAAAACCTCAGCATTTCAGTCCCCTGCCATTACTACTTGCAAGAAAGATCCAAGGGGCAGCCAAGTGAACG
AAgtaagtataccgaattaaaagtgcgttttaaaaactttatctctgt**gggtactgagtcagtgctg**

Exon18A: **ccaggactgtgagcaaga**gggtgtctcaaatgtggagtaaaatttaactccagatatttcttttctgcattag **CTGCCCTGGACTAAGAAATACTTCCG**
GAATAGATTACCTTGGAAAAAACAGGAAAGAACAGAAAATTGAAGTCCAAGCGGGTCAAACCTCGAGACTCATCT
GAGAGCACCGGATCTGGGGGGCCCGTGTCCGCCCGGCCCGCTGGTGGGCTTGAACGCCACAGCCTGGTCAACCCTCA
GACACGTCCAGTCCAGCTGCCAGCCGTGCCCTTTCGCCCCAGTGCCAGCAGCTTATTACTGCCCGTGTTCAGC
GCCAGGGACTGTGGCAGCACCCCGGCCACCTCCCCACGCCAGCTTACAGTGCCTGCTGTGCCCGTGGACCTCCAGCAC
CAGTTTGCAGTCCAGCCCCACCTTTCCTGCCCTTTCGGCGCTGTCATGGCATTATGCTACCCAGTTATTCCTTCCC
TCGGGGACCCCAAACCTGCCCCAGGCCTTCTTCCC**agccagcctcagttccagag**

Exon18B: **ctctgcatggcattcatgct**ACCAGTTATTCTTCCCCTCGGGGACCCCAAACCTGCCCCAGGCCTTCTTCCCAGCCAG
CCTCAGTTTCCGAGCCACCCACACTCACATCCGAGATGGCCTCTGCCTCACAGCCTGAGTTCCCAGCCGGACCTCGA
TCCCAGACAGCCATGTGCTTGTCCAGCCACCCGGGCCACCCACCATCGGCCATGGGTAGGGCCTCCCACCGCTCTT
TCAGTCCCGCAGCAGCTCGCCCCTGCAGCTCAACCTGCTGCAGCTGGAGGAAGCCCCTGAGGGTGGCACTGGAGCCAT
GGGGACCACAGGGGCCACAGAGACAGCAGCTGTAGGGGGCGGACTGCAAACCTGGCACTTCTCGGGACCAGCAGCCGA
AGGCGCCTCTGACCgtaaggatttctgatgctcttccccaaagcaggcagcaaacagcacacctggcaggccggccgc**acatcctcagttcagacatg**

Exon19: **tatagctgtctcctgactgag**cccctgaacagcagatctgcttctctcctaaag **CGTGATGAACCCCTCAGACACACAGAACAGTGACGCCCT**
TTCCAGTCAAGCGGCCTCCTAAACCTCCTGCTGAATGAGGACCTCTGCTCAGCCTCGGGCTCTGCTGCTTCGGAGTCTC
TGGGCTCCGGCTCACTGGGCTGCGACGCCTCCCCGAGTGGGGCAGgtatgttggccctggcgggtgttaggcacttgggaggttctcagga**tgact**
tgctccagagtcac

Exon20: **gaggaagcacattatgcaag**gtttaattcatatgtcaatgtttgacgaccacgtttttgttttaag **GCAGTAGTGACACAAGTCATACCAGCAAATA**
TTTTGGAAGCATTGACTCCTCAGAGAATAATCACAAAGCAAAAATGAACACTGGTATGGAAGAAAGTGAGCATTTCAT
TAAGTGCCTCTGCAGGATCCCATCTGGCTGCTGATGGCAGATGCGGACAGCAGCTCATGATGACGTACCAGCTGCCT
TCCCgtaaccaccagcgttttcttaggcacctggggaggatgggttcaggagctcccagaaa**caacaaggtaaggctcattc**

Exon21: **catctaaaactacattattctgaa**agaataaaaatagatacccttaagacatttgaagcttaccgatttctaataatcttgcgaag **AAATTTAGAAGCGGTTTTGAA**
GGAGGACAGAGAGAAGCTGAAAGCTCCTACAGAAACTCCAGCCAGGTTACGGAGAGTCAGAAGCAGGAGCTGCGCGA
GGTCCACCAGTGGATGCAGACGGGCGGCCTGCCCGCAGCCATCGACGTGGCAgtaagctcacgggactcatttctgatatggccctaaa**aggct**
ctgtgatgggatt

Exon22: **ggccaatttgaatgacttttg**Aacaactcagatctcaagttgtactgatttctctttttttctttaa**GAATGTGTTTACTGTGAAAACAAGGAAAAAG**
GTAATATTTGCATACCATATGAGGAAGATATTCTTCTCTGGGACTCAGCGAAGTGTGCGACACCAAAGAAGACGAAA
ATGGATCCCCCTTGAATCACAGGATCGAAGAGCAGACGTAACCCCTGCCACCTCAGCCGGCAGCCAGCG**AGGTAC**
ACCAGGTGGTGCT

PER3

Exon1: **caagtgagcgagaagcagg**ctgcgggcgtccagcagcagctggagccccgcggagacctcgag**ATGCCCCGCGGGGAAGCTCCTGGCCCCGGG**
AGACGGGGGGCTAAGGACGAGGCCCTGGGCGAAGAATCGGGGGAGCGGTGGAGCCCCGAGTTCATCTGCAGAGGAA
ATTGGCGGACAGCAGCCACAGgtgacgcgctgcttcagccgagggccc**catgcttctgttctctcc**

Exon2: **gtgttccctaagccgaag**atgctgttctcagagatgaagtgttaattttttatctccag**TGAACAGCAAGATCGAAACAGAGTTTCTGAAGAA**
CTTATCATGGTTGTCCAAGAAAATGAAAAAATACTTCCCCTCGGAGAGACGCAATAAACCAAGCACTCTAGATGCCCTCA
ACTATGCTCTCCGCTGTGTCCACAGCGTTCAAGgtaacaagccggagagaatttcctctacgaatgcaccagactcata**caagcagccagaggagt**

Exon3: **ccagcttgatagtgatgaat**ggttccaaagatactgttgcactgactacctgtttatctccctgtgttcttag**CAAACAGTGAGTTTTCCAGATTCTCAG**
TCAGAAATGGAGCACCTCAGGCAGATGTGAGCATGTACAGTCTTGAGGAGCTGGCCACTATCGCTTCAGAACACACTTCC
AAAAACACAgtaagaattcatgcattttgcatacaac**ctgggtgacttttctaagg**

Exon4: **ctttcagggaaatattgctag**tgatctcaatattgcattattttaaatgttttcatag**GATACCTTTGTGGCAGTATTTTCATTTCTGTCTGGAAGG**
TTAGTGCACATTTCTGAACAGGCTGCTTTGATCCTGAATCGTAAGAAAGATGTCCTGGCGTCTTCTCACTTTGTTGACCT
GCTTGCACCTCAAGACATGAGGGTATTCTACGCGCACACTGCCAGAGCTCAGCTTCTTTCTGGAACAACCTGGACCCAA
AGAgtaacaggaccaatgttcagatgtctatcttctcatcaagatcagtttcttcttacaggaatagtagacaataacatattattagaacatgcacactatctggtttt**cttattctgttatag**
aaagtca

Exon5: **cactgagaaagacctggata**agaggagtgactgaccaggcacttttcttctag**GCTGCACGGTATGAATGTGCTCCGGTGAAACCTTTTTTCT**
GCAGGATCCGgtaagtatagtgctc**tggaagccagcaacagtga**

Exon6: **cccagcttgttctgcc**atgggccagtagggtgcgctcagaccagcactaatactttaaactctcctag**GGAGGTGAAGACAGAAAGCAAGAGAAGTGTG**
ACTCCCCATTCCGGATCATCCCCTATCTGATTCATGTACATCACCTGCCAGCCAGAATTGGAATCGGAACCTTGCTGT
CTCACTGTGGTTGAAAAGATTCACTCTGGTTATGAAGgtaagtcagtagataagatgcagaaatgtcagcaatcag**ataggaacatgggaaagctg**

Exon7: **agtggtagtagtagg**ataaataaggatattgccttaaatggcttctgttttttcttag**CTCCTCGGATCCCAGTGAATAAAAAGAACTTCACCA**
CCACACACACCCAGGGTGTGTTTTCTTGAAGTAGATGAAAgtaagtagtctttaaagcctaaaagaattgttctgaaaataataataatgtaagaa
gattacattatgtt**gcatgtttatacatatgtaattg**

Exon8: **gaattacctgatagtatgcc**acctgtgtgtgtatctgtatccag**AGCAGTGCCTTTGCTGGGTTACCTACCTCAGGACCTGATTGGAACA**
TCGATCCTAAGCTACCTGCACCCTGAAGATCGTTCTCTGATGGTTGCCATACACCAAAAAAGgtcaggacctactccttataggagaaat
attttctctcattgattgttctaatttttcttctcatctcattag**agcgcaacctttaaccaga**

Exon9: **ggcaacagagcgagactcaatctc**aaaaaaaaaccactaaacatttacaataaatgcttataaaaggacatttgaatcagtagtctgtgtaagtaactctattttcttattttatata
g**TTTTGAAGTATGCAGGGCATCCTCCCTTTGAACATTCTCCATTTCGATTTTGTACTCAAAACGGAGACTACATCATACT**
GGATTCCAGTTGGTCCAGCTTTGTGAATCCCTGGAGCCGGAAGATTTCTTTCATCATTGGTCGGCATAAAGTTCGAACgta
agccagtcagtttcatattttctaaacatctctgtatcaataata**ttcttagcttattgactgcc**

Exon10: **gtttgactcagctctctcact**gggcatttctag**GAGCCACTAAATGAGGATGTTTTGCTACCAAAATTA AAAAGATGAACGATA**
ATGACAAAGACATAACAGAATTACAAGAACA AATTACA AACTTCTTACAGgtaaggtgagattgtaaaaat**gcaagttccctgaattgt**
g

Exon11: **tcgtgtcagcatcagcatt**aaaagtaccaacctgcacacactaatttagtatttcaggaattgtcattttaaattttacatgattctagatgagctctcggtggctgcatttgaacacca
gcaattctgacttgttctcttttcttctccag**CCAGTTCACGTGAGCGTGTCCAGCGGCTACGGGAGCCTGGGGAGCAGCGGGTCCGAGGA**
GCAGCTTGTACGATCGCCTCCTCCAGTGAGGCCAGTGGGCACCGTGTGGAGGAGACGAAGGCGGAGCAGgtgcatgggctta
tgtcacattctatacaggcatcgtgtttctgtactacctcggtctgaatgtggtgacatcttagtatattctgactt**gaagacctcaactgataaacg**

Exon20: **gaagtgtattcctagatgac**gggaaaagaacctgtgtcttattcaggactattaagattctgtttgtttgtttcagGGTTAAAGAAGTTGTACTAAAAGAAG
ACCTGGAAAAGCTAGAAAAGTATGAGGCAGCAGCAGCCCCAGTTTTCTCATGGGCAAAAAGGAGGAGCTGGCTAAGGTGT
ATAATTGGATTCAAAGCCAGACTGTCACTCAAGAAATCGACATTCAAgtagcacagtaataatggctgtcatatactcatgtatttggccaggtagt
ctftaatata**ggctgtgtcttgcagatc**

Exon21: **ttagaaacatgtgaccagcctt**tactgtttaaaactcttaggtgacattgacatcaagtaactcgcttcttctttttggagGCCTGTGTCACTTGTGAAAATG
AAGATTCAGCTGATGGTGCGGCCACATCCTGTGGTCAGGTTCTGGTAGAAGACAGCTGTTGAgtgactgtgaggatgaacctcatacc
ttccaag**acgtgttacagacagacc**