Polymorphic Variation in Human Circadian Genes in Mental Illness

Andrew A. Pieper*, A. John Rush+, Annie John*, Lindsay Choate*, Amy Gibson*, Sharon Ayacannoo*, Krista R. Noack*, Tina W. Han*, Charles Quinn*, Tokuku Ihara*, Brandon Probst*, and Steven L. McKnight*

Departments of Biochemistry* and Psychiatry+
University of Texas Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, Texas 75390-9152

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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 GVs in *BMAL1, BMAL2, CRY1, CRY2, CLOCK, NPAS2* and *PER2*. We report here all GVs identified in these nine genes, as well as pertinent characteristics of the subjects identified with exonic GVs producing changes in amino acid sequence. We have categorized and ranked these GVs 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 GVs were found in the *PER3* gene. Overall, we identified almost twice as many GVs 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 GVs, 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 GVs 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 GVs 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 retinohypothalmic 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 GVs 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*.

	INTRONIC CHANGES		EXONIC CHANGES (SILENT)			EXONIC CHANGES (MEANINGFUL)		
GENE	**Exon**	**Description**	**Exon**	**Description**	**Frequency**	**Exon**	**Description**	**Frequency**
BMAL1	2	-15 C→T	NONE			NONE		
	4	-8 T→C						
	5	+31 C→T						
	6	-35 A→G						
BMAL2	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						
CRY1	9	+15 6bp INS	5	G(GGC) 212 G(GGT)	1.04%	NONE		
	10	+52 A→T						
	11	+32 A→G						
CRY2	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						
CLOCK	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*.

	INTRONIC CHANGES		EXONIC CHANGES (SILENT)			EXONIC CHANGES (MEANINGFUL)		
GENE	**Exon**	**Description**	**Exon**	**Description**	**Frequency**	**Exon**	**Description**	**Frequency**
NPAS2	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						
PER2	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 GVs 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 PSQSGIMTEKVVEKLSQNPLTYLLSTRIEISASSGSRVEDGEHQVKMKAFR----EAHSQ
dogBMAL2     50 PSQSGIMTEKMVEKLSKNPFTYLLSTRIEISASSGSRMEDGEQQVKMNQVLFLLREAHSQ
btBMAL2       7 PSRSGIMKEKVMEKLSQNPFTCLLSTRVEMSAFSCSRMEDGEQQVKIKS----FREAHSQ
mBMAL2       14 PLQSEFMTDTTVESLPQNPFASLLSTRTGVSAPSG-----------------IREAHSQ
ratBMAL2      7 LLQSEFRTDAMVENLPRSPFTSVLSTRTGVAVPNG-----------------IREAHSQ
gallBMAL2    40 NPITKPATTSFNNSVVEIPRKRKGSDSDNQDTVEVDGDPQKRNEDEEHLKIKDFREAHSQ
danioBMAL2    1 --------------------MDNLEMKSASNLDEDMEDDAGRSEDDQHLKIKCIREPHSQ
```

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 AEGFLFVVGCERGKILFVSKSVSKILNYDQASLTGQSLFDFLHPKDVAKVKEQLSSFDIS
dogBMAL2    185 AEGFLFVVGCERGKILFVSKSVSKILNYDQASLTGRSLFDFLHPKDVAKVKEQLSSSDIS
btBMAL2     138 AEGFLFVVGCERGKILFVSKSVSRILNYDQASLIGQSLFDFLHPKDVSKVKEQLSSSDIS
mBMAL2      131 AEGFLFVVGCERGRIFYVSKSVSKTLRYDQASLIGQNLFDFLHPKDVAKVKEQLS-CDGS
ratBMAL2    124 AEGFLLVVGCEGGRILFVSKSVSKTLHYDQASLMGQNLFDFLHPKDVAKVKEQLS-CDVS
gallBMAL2   175 ADGFLFVVGCNRGKILFVSESVCKILNYDQTSLIGQSLFDYLHPKDVAKVKEQLSSSDVS
danioBMAL2  116 ADGFLFVVGCDRGKIVFVSESVSKTLNYSRTELIGQSLFDYVHPKDIGKVKEQLSASELY
```

***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.

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*.

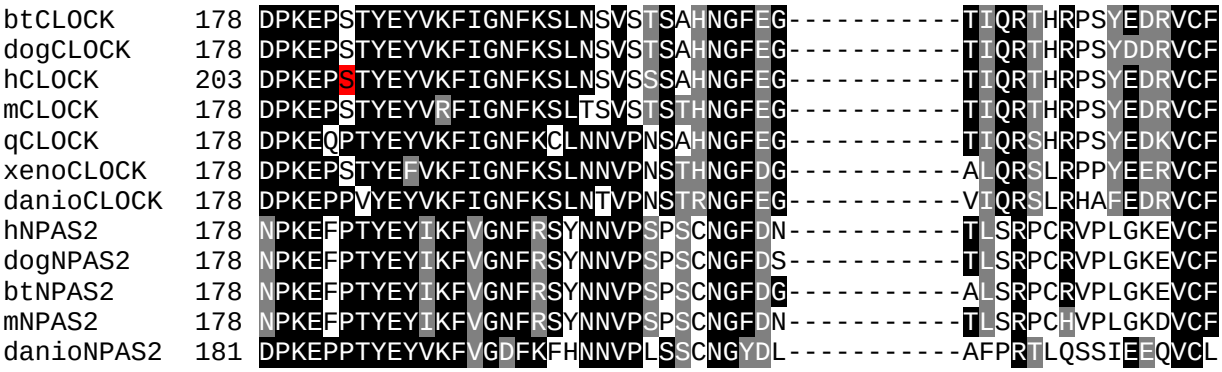
CRY2: **Table 3** shows that in 288 study subjects, 10 GVs were identified in CRY2. All of these GVs were intronic.

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.

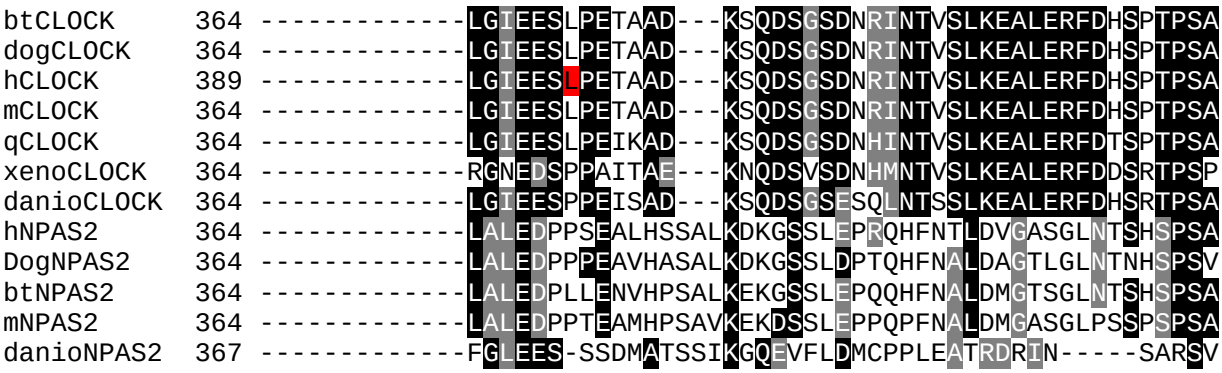
1. ***CLOCK*, E7, S(TCT) 208 C(TGT)**
   - ***Frequency:*** 1.74% (5/288)
   - ***Diagnoses*:** 100% (5/5) with Mood Disorder (3 with MDD, 1 with Bipolar Disorder, and 1 with Depression NOS)
   - ***Family History:*** 40.0% (2/5) family history of Mood Disorder
     40.0% (2/5) unknown family history
     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.



***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.



***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 GVs 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 -------------LALEDPPSEALHSSALKDKGSSLEPRQHFNTLDVGASGLNTSHSPSA
DogNPAS2     364 -------------LALEDPPPEAVHASALKDKGSSLDPTQHFNALDAGTLGLNTNHSPSV
btNPAS2      364 -------------LALEDPLLENVHPSALKEKGSSLEPQQHFNALDMGTSGLNTSHSPSA
mNPAS2       364 -------------LALEDPPTEAMHPSAVKEKDSSLEPPQPFNALDMGASGLPSSPSPSA
danioNPAS2   367 -------------FGLEES-SSDMATSSIKGQEVFLDMCPPLEATRDRIN-----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 SSFSSQSINSQTVGQSLTQPVMSQSANLPVPHGM-------------------------
dogCLOCK     453 ASFSSQSINSQSVGQSLTQPAMSQAANLPIPQGM-------------------------
hCLOCK       479 SSFSSQSINSQSVGSSLTQPVMSQATNLPIPQGM-------------------------
mCLOCK       453 SSFSSQSINSQSVGPSLTQPAMSQAANLPIPQGM-------------------------
qCLOCK       453 SSLSSQSLSSQSLGQPVTQPTMSQPATLQLQS---------------------------
xenoCLOCK    451 SSISSQSMSSQSVSQPLSQSVMKQTASIQLQQGMT-------------------------
danioCLOCK   454 SSISSQSMSSQTTGQTMGTSLVSQPQQPQTLQATV-------------------------
hNPAS2       456 GLSQAATMPAPLPSPSSCDLTQQLLPQTVLQS---------------------------
DogNPAS2     456 GLSQAATMPAPLPAPSSCNLTQQLLPQTILQS---------------------------
btNPAS2      453 GLGQAAAMPAPLPAPASCDLTQQLLPQTILQS---------------------------
mNPAS2       456 GLSQAATMPTALHSSASCDLTKQLLLQSLPQTGLQS-----------------------
danioNPAS2   453 MTHTGTKTLIQRQSSSEPPSLSPSCSQHSAMT---------------------------
```

PER2: **Table 3** shows that in 288 study subjects, 18 intronic GVs and 7 exonic GVs were identified in *PER2*. Five of the exonic GVs 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 GVs 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 GVs in *PER2* are outlined below.

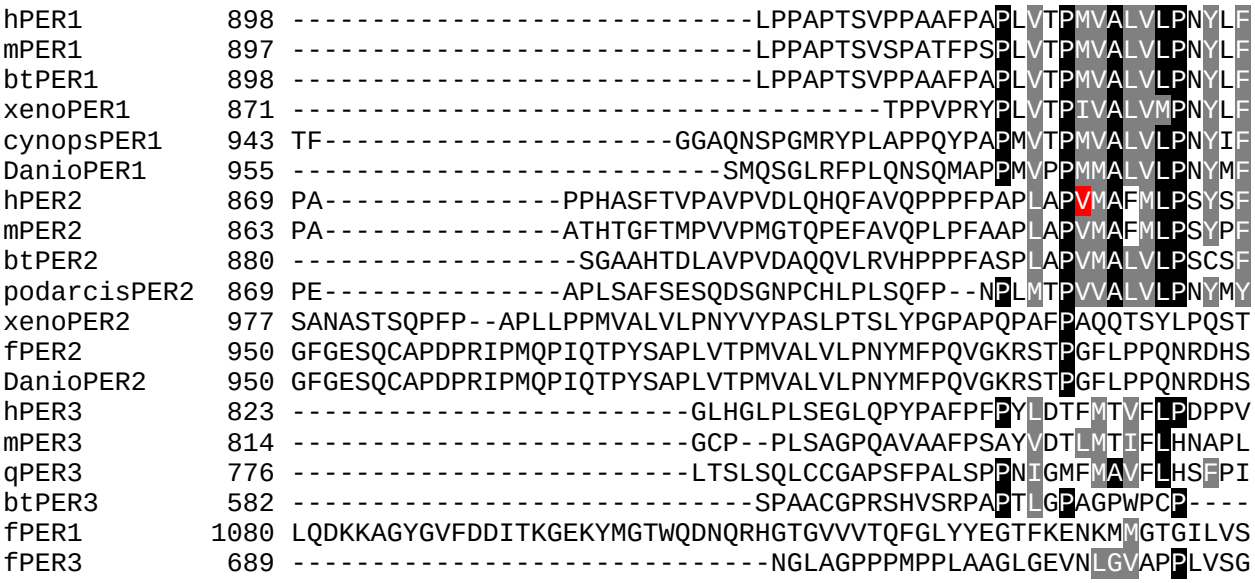
1. ***PER2,* E17, R(CGA) 773 Q(CAA)**
   - ***Frequency:*** 0.35% (1/288) of subjects
   - ***Diagnoses:*** Mood Disorder (MDD)
   - ***Family History:*** Mood Disorder
   - ***Ethnicity:*** Caucasian
   - ***Sex:*** female

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 GVs 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 ----------------SSSTAPSALGERGCHHGPAPPSRRHHCRSKAKRS--RHHQNPRA
mPER1          809 ----------------TSSVAPSAPG---CHHGPIPPGRRHHCRSKAKRSRHHHHQTPRP
btPER1         809 ----------------SSSTAPSAPGERGCHHSLAIPGRRHHCRSKAKRS--RHHQTTRA
xenoPER1       777 HNQHPQ-------RGSKPSRASQHHHASSCNPPSPSKGESNSGRRRGKSGKSKAKRPKQG
cynopsPER1     832 PRHSGQ-------HADKGHRGSRHNANGNGGPGSSRRGKS--GKSKPKRIKHQKQSDSTT
danioPER1      842 NAPLSRGVRCSRDYPAAGSSGRRRGRGGKRLKHQESSEQTGSCSPAGPIRGLLPGVPALG
hPER2          765 RSKGQP-------SERTAPGLRNTSG----IDSPWKKTGKNRKLKSKRVKPRDSSESTGS
mPER2          757 RSRAQA-------SDR---GLRNTSG----LESSWKKTGKNRKLKSKRVKTRDSSESTGS
btPER2         771 RSKGHL-------SNRTAPGLRNTPG----IDSSWKKNGKNRKLKSKRVKPRDSSGSTGS
podarcisPER2   766 RPKGHP-------GNRGVHGPRHGSG----VDQSWKKNGKNRKSKPKRQKPHNSSDSTTS
xenoPER2       877 RP--------------GAPHTRRAQG----AYTSWKRTGKTRKPKTKRVRP-ESWDSSSS
fPER2          838 QKGQVT-------SEAVPAARSCKAGGGGAQETTTTRRGRNKKTKSKRVKPNESSDSTPS
danioPER2      838 QKGQVT-------SEAVPAARSCKAGGGGAQETTTTRRGRNKKTKSKRVKPNESSDSTPS
hPER3          714 KAKYSYF---------QGDSTSKQTRSAGCRKGKHKRKKLPEPPDSSSSNTGSGPRRG-A
mPER3          704 RAQYSCV---------QAGSTAKHSRCAGSERQKHKRKKLPAPVDTSSPGAHLCPHVTGL
qPER3          665 TNGHSCD---------QGNSPSKEMIPASCKNGKKGKLKHQKPQRRSSDRRSFSKNRNSL
btPER3         511 --------------------------------PRGQGPGPTHPCAGTRPGTPRTLHTETL
fPER1          960 YTFYKEGRLRDATYEGSWCAGKPNGRGVLKWPDGRIYTGTFKNGLEDGFGEFIAPNKTLS
fPER3          615 KEIERN----------------------------PPPQNKRGQRGQNQMSQNQNQNQQA
```

***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.



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

Table 4: GVs in *PER1*.

INTRONIC CHANGES		EXONIC CHANGES (SILENT)			EXONIC CHANGES (MEANINGFUL)		
Exon	**Description**	**Exon**	**Description**	**Frequency**	**Exon**	**Description**	**Frequency**
1	+7 A→G	3	R(CGC) 158 R(CGT)	0.10%	1	P(CCA) 37 S(TCA)	0.10%
1	+17 A→G	4	T(ACA) 213 T(ACC)	33.9%	3	R(CGC) 158 C(TGT)	0.20%
2	-19 G→T	5	G(GGC) 229 G(GGT)	0.10%	4	E(GAG) 191 C(TGT)	0.15%
2	+39 A→G	8	R(AGG) 358 R(AGA)	0.15%	5	V(GTC) 240 I(ATC)	0.45%
2	-30 C→A	10	T(ACC) 439 T(ACT)	0.05%	6	S(TCC) 296 C(TGC)	0.05%
3	+14 C→T	12	T(ACG) 507 T(ACA)	0.10%	7	R(CGG) 307 Q(CAG)	0.10%
3	+37 T→ C	12	T(ACA) 516 T(ACG)	0.05%	7	Q(CAG) 314 R(CGG)	0.05%
3	+19 G→A	17	G(GGT) 749 G(GGC)	24.4%	15	S(AGC) 640 N(AAC)	0.05%
4	+6 C→T	17	T(ACG) 787 T(ACA)	24.4%	17	DEL 758-761 PAPS	0.05%
4	+7 G→A	18	G(GGC) 894 G(GGT)	0.35%	18	Q(CAG) 846 R(CGG)	0.05%
5	-12 C→G	18	L(CTG) 973 L(CTA)	2.68%	18	P(CCC) 859 S(TCC)	0.20%
5	-5 1bp DEL	18	L(CTC) 992 L(CTT)	2.68%	18	P(CCC) 962 A(GCC)	11.92%
5	-11 C→T	18	A(GCC) 1008 A(GCT)	0.05%	19	V(GTC) 1027 I(ATC)	0.40%
5	-46 1bp INS/DEL	19	D(GAC) 1034 D(GAT)	0.05%	19	S(TCG) 1060 L(TTG)	0.05%
6	-55 C→T	19	H(CAT) 1076 H(CAC)	0.05%	20	A(GCT) 1108 S(TCT)	0.20%
7	+40 G→A	21	V(GTG) 1184 V(GTC)	0.05%	20	V(GTC) 1141 I(ATC)	0.05%
7	+31 G→ A	22	E(GAA) 1272 E(GAG)	0.05%	21	A(GCT) 1196 V(GTT)	0.89%
7	-10 C→ T	22	S(TCC) 1278 S(TCT)	0.15%	22	T(ACC) 1289 I(ATC)	0.05%
7	-12 C→G						
8	+49 G→C						
8	+28 G→A						
10	+13 T→C						
10	-19 C→T						
10	+63 G→A						
10	-48 C→T						
10	+37 C→T						
11	+15 G→A						
11	-33 C→T						
11	+22 C→T						
11	-48 G→A						
12	-38 C→G						
12	-39 C→T						
13	+15 3bp DEL						
13	+17 G→A						
13	-102 G→A						
13	+19 G→A						
13	+45 1bp INS/DEL						
13	+50 T→G						
15	+34 C→G						
16	-42 A→G						
17	-7 T→C						
17	-8 C→T						
17	-66 G→T						
17	+15 C→T						
17	-11 A→T	**Intronic (cont)**					
19	-21 1bp INS	**Exon**	**Description**				
19	+55 G→C	20	+30 C→T				
19	+9 C→T	20	-6 T→A				
19	+11 C→T	20	+28 C→T				
19	-10 C→T	20	+20 3bp DEL				
19	-30 A→G	20	-37 C→T				

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. ***PER1*, E15, S(AGC) 640 N(AAC)**
   - ***Frequency:*** 0.05% (1/2012)
   - ***Diagnoses:*** unknown
   - ***Family History:*** unknown
   - ***Ethnicity:*** Caucasian
   - ***Sex:*** female

9. ***PER1*, E17, DEL 758 PAPS**
   - ***Frequency:*** 0.05% (1/2012)
   - ***Diagnoses:*** unknown
   - ***Family History:*** unknown
   - ***Ethnicity:*** Caucasian
   - ***Sex:*** female

10. ***PER1*, E18, Q(CAG) 846 R(CGG)**
    - ***Frequency:*** 0.05% (1/2012)
    - ***Diagnoses:*** unknown
    - ***Family History:*** unknown
    - ***Ethnicity:*** Caucasian
    - ***Sex:*** male

11. ***PER1*, 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. ***PER1*, 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. ***PER1*, 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. ***PER1*, 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. ***PER1*, 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. ***PER1*, 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: GVs 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	Intronic (cont)					
17	+51 A→G	Exon	Description				
18	+43 G→A	20	+58 C→G				
18	+16 A→G	20	+19 G→A				
19	+67 T→C	20	+48 G→A				
19	+39 1bp DEL	21	-49 T→C				
19	+70 2bp DEL	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

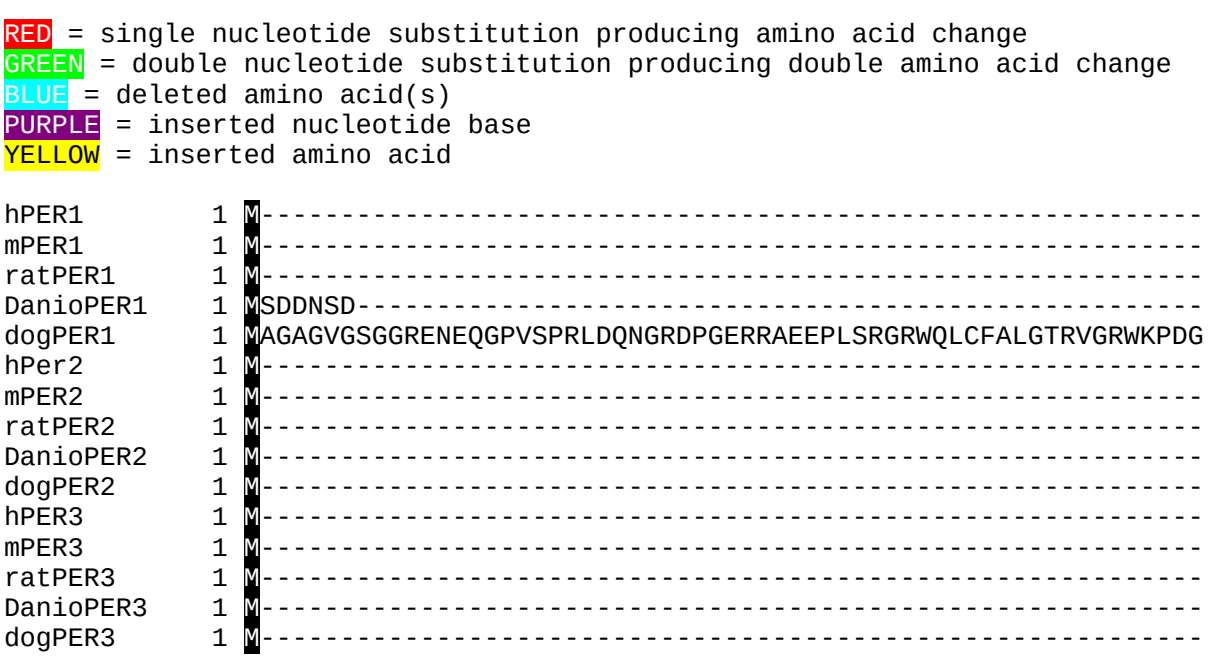
28. ***PER3,*** **E19, T(ACA) 1111 I(ATA)**
    - ***Frequency:*** 0.05% (1/2012)
    - ***Diagnoses:*** Mood Disorder (MDD)
    - ***Family History:*** Mood Disorder
    - ***Ethnicity:*** Caucasian
    - ***Sex:*** female

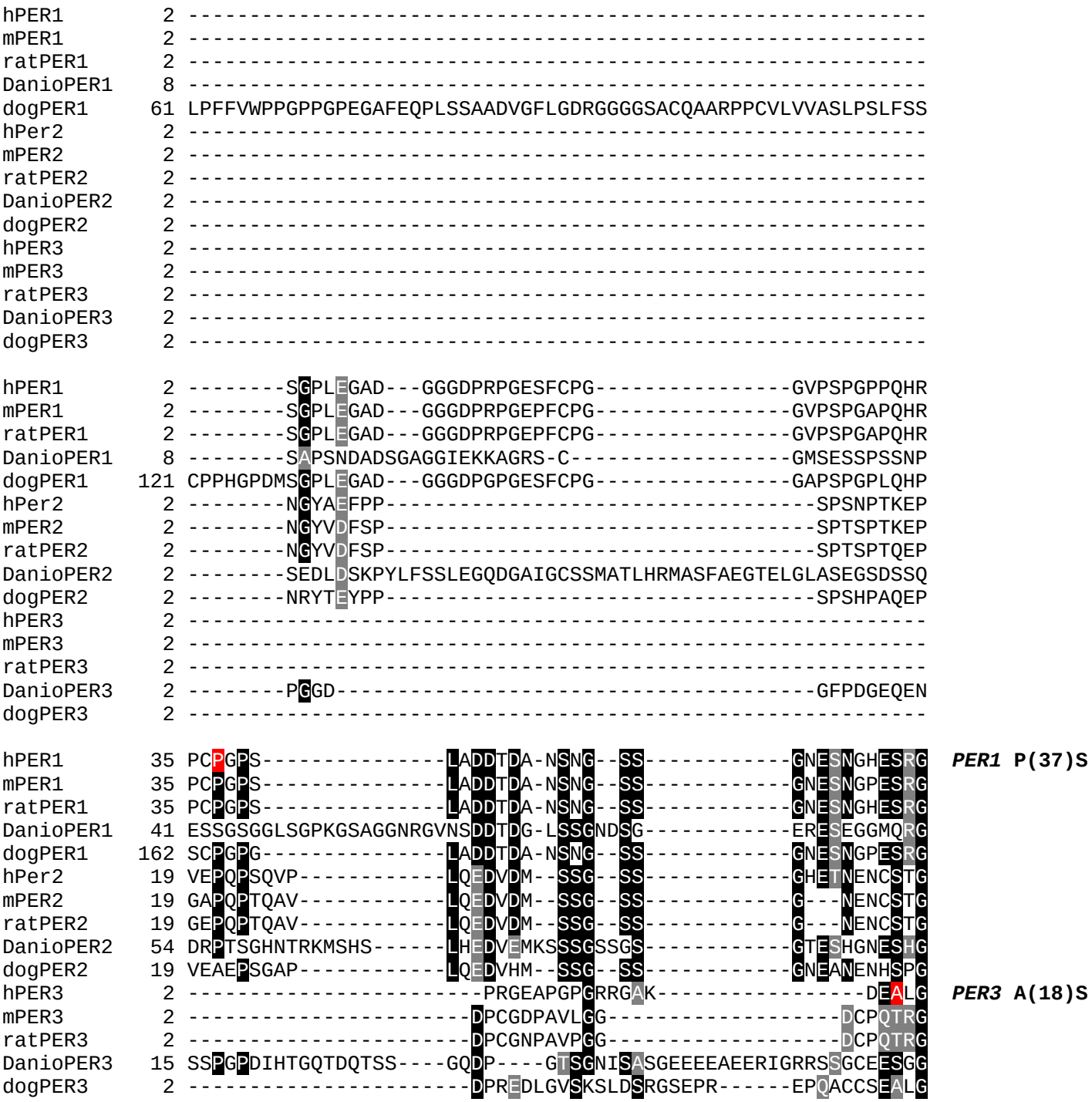
29. ***PER3,*** **E20, T(ACT) 1168 A(GCT)**
    - ***Frequency:*** 0.05% (1/2012)
    - ***Diagnoses:*** Mood Disorder (MDD)
    - ***Family History:*** Mood Disorder
    - ***Ethnicity:*** Caucasian
    - ***Sex:*** female

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 GVs 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 GVs and exonic GVs 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* GVs 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.




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 CPPHGPDMSGPLEGAD---GGGDPGPGESFCPG----------GAPSPGPLQHP
hPer2 2 --------NGYAEFPP----------SPSNPTKEP
mPER2 2 --------NGYVDFSP----------SPTSPTKEP
ratPER2 2 --------NGYVDFSP----------SPTSPTQEP
DanioPER2 2 --------SEDLDSKPYLFSSLEGQDGAIGCSSMATLHRMASFAEGTELGLASEGSDSSQ
dogPER2 2 --------NRYTEYPP----------SPSHPAQEP
hPER3 2 ----------
mPER3 2 ----------
ratPER3 2 ----------
DanioPER3 2 --------PGGD----------GFPDGEQEN
dogPER3 2 ----------
hPER1 35 PCPGPS----------LADDTDA-NSNG--SS----------GNESNGHESRG
mPER1 35 PCPGPS----------LADDTDA-NSNG--SS----------GNESNGPESRG
ratPER1 35 PCPGPS----------LADDTDA-NSNG--SS----------GNESNGHESRG
DanioPER1 41 ESSGSGGLSGPKGSAGGNRGVNSDDTDG-LSSGNDSG----------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-----LHEDVEMKSSGSSGS----------GTESHGNESHG
dogPER2 19 VEAEPSGAP----------LQEDVHM--SSG--SS----------GNEANENHSPG
hPER3 2 ----------PRGEAPGPGRRGAK----------DEALG
mPER3 2 ----------DPCGDPAVLGG----------DCPQTRG
ratPER3 2 ----------DPCGNPAVPGG----------DCPQTRG
DanioPER3 15 SSPGPDIHTGQTDQTSS----GQDP----GTSGNISASGEEEEAEERIGRRSSGCEESGG
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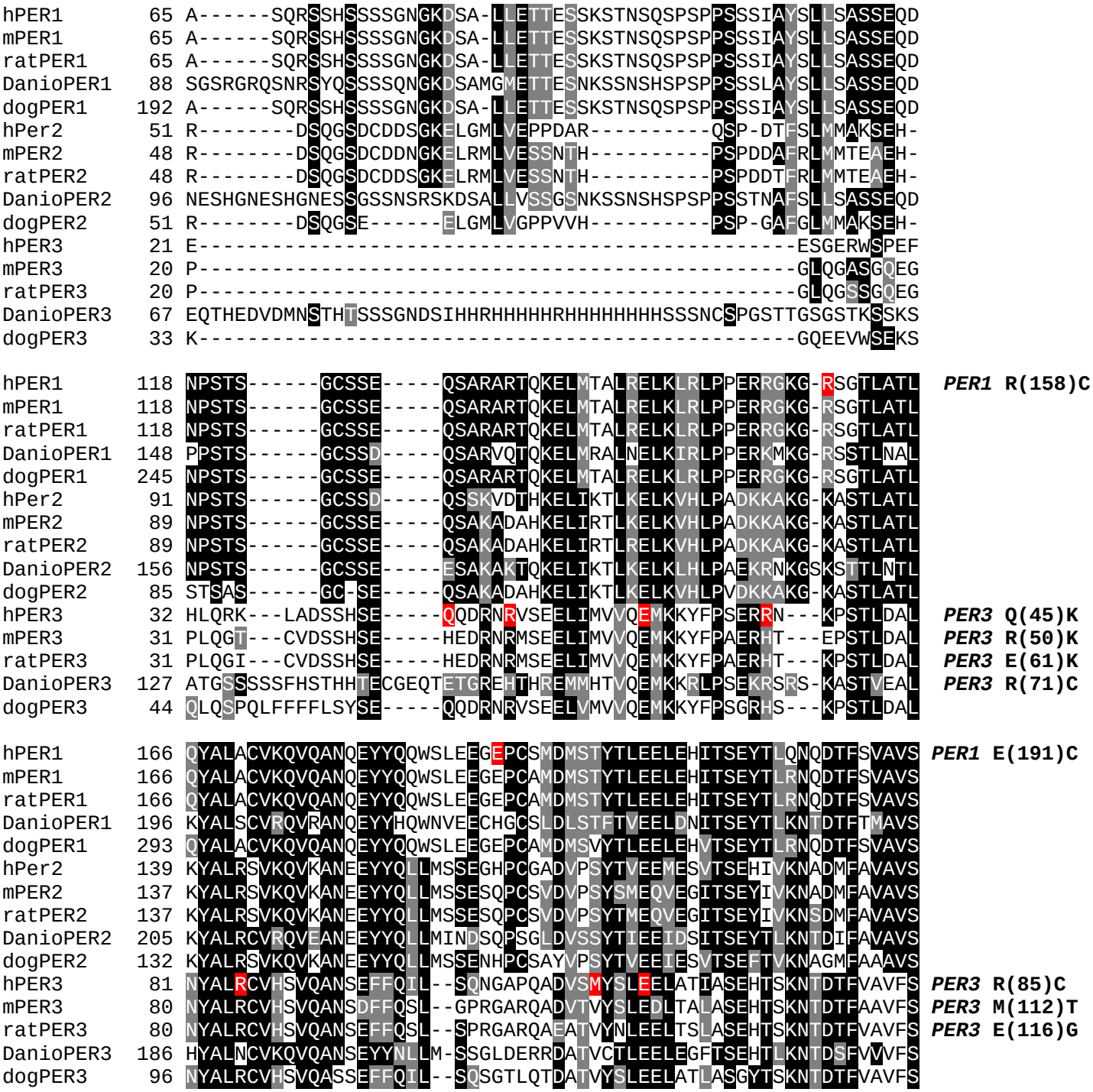
PER1 P(37)S
PER3 A(18)S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DanioPER1 88 SGSRGRQSNRSYQSSSSQNGKDSAMGMETTESNKSSNSHSPSPPSSSLAYSLLSASSEQD
dogPER1 192 A------SQRSSHSSSSGNGKDSA-LLETTESSKSTNSQSPSPPSSSIAYSLLSASSEQD
hPer2 51 R--------DSQGSDCDDSGKELGMLVEPPDAR----------QSP-DTFSLMMAKSEH-
mPER2 48 R--------DSQGSDCDDNGKELRMLVESSNTH----------PSPDDAFRLMMTEAEH-
ratPER2 48 R--------DSQGSDCDDSGKELRMLVESSNTH----------PSPDDTFRLMMTEAEH-
DanioPER2 96 NESHGNESHGNESSGSSNSRSKDSALLVSSGSNKSSNSHSPSPPSSTNAFSLLSASSEQD
dogPER2 51 R--------DSQGSE------ELGMLVGPPVVH----------PSP-GAFGLMMAKSEH-
hPER3 21 E---ESGERWSPEF
mPER3 20 P---GLQGASGQEG
ratPER3 20 P---GLQGSSGQEG
DanioPER3 67 EQTHEDVDMNSTHTSSSGNDSIHHRHHHHHRHHHHHHHHSSSNCSPGSTTGSGSTKSSKS
dogPER3 33 K---GQEEVWSEKS
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PER1 R(158)C
mPER1 118 NPSTS------GCSSE-----QSARARTQKELMTALRELKLRLPPERRGKG-RSGTLATL
ratPER1 118 NPSTS------GCSSE-----QSARARTQKELMTALRELKLRLPPERRGKG-RSGTLATL
DanioPER1 148 PPSTS------GCSSD-----QSARVQTQKELMRALNELKIRLPPERKMKG-RSSTLNAL
dogPER1 245 NPSTS------GCSSE-----QSARARTQKELMTALRELKLRLPPERRGKG-RSGTLATL
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ratPER2 89 NPSTS------GCSSE-----QSAKADAHKELIRTLRELKVHLPADKKAKG-KASTLATL
DanioPER2 156 NPSTS------GCSSE-----ESAKAKTQKELIKTLKELKLHLPAEKRNKGSKSTTLNTL
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PER3 R(50)K
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dogPER1 293 QYALACVKQVQANQEYYQQWSLEEGEPCAMDMSVYTLEELEHVTSEYTLRNQDTFSVAVS
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DanioPER2 205 KYALRCVRQVEANEEYYQLLMINDSQPSGLDVSSYTIEEIDSITSEYTLKNTDIFAVAVS
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PER3 R(85)C
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PER3 E(116)G
DanioPER3 186 HYALNCVKQVQANSEYYNLLM-SSGLDERRDATVCTLEELEGFTSEHTLKNTDSFVVVFS
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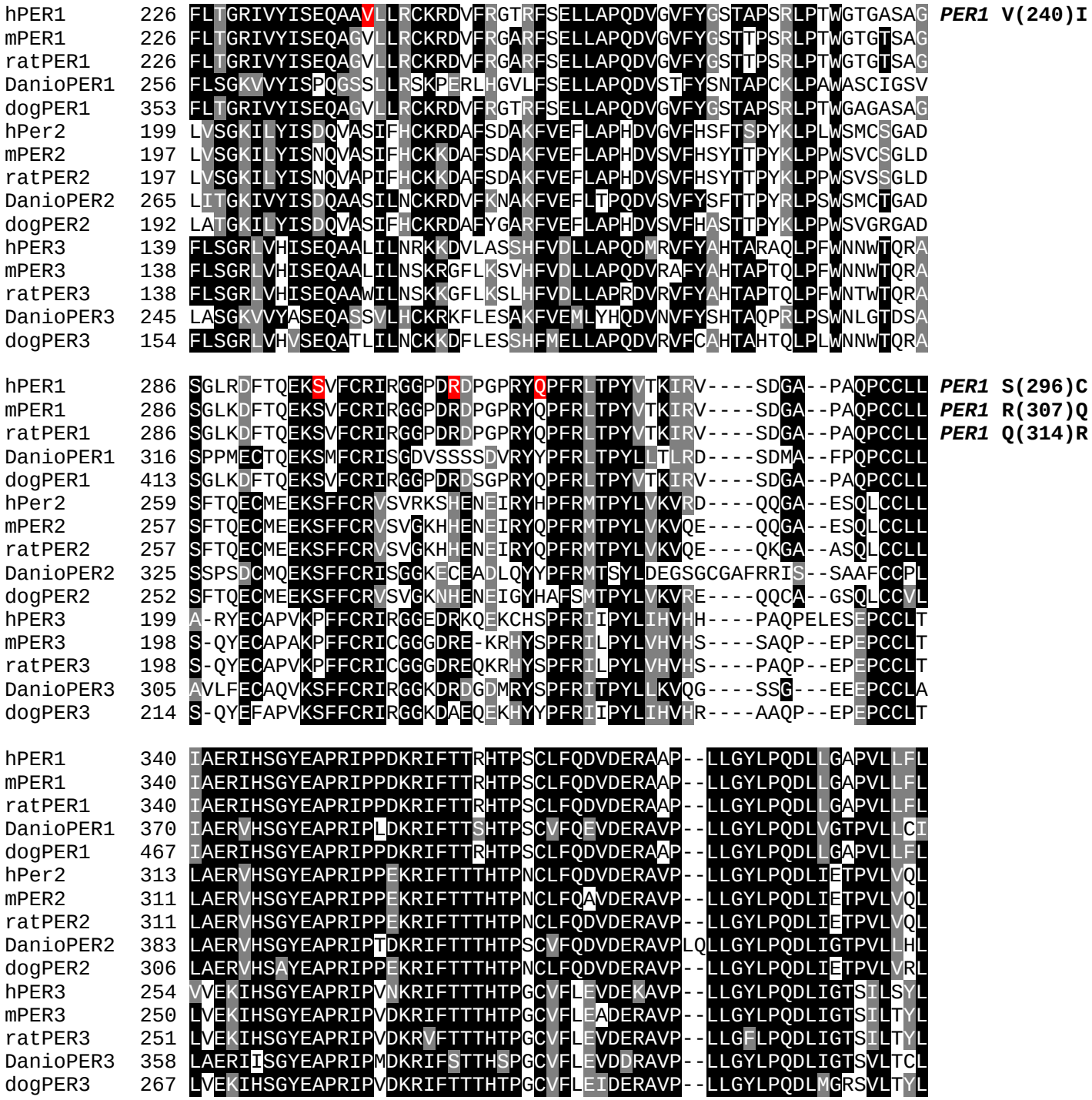
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DanioPER1 256 FLSGKVVYISPQGSSLLRSKPERLHGVLFSELLAPQDVSTFYSNTAPCKLPAWASCIGSV
dogPER1 353 FLTGRIVYISEQAGVLLRCKRDVFRGTRFSELLAPQDVGVFYGSTAPSRLPTWGAGASAG
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DanioPER2 265 LITGKIVYISDQAASILNCKRDVFKNAKFVEFLTPQDVSVFYSFTTPYRLPSWSMCTGAD
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DanioPER3 245 LASGKVVYASEQASSVLHCKRKFLESAKFVEMLYHQDVNVFYSHTAQPRLPSWNLGTDSA
dogPER3 154 FLSGRLVHVSEQATLILNCKKDFLESSHFMELLAPQDVRVFCAHTAHTQLPLWNNWTQRA
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ratPER1 286 SGLKDFTQEKSVFCRIRGGPDRDPGPRYQPFRLTPYVTKIRV----SDGA--PAQPCCLL
DanioPER1 316 SPPMECTQEKSMFCRISGDVSSSSDVRYYPFRLTPYLLTLRD----SDMA--FPQPCCLL
dogPER1 413 SGLKDFTQEKSVFCRIRGGPDRDSGPRYQPFRLTPYVTKIRV----SDGA--PAQPCCLL
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ratPER2 257 SFTQECMEEKSFFCRVSVGKHHENEIRYQPFRMTPYLVKVQE----QKGA--ASQLCCLL
DanioPER2 325 SSPSDCMQEKSFFCRISGGKECEADLQYYPFRMTSYLDEGSGCGAFRRIS--SAAFCCPL
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ratPER3 251 LVEKIHSGYEAPRIPVDKRVFTTTHTPGCVFLEVDERAVP--LLGFLPQDLIGTSILTYL
DanioPER3 358 LAERITSGYEAPRIPMDKRIFSTTHSPGCVFLEVDDRAVP--LLGYLPQDLIGTSVLTCL
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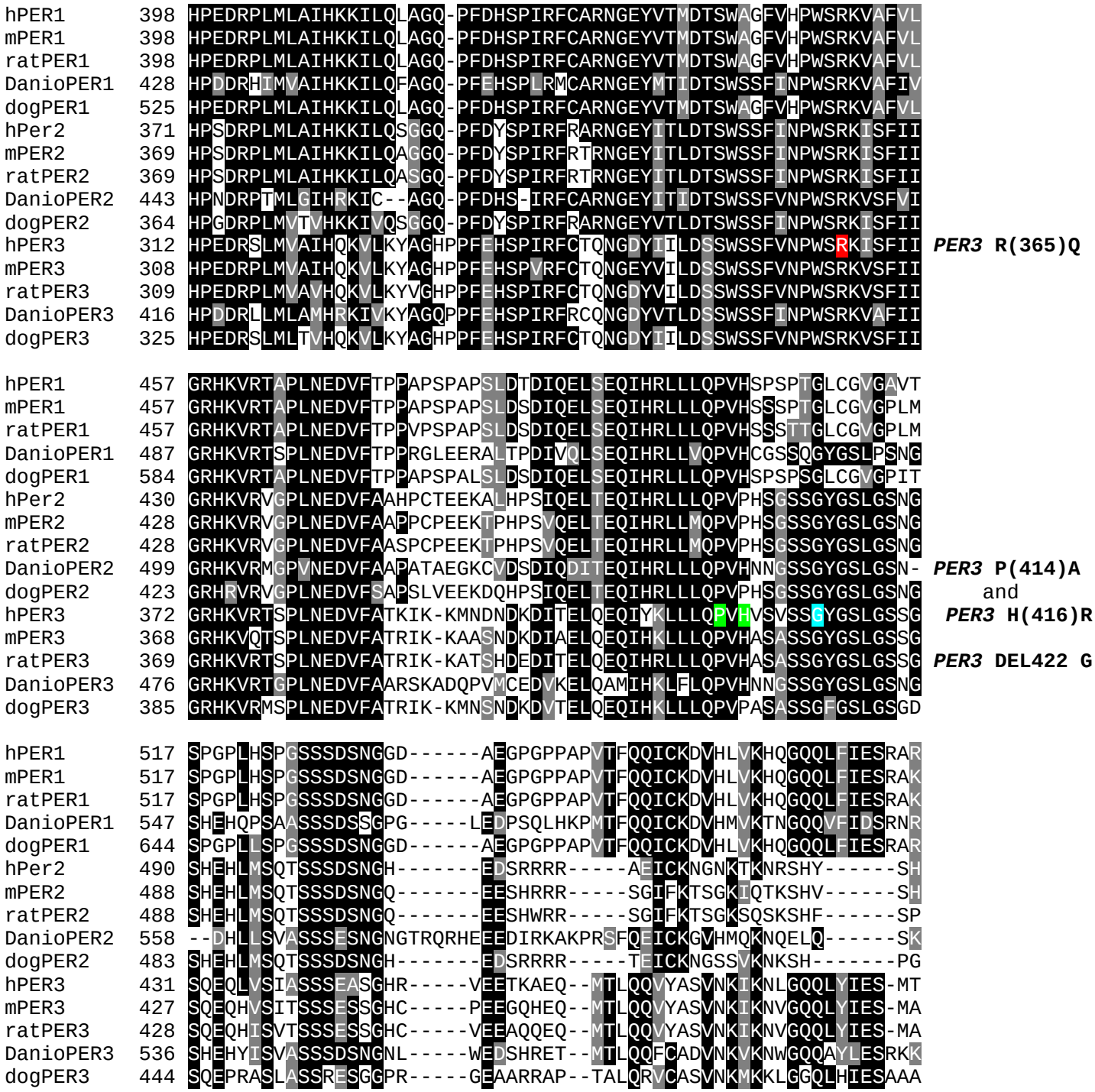
PER1 Q(314)R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DanioPER1 428 HPDDRHIMVAIHKKILQFAGQ-PFEHSPLRMCARNGEYMTIDTSWSSFINPWSRKVAFIV
dogPER1 525 HPEDRPLMLAIHKKILQLAGQ-PFDHSPIRFCARNGEYVTMDTSWAGFVHPWSRKVAFVL
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PER3 P(414)A
and
PER3 H(416)R
PER3 DEL422 G
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DanioPER1 547 SHEHQPSAASSSDSSGPG-----LEDPSQLHKPMTFQQICKDVHMVKTNGQQVFIDSRNR
dogPER1 644 SPGPLLSPGSSSDSNGGD------AEGPGPPAPVTFQQICKDVHLVKHQGQQLFIESRAR
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DanioPER2 558 --DHLLSVASSSESNGNGTRQRHEEEDIRKAKPRSFQEICKGVHMQKNQELQ------SK
dogPER2 483 SHEHLMSQTSSSDSNGH-------EDSRRRR-----TEICKNGSSVKNKSH-------PG
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ratPER3 428 SQEQHISVTSSSESSGHC-----VEEAQQEQ--MTLQQVYASVNKIKNVGQQLYIES-MA
DanioPER3 536 SHEHYISVASSSDSNGNL-----WEDSHRET--MTLQQFCADVNKVKNWGQQAYLESRKK
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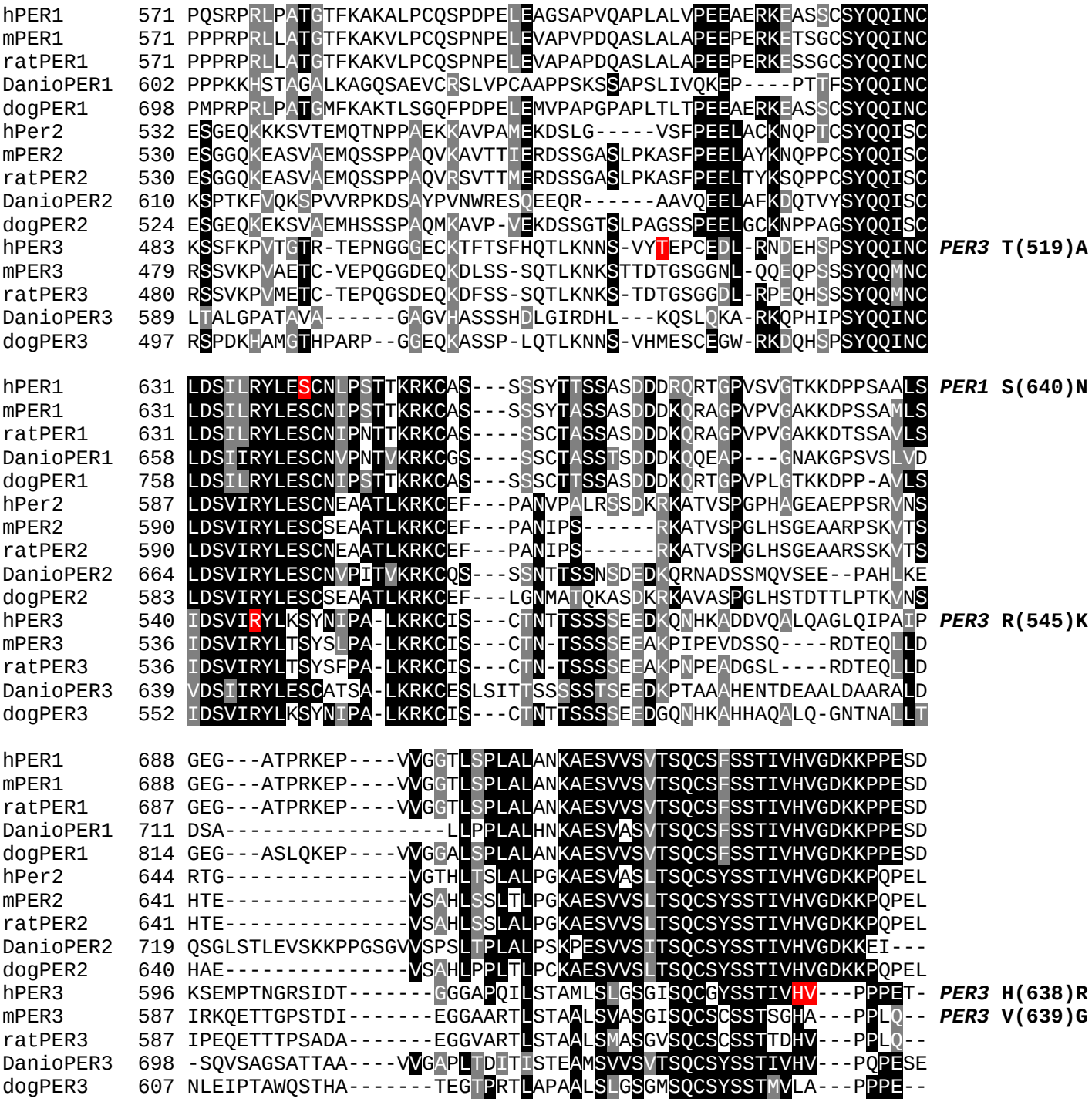
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dogPER2 524 ESGEQKEKSVAEMHSSSPAQMKAVP-VEKDSSGTSLPAGSSPEELGCKNPPAGSYQQISC
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ratPER3 480 RSSVKPVMETC-TEPQGSDEQKDFSS-SQTLKNKS-TDTGSGGDL-RPEQHSSSYQQMNC
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dogPER1 758 LDSILRYLESCNIPSTTKRKCAS---SSSCTTSSASDDDKQRTGPVPLGTKKDPP-AVLS
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mPER2 590 LDSVIRYLESCSEAATLKRKCEF---PANIPS------RKATVSPGLHSGEAARPSKVTS
ratPER2 590 LDSVIRYLESCNEAATLKRKCEF---PANIPS------RKATVSPGLHSGEAARSSKVTS
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dogPER3 552 IDSVIRYLKSYNIPA-LKRKCIS---CTNTTSSSSEEDGQNHKAHHAQALQ-GNTNALLT
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ratPER1 687 GEG---ATPRKEP----VVGGTLSPLALANKAESVVSVTSQCSFSSTIVHVGDKKPPESD
DanioPER1 711 DSA-----------------LLPPLALHNKAESVASVTSQCSFSSTIVHVGDKKPPESD
dogPER1 814 GEG---ASLQKEP----VVGGALSPLALANKAESVVSVTSQCSFSSTIVHVGDKKPPESD
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mPER3 587 IRKQETTGPSTDI-------EGGAARTLSTAALSVASGISQCSCSSTSGHA---PPLQ--
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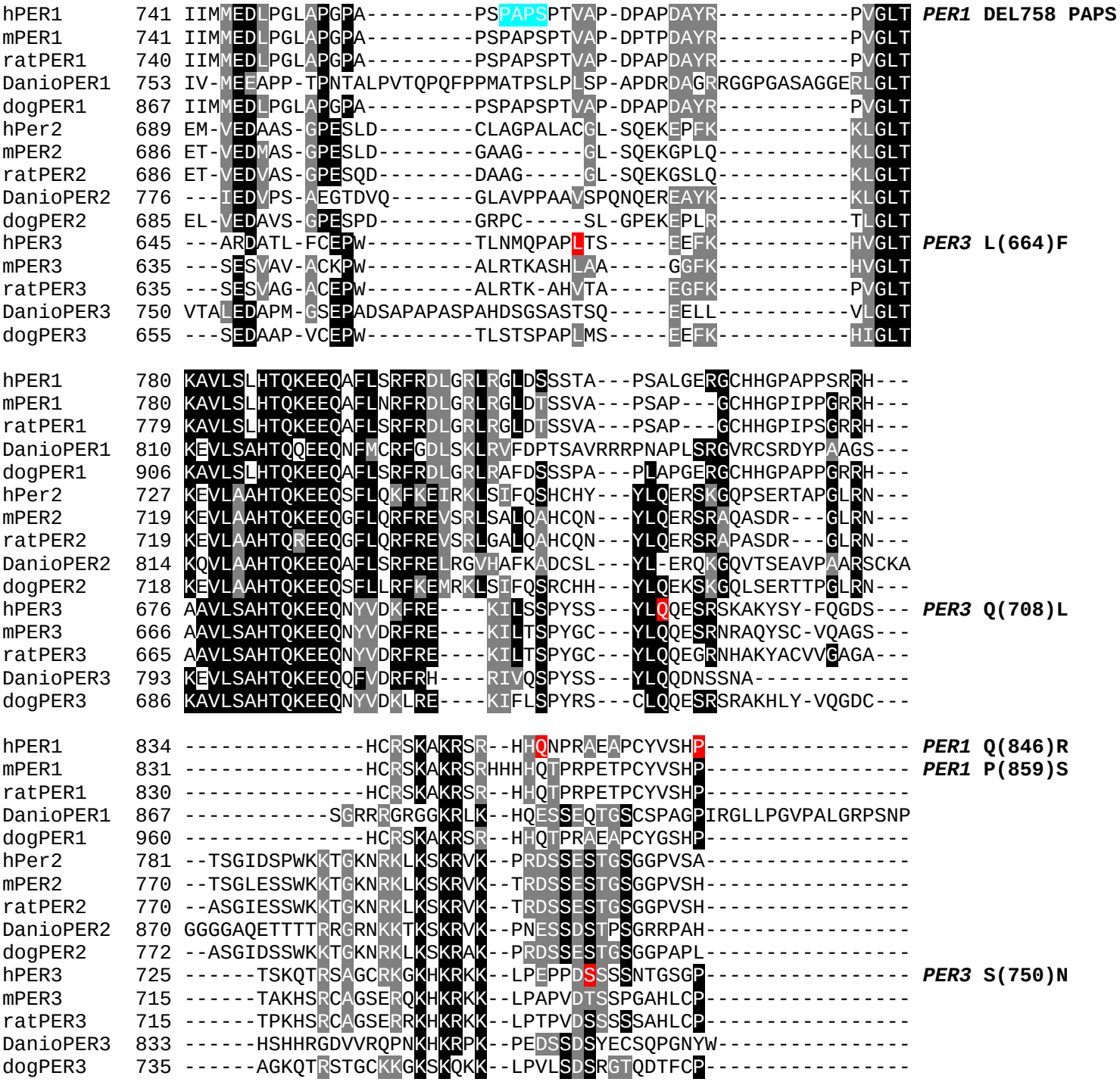
ratPER3 587 IPEQETTTPSADA-------EGGVARTLSTAALSMASGVSQCSCSSTTDHV---PPLQ--
DanioPER3 698 -SQVSAGSATTAA----VVGAPLTDITISTEAMSVVSVTSQCSYSSTIVHV---PQPESE
dogPER3 607 NLEIPTAWQSTHA-------TEGTPRTLAPAALSLGSGMSQCSYSSTMVLA---PPPE--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mPER1 741 IIMMEDLPGLAPGPA---------PSPAPSPTVAP-DPTPDAYR----------PVGLT
ratPER1 740 IIMMEDLPGLAPGPA---------PSPAPSPTVAP-DPAPDAYR----------PVGLT
DanioPER1 753 IV-MEEAPP-TPNTALPVTQPQFPPMATPSLPLSP-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-------GLAVPPAAVSPQNQERAEYK----------KLGLT
dogPER2 685 EL-VEDAVS-GPESPD--------GRPC-----SL-GPEKEPLR----------TLGLT
hPER3 645 ---ARDATL-FCEPW---------TLNMQPAPLTS-----EEFK----------HVGLT PER3 L(664)F
mPER3 635 ---SESVAV-ACKPW---------ALRTKASHLAA-----GGFK----------HVGLT
ratPER3 635 ---SESVAG-ACEPW---------ALRTK-AHVTA-----EGFK----------PVGLT
DanioPER3 750 VTALEDAPM-GSEPADSAPAPASPAHDSGSASTSQ-----EELL----------VLGLT
dogPER3 655 ---SEDAAP-VCEPW---------TLSTSPAPLMS-----EEFK----------HIGLT
hPER1 780 KAVLSLHTQKEEQAFLSRFRDLGRLRGLDSSSTA---PSALGERGCHHGPAPPSRRH---
mPER1 780 KAVLSLHTQKEEQAFLNRFRDLGRLRGLDTSSVA---PSAP---GCHHGPIPPGRRH---
ratPER1 779 KAVLSLHTQKEEQAFLSRFRDLGRLRGLDTSSVA---PSAP---GCHHGPIPSGRRH---
DanioPER1 810 KEVLSAHTQQEEQNFMCRFGDLSKLRVFDPTSAVRRRPNAPLSRGVRCSRDYPAAGS---
dogPER1 906 KAVLSLHTQKEEQAFLSRFRDLGRLRAFDSSSPA---PLAPGERGCHHGPAPPGRRH---
hPer2 727 KEVLAAHTQKEEQSFLQKFKEIRKLSIFQSHCHY---YLQERSKGQPSERTAPGLRN---
mPER2 719 KEVLAAHTQKEEQGFLQRFREVSRLSALQAHCQN---YLQERSRAQASDR---GLRN---
ratPER2 719 KEVLAAHTQREEQGFLQRFREVSRLGALQAHCQN---YLQERSRAPASDR---GLRN---
DanioPER2 814 KQVLAAHTQKEEQAFLSRFRELRGVHAFKADCSL---YL-ERQKGQVTSEAVPAARSCKA
dogPER2 718 KEVLAAHTQKEEQSFLLRFKEMRKLSIFQSRCHH---YLQEKSKGQLSERTTPGLRN---
hPER3 676 AAVLSAHTQKEEQNYVDKFRE----KILSSPYSS---YLQQESRSKAKYSY-FQGDS--- PER3 Q(708)L
mPER3 666 AAVLSAHTQKEEQNYVDRFRE----KILTSPYGC---YLQQESRNRAQYSC-VQAGS---
ratPER3 665 AAVLSAHTQKEEQNYVDRFRE----KILTSPYGC---YLQQEGRNHAKYACVVGAGA---
DanioPER3 793 KEVLSAHTQKEEQQFVDRFRH----RIVQSPYSS---YLQQDNSSNA------------
dogPER3 686 KAVLSAHTQKEEQNYVDKLRE----KIFLSPYRS---CLQQESRSRAKHLY-VQGDC---
hPER1 834 ---------------HCRSKAKRSR--HHQNPRAEAPCYVSHP---------------- PER1 Q(846)R
mPER1 831 ---------------HCRSKAKRSRHHHHQTPRPETPCYVSHP---------------- PER1 P(859)S
ratPER1 830 ---------------HCRSKAKRSR--HHQTPRPETPCYVSHP----------------
DanioPER1 867 ------------SGRRRGRGGKRLK--HQESSEQTGSCSPAGPIRGLLPGVPALGRPSNP
dogPER1 960 ---------------HCRSKAKRSR--HHQTPRAEAPCYGSHP----------------
hPer2 781 --TSGIDSPWKKTGKNRKLKSKRVK--PRDSSESTGSGGPVSA----------------
mPER2 770 --TSGLESSWKKTGKNRKLKSKRVK--TRDSSESTGSGGPVSH----------------
ratPER2 770 --ASGIESSWKKTGKNRKLKSKRVK--TRDSSESTGSGGPVSH----------------
DanioPER2 870 GGGGAQETTTTRRGRNKKTKSKRVK--PNESSDSTPSGRRPAH----------------
dogPER2 772 --ASGIDSSWKKTGKNRKLKSKRAK--PRDSSESTGSGGPAPL----------------
hPER3 725 ------TSKQTRSAGCRKGKHKRKK--LPEPPDSSSSSNTGSGP---------------- PER3 S(750)N
mPER3 715 ------TAKHSRCAGSERQKHKRKK--LPAPVDTSSPGAHLCP----------------
ratPER3 715 ------TPKHSRCAGSERRKHKRKK--LPTPVDSSSSSAHLCP----------------
DanioPER3 833 ------HSHHRGDVVRQPNKHKRPK--PEDSSDSYECSQPGNYW----------------
dogPER3 735 ------AGKQTRSTGCKKGKSKQKK--LPVLSDSRGTQDTFCP----------------

```
hPER1       860 ----SPVPPSTPWPTPPAT------TPFPAV-----VQPYPLPVF------------SP
mPER1       859 ----SPVPSSGPWPPPPAT------TPFPAM-----VQPYPLPVF------------SP
ratPER1     856 ----SPVPSSGPWPPPPAT------TPFPAV-----VQPYPLPVF------------SP
DanioPER1   913 SIPMGPTASSSSW-PTSGSQASVPNVQYP---------PTVLPLYPVYPPISHPVSDPSM
dogPER1     986 ----PPVSPSAPWPPPPAT------TPFPAV-----VQPYPLPVF------------SP
hPer2       820 -RPPLVGLNATAWSPSDTSQSSCPAVPFPAP--VPAAYS--LPVFPA------PGTVAAP
mPER2       809 -RPPLMGLNATAWSPSDTSQSSCPSAPFPTA--VP-AYP--LPVFQAPGIVSTPGTVVAP
ratPER2     809 -RPPLVGLNATAWSPSDTSQSSCPSAPFPAP--VP-AYP--LPVFPAPGIVSTPGTVVAP
DanioPER2   911 -RPQLQGLNQTSWSPSDTSQSTFP-IAYPAV--MP-AYP--LQMYPGAGGMQPRVDPPMP
dogPER2     811 -RPPLLGLNATAWSPSDTSQSSCPTTPFPAS--VP-AYP--LPVFPAPGILPTPGAVAAA
hPER3       760 -R-RGAHQNAQPCCPSAASSPHTSSPTFPPAAMVPSQAPYLVPAFPLPAATSPGREYAAP  PER3 INS804 C
mPER3       750 -HVTGLLPDEQHWGPSASPSPLGAGLAFPSALVVPSQTPYLLPSFPLQDMASQGVGVSAA
ratPER3     750 -HVRGLLPDVQHWSASVTS-PCATGLALPSALVVPNQTPYLLSSFPLQDMAPHGVGDSAP
DanioPER3   869 SLPGPTAAPHSSWPSSESSQPPPSNIGFVPPMAVPMQTP---PYFNIIGADQQ-------
dogPER3     770 -HFGGESESRQPWGPALSSCLQAPGLSFPAAMMVPSLAPYFVPALRIPALPSVQREPGAS

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 PAPPHASFTVPAVPVDLQHQFAVQP--PPFPAPLA-PVMAFMLPSYS---------FPSG
mPER2       863 PAATHTGFTMPVVPMGTQPEFAVQP--LPFAAPLA-PVMAFMLPSYP---------FPPA
ratPER2     863 PAAAHTGFTMPVVPMGTQPEFAVQP--LPFAAPLA-PVMAFMLPSYP---------FPPA
DanioPER2   964 GFGESQCAPDP--------RIPMQPIQTPYSAPLVTPMVALVLPNYM---------FPQV
dogPER2     865 PVAPHASFAVPPLPVDARHEFGLQP--SPFAVPLA-PVMALVLPNYP---------LPAV
hPER3       818 GTAPEGLHGLPL-------SEGLQPY-PAFPFPYLDTFMTVFLPDPPV--------CPLL  PER3 P(828)L
mPER3       809 WGAAAGC--PPL-------SAGPQAV-AAFPSAYVDTLMTIFLHNAPL--------FPLW  PER3 P(835)S
ratPER3     808 WGAAAEC--PPL-------SAGPHPV-STFPSAYMGTFMTVLLHNSPL--------FPLW  PER3 D(854)H
DanioPER3   919 ---PVMLQPDPG-------VQNLQPM-TP--------MMVVLLPSFPMYPPNNGMYFPMA  PER3 P(856)A
dogPER3     829 LTTLDYLLKPPL-------LNGLHSF-PALPSPSSDTVMTTFLPDPTG--------CPLL  PER3 L(860)M

hPER1       930 ------------------------TPSSYPYGA--LQTPAEGPPTPASHSPSPSLP---
mPER1       929 ------------------------TPPSYPYGV--SQAPVEGPPTPASHSPSPSLP---
ratPER1     926 ------------------------SPTSYPYGV--SQAPVEGPPTPASHSPSPSLP---
DanioPER1   997 SVGMA--------------------QPFYSPNSAFPFAAANMGSPAPCQIQTPIQRA---
dogPER1    1056 ------------------------TPSGYPYGV--PQTPAEGPPTPASHSPSPSLP---
hPer2       917 ------------------------TPNL-PQAFFPSQPQFPSHPTLTSEMASASQPEF-
mPER2       911 ------------------------TPNL-PQAFLPSQPHFPAHPTLASEITPASQAEF-
ratPER2     911 ------------------------TPNL-PQAFFPSQPHFPAHPTLASEITPASQAEF-
DanioPER2  1007 GKRSTPGFLPPQNRDHSPPSPPFRLQPGFTPQASFPPQSTFTIQTQFTSQNPFSSQPTFQ
dogPER2     913 ------------------------PPGL-PQAFFPGQPDFLSH------VIPASQPEL-
hPER3       862 ------------------------SPSFLPCPFLGATASSAISPSMSSAMSPTLDP---
mPER3       851 ------------------------PPSFSPYPSLGAAGSSELAP-LVPAMAPNPEP---
ratPER3     850 ------------------------PASFSPYPFLGATGPSQMAP-LVPAMAPDLEP---
DanioPER3   960 ------------------------APGVVPYNIGGFVPPGTPMPAEAPLQGHNLESAGV
dogPER3     873 ------------------------SPSFCPYAFLGAAGSSGTPP-FVSAVAPHLEQ---
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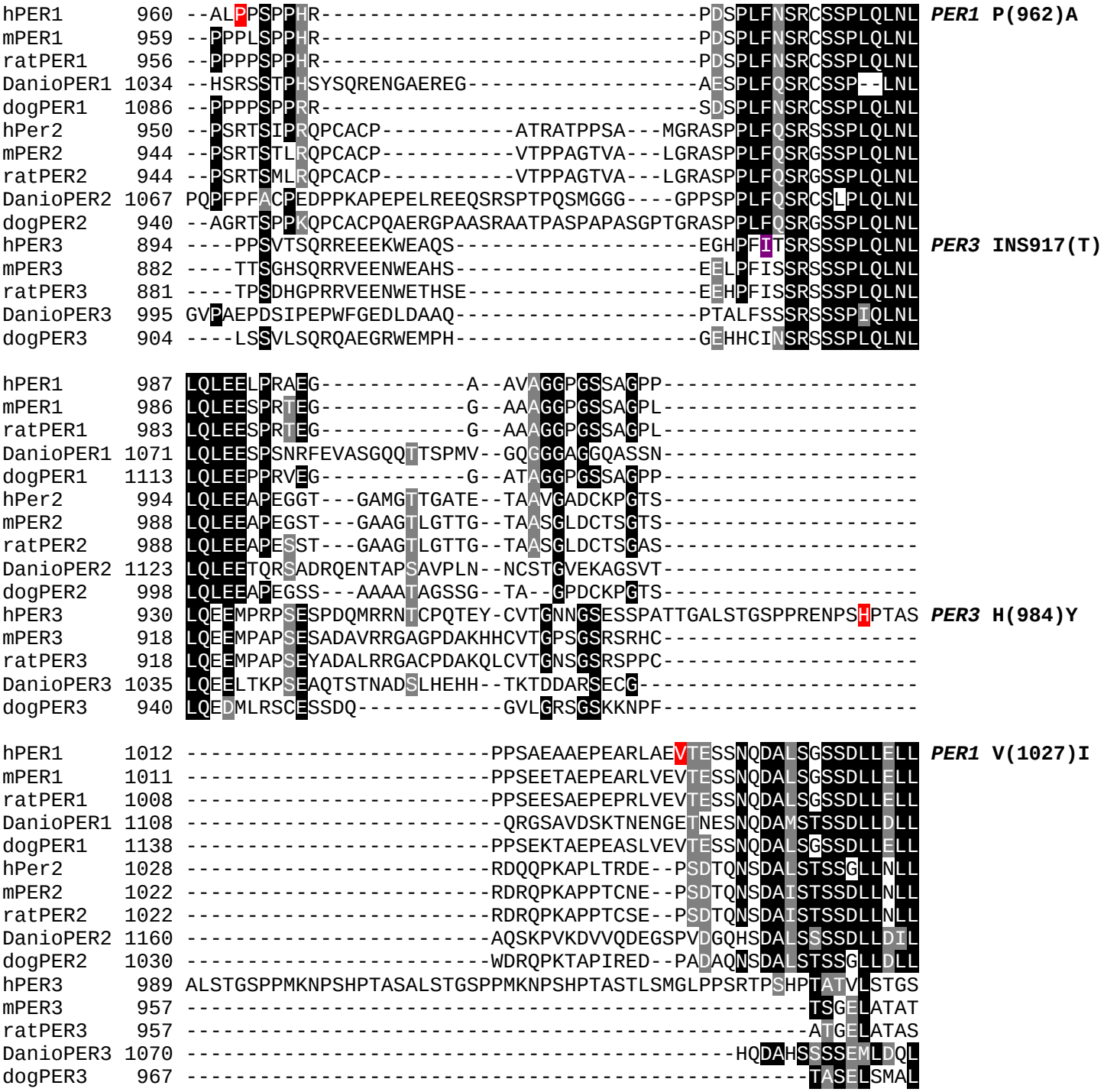
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ratPER1 956 --PPPPSPPHR PDSPLFNSRCSSPLQLNL
DanioPER1 1034 --HSRSSTPHSYSQRENGAEREG AESPLFQSRCSSP--LNL
dogPER1 1086 --PPPPSPPRR SDSPLFNSRCSSPLQLNL
hPer2 950 --PSRTSIPRQPCACP ATRATPPSA---MGRASPPLFQSRSSSPLQLNL
mPER2 944 --PSRTSTLRQPCACP VTPPAGTVA---LGRASPPLFQSRGSSPLQLNL
ratPER2 944 --PSRTSMLRQPCACP VTPPAGTVA---LGRASPPLFQSRGSSPLQLNL
DanioPER2 1067 PQPFPFACPEDPPKAPEPELREEQSRSPTPQSMGGG GPPSPPLFQSRCSLPLQLNL
dogPER2 940 --AGRTSPPKQPCACPQAERGPAASRAATPASPAPASGPTGRASPPLFQSRGSSPLQLNL
hPER3 894 ----PPSVTSQRREEEKWEAQS EGHPFITSRSSSPLQLNL PER3 INS917(T)
mPER3 882 ----TTSGHSQRRVEENWEAHS EELPFISSRSSSPLQLNL
ratPER3 881 ----TPSDHGPRRVEENWETHSE EEHPFISSRSSSPLQLNL
DanioPER3 995 GVPAEPDSIPEPWFGEDLDAAQ PTALFSSSRSSSPIQLNL
dogPER3 904 ----LSSVLSQRQAEGRWEMPH GEHHCINSRSSSPLQLNL
hPER1 987 LQLEELPRAEG A--AVAGGPGSSAGPP
mPER1 986 LQLEESPRTEG G--AAAGGPGSSAGPL
ratPER1 983 LQLEESPRTEG G--AAAGGPGSSAGPL
DanioPER1 1071 LQLEESPSNRFEVASGQQTTSPMV--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
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mPER3 918 LQEEMPAPSESADAVRRGAGPDAKHHCVTGPSGSRSRHC
ratPER3 918 LQEEMPAPSEYADALRRGACPDAKQLCVTGNSGSRSPPC
DanioPER3 1035 LQEELTKPSEAQTSTNADSLHEHH--TKTDDARSECG
dogPER3 940 LQEDMLRSCESSDQ GVLGRSGSKKNPF
hPER1 1012 PPSAEAAEPEARLAEVTESSNQDALSGSSDLLELL PER1 V(1027)I
mPER1 1011 PPSEETAEPEARLVEVTESSNQDALSGSSDLLELL
ratPER1 1008 PPSEESAEPEPRLVEVTESSNQDALSGSSDLLELL
DanioPER1 1108 QRGSAVDSKTNENGETNESNQDAMSTSSDLLDLL
dogPER1 1138 PPSEKTAEPEASLVEVTESSNQDALSGSSDLLELL
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mPER2 1022 RDRQPKAPPTCNE--PSDTQNSDAISTSSDLLNLL
ratPER2 1022 RDRQPKAPPTCSE--PSDTQNSDAISTSSDLLNLL
DanioPER2 1160 AQSKPVKDVVQDEGSPVDGQHSDALSSSSDLLDIL
dogPER2 1030 WDRQPKTAPIRED--PADAQNSDALSTSSGLLDLL
hPER3 989 ALSTGSPPMKNPSHPTASALSTGSPPMKNPSHPTASTLSMGLPPSRTPSHPTATVLSTGS
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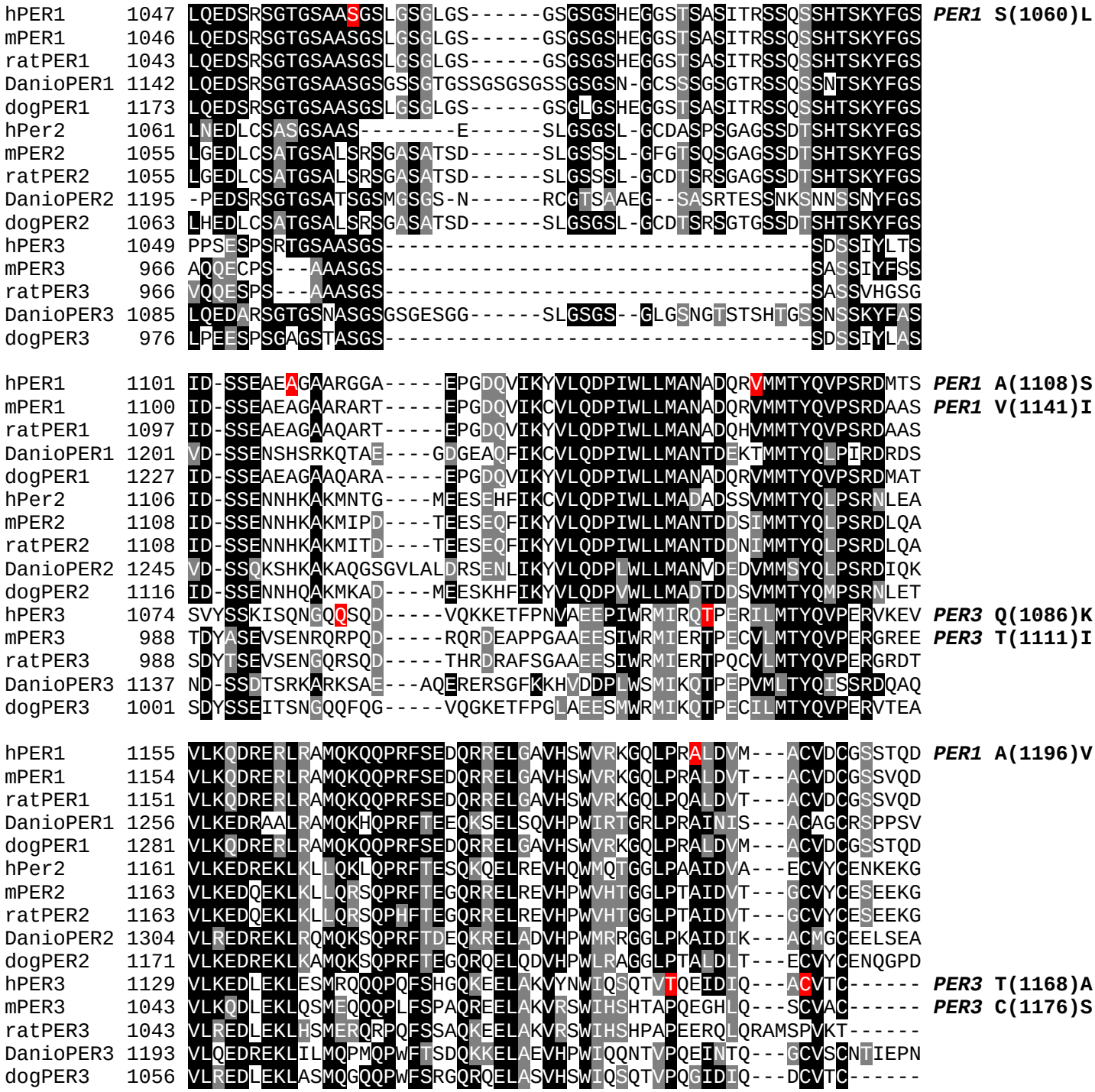
ratPER3 957 ATGELATAS
DanioPER3 1070 HQDAHSSSSEMLDQL
dogPER3 967 TASELSMAL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ratPER1 1043 LQEDSRSGTGSAASGSLGSGLGS------GSGSGSHEGGSTSASITRSSQSSHTSKYFGS
DanioPER1 1142 LQEDSRSGTGSAASGSGSSGTGSSGSGSGSSGSGSN-GCSSSGSGTRSSQSSNTSKYFGS
dogPER1 1173 LQEDSRSGTGSAASGSLGSGLGS------GSGLGSHEGGSTSASITRSSQSSHTSKYFGS
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mPER2 1055 LGEDLCSATGSALSRSGASATSD------SLGSSSL-GFGTSQSGAGSSDTSHTSKYFGS
ratPER2 1055 LGEDLCSATGSALSRSGASATSD------SLGSSSL-GCDTSRSGAGSSDTSHTSKYFGS
DanioPER2 1195 -PEDSRSGTGSATSGSMGSGS-N------RCGTSAAEG--SASRTESSNKSNNSSNYFGS
dogPER2 1063 LHEDLCSATGSALSRSGASATSD------SLGSGSL-GCDTSRSGTGSSDTSHTSKYFGS
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mPER3 966 AQQECPS---AAASGS----------SASSIYFSS
ratPER3 966 VQQESPS---AAASGS----------SASSVHGSG
DanioPER3 1085 LQEDARSGTGSNASGSGSGESGG------SLGSGS--GLGSNGTSTSHTGSSNSSKYFAS
dogPER3 976 LPEESPSGAGSTASGS----------SDSSIYLAS
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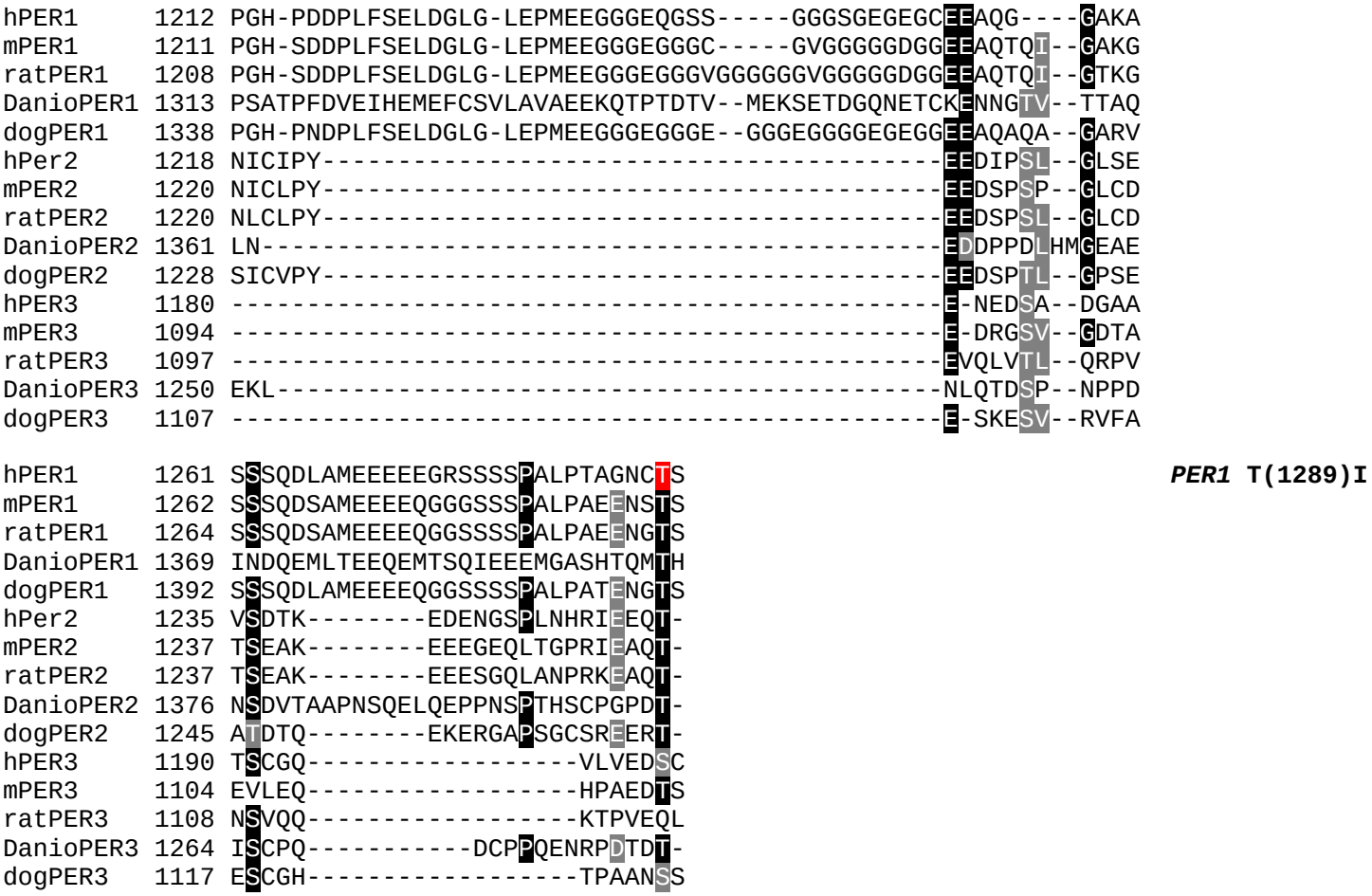
mPER1 1100 ID-SSEAEAGAARART-----EPGDQVIKCVLQDPIWLLMANADQRVMMTYQVPSRDAAS PER1 V(1141)I
ratPER1 1097 ID-SSEAEAGAAQART-----EPGDQVIKYVLQDPIWLLMANADQHVMMTYQVPSRDAAS
DanioPER1 1201 VD-SSENSHSRKQTAE----GDGEAQFIKCVLQDPIWLLMANTDEKTMMTYQLPIRDRDS
dogPER1 1227 ID-SSEAEAGAAQARA-----EPGDQVIKYVLQDPIWLLMANADQRVMMTYQVPSRDMAT
hPer2 1106 ID-SSENNHKAKMNTG----MEESEHFIKCVLQDPIWLLMADADSSVMMTYQLPSRNLEA
mPER2 1108 ID-SSENNHKAKMIPD----TEESEQFIKYVLQDPIWLLMANTDDSIMMTYQLPSRDLQA
ratPER2 1108 ID-SSENNHKAKMITD----TEESEQFIKYVLQDPIWLLMANTDDNIMMTYQLPSRDLQA
DanioPER2 1245 VD-SSQKSHKAKAQGSGVLALDRSENLIKYVLQDPLWLLMANVDEDVMMSYQLPSRDIQK
dogPER2 1116 ID-SSENNHQAKMKAD----MEESKHFIKYVLQDPVWLLMADTDDSVMMTYQMPSRNLET
hPER3 1074 SVYSSKISQNGQQSQD-----VQKKETFPNVAEEPIWRMIRQTPERILMTYQVPERVKEV PER3 Q(1086)K
mPER3 988 TDYASEVSENRQRPQD-----RQRDEAPPGAAEESIWRMIERTPECVLMTYQVPERGREE PER3 T(1111)I
ratPER3 988 SDYTSEVSENGQRSQD-----THRDRAFSGAAEESIWRMIERTPQCVLMTYQVPERGRDT
DanioPER3 1137 ND-SSDTSRKARKSAE---AQERERSGFKKHVDDPLWSMIKQTPEPVMLTYQISSRDQAQ
dogPER3 1001 SDYSSEITSNGQQFQG-----VQGKETFPGLAEESMWRMIKQTPECILMTYQVPERVTEA
hPER1 1155 VLKQDRERLRAMQKQQPRFSEDQRRELGAVHSWVRKGQLPRALDVM---ACVDCGSSTQD PER1 A(1196)V
mPER1 1154 VLKQDRERLRAMQKQQPRFSEDQRRELGAVHSWVRKGQLPRALDVT---ACVDCGSSVQD
ratPER1 1151 VLKQDRERLRAMQKQQPRFSEDQRRELGAVHSWVRKGQLPQALDVT---ACVDCGSSVQD
DanioPER1 1256 VLKEDRAALRAMQKHQPRFTEEQKSELSQVHPWIRTGRLPRAINIS---ACAGCRSPPSV
dogPER1 1281 VLKQDRERLRAMQKQQPRFSEDQRRELGAVHSWVRKGQLPRALDVM---ACVDCGSSTQD
hPer2 1161 VLKEDREKLKLLQKLQPRFTESQKQELREVHQWMQTGGLPAAIDVA---ECVYCENKEKG
mPER2 1163 VLKEDQEKLKLLQRSQPRFTEGQRRELREVHPWVHTGGLPTAIDVT---GCVYCESEEKG
ratPER2 1163 VLKEDQEKLKLLQRSQPHFTEGQRRELREVHPWVHTGGLPTAIDVT---GCVYCESEEKG
DanioPER2 1304 VLREDREKLRQMQKSQPRFTDEQKRELADVHPWMRRGGLPKAIDIK---ACMGCEELSEA
dogPER2 1171 VLKEDREKLKAMQKSQPRFTEGQRQELQDVHPWLRAGGLPTALDLT---ECVYCENQGPD
hPER3 1129 VLKEDLEKLESMRQQQPQFSHGQKEELAKVYNWIQSQTVTQEIDIQ---ACVTC------ PER3 T(1168)A
mPER3 1043 VLKQDLEKLQSMEQQQPLFSPAQREELAKVRSWIHSHTAPQEGHLQ---SCVAC------ PER3 C(1176)S
ratPER3 1043 VLREDLEKLHSMERQRPQFSSAQKEELAKVRSWIHSHPAPEERQLQRAMSPVKT------
DanioPER3 1193 VLQEDREKLILMQPMQPWFTSDQKKELAEVHPWIQQNTVPQEINTQ---GCVSCNTIEPN
dogPER3 1056 VLREDLEKLASMQGQQPWFSRGQRQELASVHSWIQSQTVPQGIDIQ---DCVTC------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ratPER1 1208 PGH-SDDPLFSELDGLG-LEPMEEGGGEGGGVGGGGGGVGGGGGDGGEEAQTQI--GTKG
DanioPER1 1313 PSATPFDVEIHEMEFCSVLAVAEEKQTPTDTV--MEKSETDGQNETCKENNGTV--TTAQ
dogPER1 1338 PGH-PNDPLFSELDGLG-LEPMEEGGGEGGGE--GGGEGGGGEGEGGEEAQAQA--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 SSSQDLAMEEEEEGRSSSSPALPTAGNCTS
mPER1 1262 SSSQDSAMEEEEQGGGSSSPALPAEENSTS
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DanioPER1 1369 INDQEMLTEEQEMTSQIEEEMGASHTQMTH
dogPER1 1392 SSSQDLAMEEEEQGGSSSSPALPATENGTS
hPer2 1235 VSDTK--------EDENGSPLNHRIEEQT-
mPER2 1237 TSEAK--------EEEGEQLTGPRIEAQT-
ratPER2 1237 TSEAK--------EEESGQLANPRKEAQT-
DanioPER2 1376 NSDVTAAPNSQELQEPPNSPTHSCPGPDT-
dogPER2 1245 ATDTQ--------EKERGAPSGCSREERT-
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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 ITELQEQIYKLLLQPVH), 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 CKIε (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.

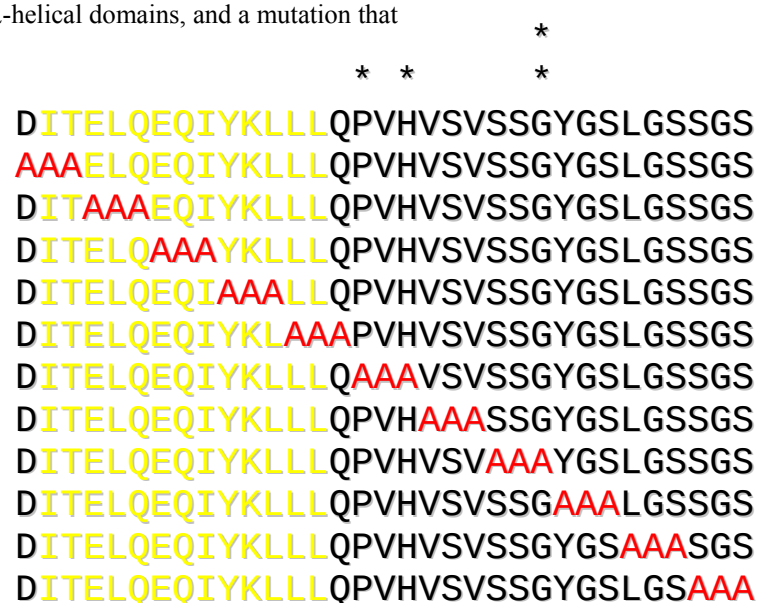

Figure 2. Triple alanine scanning mutagenesis of residues 400-432 of hPer3. The NES is highlighted in yellow while the various positions of the substituted alanines are in red. Single asterisks indicate the site of the *PER3* P(414)A *and* H(416)R double mutation. Double asterisks indicate the site of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

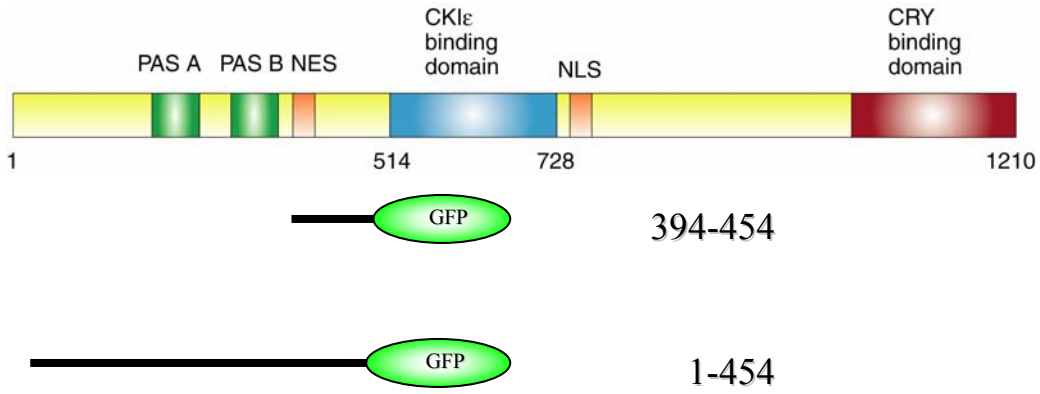

Figure 3. Truncated Per3 GFP fusion constructs. C-terminal Per3 truncation contructs were generated with either residues 394-454 (consisting of the NES and surrounding conserved regions) or 1-454 (includes both PAS domains and the NES) fused to an enhanced GFP to investigate the role of various mutations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

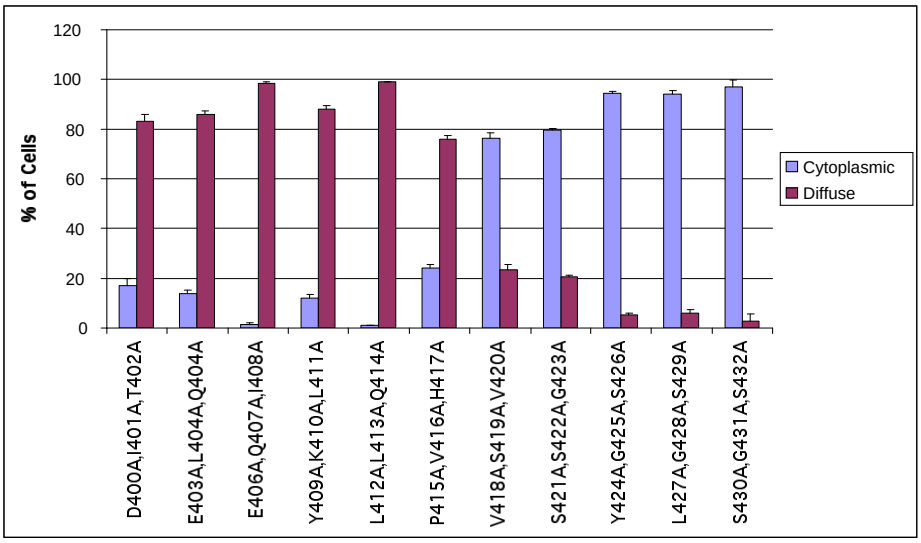

Figure 4. Subcellular localization of NES triple alanine mutants. Following transfection of the various mPer3 (1-454)-GFP constructs, cells were stained with DAPI and scored based on the exclusion of GFP from the nucleus.

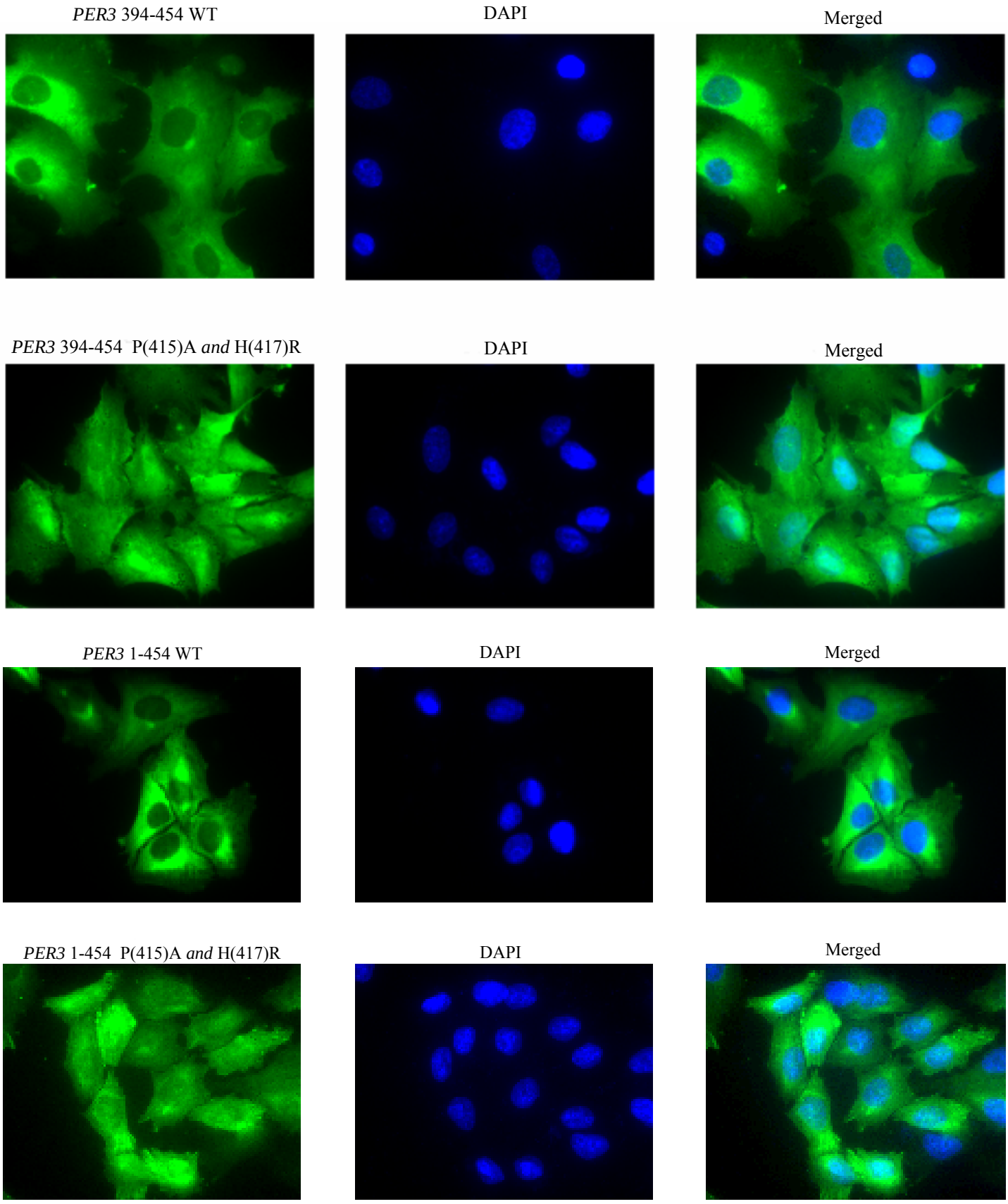

Figure 5. *PER3* P(415)A *and* H(417)R lesions affect cytoplasmic shuttling of Per3. *PER3* P(415)A *and* H(417)R-GFP fusions displayed diffuse fluorescence whereas the wildtype distribution is confined to the cytoplasm. Nuclei were stained with DAPI.

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 carring 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 circardian 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

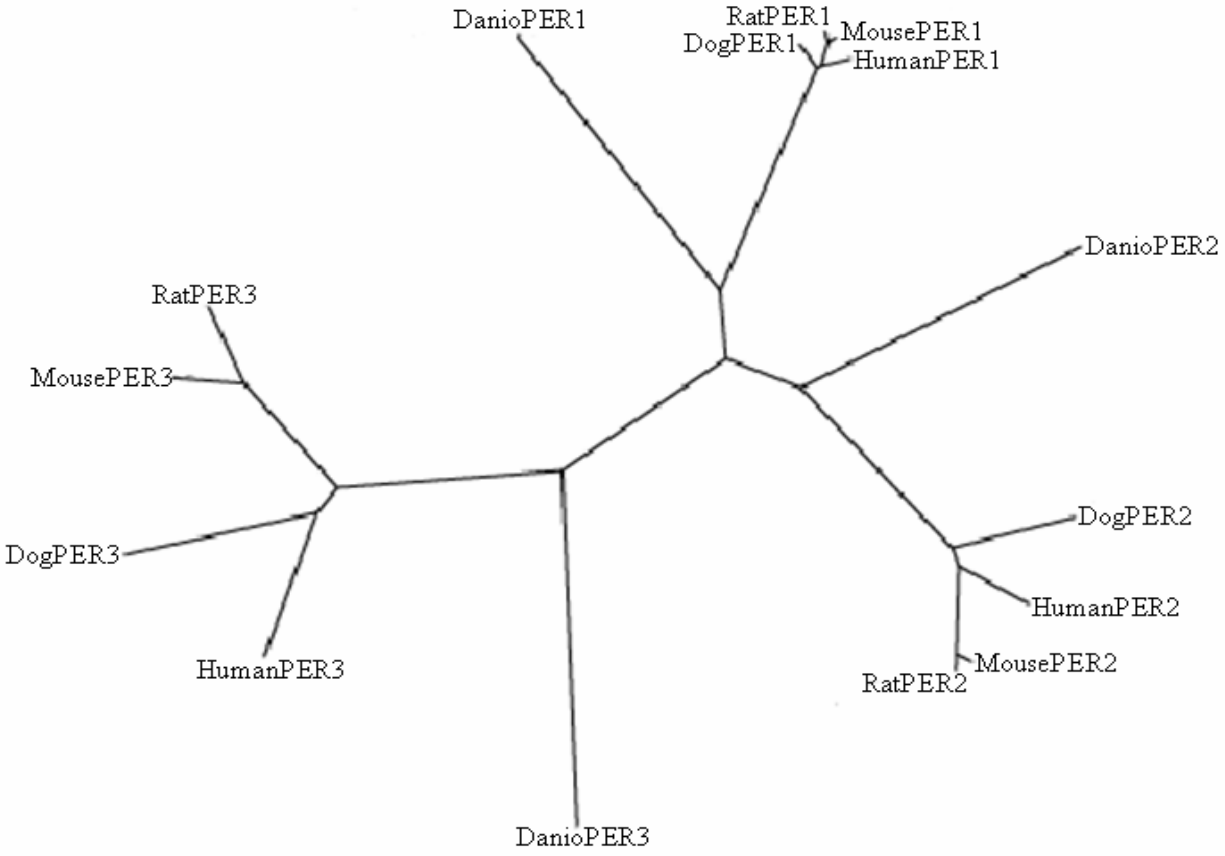

Figure 6. Phylogenetic tree of PER1, PER2 and PER3 proteins from all species from their genes have been fully sequenced. The line distance is inversely proportional to similarity in amino acid sequence.

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REFERENCES

1. Reppert, S.M. and Weaver, D.R. 2001. Molecular analysis of mammalian circadian rhythms. *Ann Rev Physiol* **63**, 647-76.
2. Morre, R.Y. Circadian rhythms: basic neurobiology and clinical applications. *Ann Rev Med* **48**, 253-66.
3. Gooley, J.J., Schomer, A. and Saper, C.B. (2006). The dorsomedial hypothalamic nucleus is critical for the expression of food-entrainable circadian rhythms. *Nat Neurosci* **9**, 498-407.
4. Damiola, F., Le Minh, N., Preitner, N., Kornmann, B., Fleury-Olela, F. and Schibler, U. 2000. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes & Development* **14**, 2950-61.
5. Stokkan, K-A., Yamazaki, S., Tei, H., Sakaki, Y. & Menaker, M. 2001. Entrainment of the circadian clock in the liver by feeding. *Science* **291**, 490-93.
6. LeMinh, N., Damiola, F., Tronche, F., Schutz, G. and Schibler, U. 2001. Glucocorticoid hormones inhibit food-induced phase-shifting of peripheral circadian oscillators. *EMBO J* **20**, 7128-36.
7. Dudley, C.A., Erbel-Sieler, C., Estill, S.J., Reick, M., Franken, P., Pitts, S. and McKnight, S.L. 2003. Altered patterns of sleep and behavioral adaptability in NPAS2-deficient mice. *Science* **301**, 379-83.
8. Edery, I. 2000. Circadian rhythms in a nutshell. *Physiol Genomics* **3**, 59-74.
9. Levi, F. 1999. Cancer chemotherapy. *J Pharm Pharmacol* **51**, 891-898.
10. Stevens, R.G. and Rea, M.S. 2001. Light in the built environment: potential role of circadian disruption in endocrine disruption and breast cancer. *Cancer Causes Control* **12**, 279-87.
11. Keith, L.G., Oleszczuk, J.J. and Laguens, M. 2001. Circadian rhythm chaos: a new breast cancer marker. *Int. J. Fertil.* **46**, 238-47.
12. Rafnsson, V., Tulinius, H., Jonasson, J.G. and Hrafnelsson, J. 2001. Risk of breast cancer in female flight attendants: a population-based study (Iceland). *Cancer Causes Control* **12**, 95-101.
13. Schernhammer, E.S., Laden, F., Speizer, F.E., Willet, W.C., Hunter, D.J., Kawachi, I. and Colditz, G.A. 2001. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J. Nat. Cancer. Inst,* **93**, 1563-8.
14. Hansen, J. 2001. Light at night, shiftwork and breast cancer risk. *J. Nat. Cancer Inst.* **93**, 1513-5.
15. Blask, D.E., Dauchy, R.T., Saucer, L.A., Krause, J.A. and Brainard, G.C. 2003. Growth and fatty acid metabolism of human breast cancer (MCF-7) xenografts in nude sats: impact of constant light-induced nocturnal melatonin suppression. *Breast Cancer Res. Treat.* **79**, 313-20.
16. Chen, S-T., Choo, K-B., Hou, M-F., Yeh, K-T., Kuo S-J. and Chang, J-G. 2005. Deregulated expression of the *PER1*, *PER2* and *PER3* genes in breast cancers. *Carcinogenesis* **26**, 1241-6.
17. Pirovano, A., Lorenzi, C., Serretti, A., Ploia, C., Landoni, S., Catalano, M. and Smeraldi, E. 2005. Two new rare variants in the circadian "clock" gene may influence sleep pattern. *Genetic IN Medicine* **7**, 455-6.
18. Serretti, A., Benedetti, F., Mandelli, L., Lorenzi, C., Pirovano, A., Colombo, C. and Smeraldi, E. 2003. Genetic dissection of psychopathological symptoms: Insomnia in mood disorders and CLOCK gene polymorphisms. *Am J Med Genet* **121B**, 39-43.
19. Serretti, A., Cusin, C., Benedetti, F., Mandelli, L., Pirovano, A., Zanardi, R., Colombo, C. and Smeraldi, E. 2005. Insomnia improvement during antidepressant treatment and CLOCK gene polymorphism. *Am J Med Genet B Neuropsychiatr Genet* **137**, 36-9.
20. Benedetti, F., Serriti, A., Colombo, C., Barbini, B., Lorenzi, C., Campori, E. and Smeraldi, E. 2003. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am J Med Genet* **123B**m 23-6.
21. Katzenberg, D., Young, T., Finn, L., Lin, L., King, D.P., Takahashi, J.S. and Mignot, E. 1998. A CLOCK polymorphism associated with human diurnal preference. *Sleep* **21**, 569-76.22.
22. Caci, H., Robert, P. and Boyer, P. 2004. Novelty seekers and impulsive subjects are low in morningness. *Eur Psychiatry* **19**, 79-84.
23. Carrier, J. and Monk, T.H. 2000. Circadian rhythms of performance: new trends. *Chronobiol Int* **17**, 719-32.

24. Diaz, J.F. and Aparicio, M. 2003. Relationships between morningness-eveningness and personality styles. *Ann Psychol* **19**, 247-56.
25. Kerkhof, G.A. 1985. Inter-individual differences in the human circadian system: a review. *Biol Psychol* **20**, 83-112.
26. Toh, K.L., Jones, C.R., He, Y., Eide, E.J., Hinz, W.A., Virshup, D.M., Ptacek, L.J. and Fu, Y.H. 2001. An *hPer2* phosphorylation site mutation in a family with advanced sleep phase syndrome. *Science* **291**, 1040-3.
27. Ebisawa, T., Uchiyama, M., Kajimura, N., Mishima, K., Kamei, Y., Katoh, M., Watanabe, T., Sekimoto, M., Shibui, K., Kim, K., Kudo, Y., Ozeki, Y., Sugishita, M., Toyoshima, R., Inoue, Y., Yamada, M., Nagase, T., Ozaki, N., Ohara, O., Ishida, N., Okawa, M., Takahashi, T. and Yamauchi, T. 2001. Association of structural polymorphisms in the human *period3* gene with delayed sleep phase syndrome. *EMBO Rep* **2**, 342-6.
28. Johansson, C., Willeit, M., Smedh, C., Ekholm, J., Paunio, T., Kieseppa, T., Lichtermann, D., Praschak-Rieder, N., Neumeister, A., Nilsson, L-G., Kasper, S., Peltonen, L., Adolfsson, R., Schalling, M. and Partonen, T. 2003. Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology* **28**, 734-9.
29. Archer, S.N., Robilliard, D.L., Skene, D.J., Smits, M., Williams, A., Arendt, J. and von Schantz, M. 2003. A length polymorphism in the circadian clock gene *Per3* is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep* **26**, 413-5.
30. Bunney, W.E. and Bunney, B.G. 2000. Molecular clock genes in man and lower animals. Possible implications for circadian abnormalities in depression. *Neuropsychopharmacology* **22**, 335-45.
31. Healy, D. and Waterhouse, J.M. 1995. The circadian system and the therapeutics of the affective disorders. *Pharmac Ther* **65**, 241-63.
32. Nievergelt, C.M., Kripke, D.F., Remick, R.A., Sadovnick, A.D., McElroy, S.L., Keck Jr., P.E. and Lelsoe, J.R. 2005. Examination of the clock gene *Cryptochrome 1* in bipolar disorder: mutational analysis and absence of evidence for linkage or association. *Psychiatric Genetics* **15**, 45-52.
33. Nievergelt, C.M., Kripke, D.F., Barrett, T.B., Burg, E., Remick, R.A., Sadnovnick, A.D., McElroy, S.L., Keck Jr., P.E., Schork, N.J. and Kelsoe, J.R. 2006. Suggestive evidence for association of the circadian genes *PERIOD3* and *ARNTL* with bipolar disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **March 9 2006 Epub ahead of print.**
34. Mansour, H.A., Wood, J., Logue, T., Chowdari, K.V., Dayal, M., Kupfer, D.J., Monk, T.H., Devlin, B. and Nimgaonkar, V.L. 2006. Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. *Genes, Brains and Behavior* **5**, 150-7.
35. Vosshall, L. B., Price, J. L., Sehgal, A., Saez, L. and Young, M. W. 1994. Block in nuclear localization of period protein by a second clock mutation, timeless. *Science* **263**, 1606-9.
36. Saez, L. and Young, M. W. 1996. Regulation of nuclear entry of the Drosophila clock proteins period and timeless. *Neuron* **17**, 911-20.
37. Kume, K., Zylka, M. J., Sriram, S., Shearman, L. P., Weaver, D. R., Jin, X., Maywood, E. S., Hastings, M. H. and Reppert, S. M. 1999. mCRY1 and mCRY2 are essential components of the negative limb of the circadian clock feedback loop. *Cell* **98**, 193-205.
38. Yagita, K., Yamaguchi, S., Tamanini, F., van Der Horst, G. T., Hoeijmakers, J. H., Yasui, A., Loros, J. J., Dunlap, J. C. and Okamura, H. 2000. Dimerization and nuclear entry of mPER proteins in mammalian cells. *Genes Dev* **14**, 1353-63.
39. Vielhaber, E., Eide, E., Rivers, A., Gao, Z. H. and Virshup, D. M. 2000. Nuclear entry of the circadian regulator mPER1 is controlled by mammalian casein kinase I epsilon. *Mol Cell Biol* **20**, 4888-99.
40. Vielhaber, E. L., Duricka, D., Ullman, K. S. and Virshup, D. M. 2001. Nuclear export of mammalian PERIOD proteins. *J Biol Chem* **276**(49), 45921-7.
41. Jones, D.T., Taylor, W.R. and Thornton, J.M. 1992. The rapid generation of mutation data matrices from protein sequences. *Comput. Appl. Biosci.* **8**, 275–82.
42. Felsenstein, J. 1993. PHYLIP (Phylogeny Inference Package), 3.5c ed, Department of Genetics, University of Washington, Seattle.

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 hilight. Green highlight indicates areas in which primer sequences overlapped with exonic sequences.

BMAL1

Exon1:**tgggttctccaccacttttg**agagctcatcgaaataaacacacctttgtgcctcttgtaacaattccagATCATCCAATGGCAGACCAGAGAATGGACATTT
CTTCAACCATCAGTGATTTCATGTCCCCGGGCCCCACCGACCTGCTTTCCAGCTCTCTTGGTACCAGTGGTGTGGATTGC
AACCGCAAACGGAAAGGCAGCTCCACTGACTACCAgtaaggcctttggggcatgtcttcctcttgtta**aacttggtgtcagttctcgg**

Exon2:**gtctttattaacatgcagtcac**attctcttttgtttttcagAGAAAGCATGGACACAGACAAAGATGACCCTCATGGAAGgtaccatgaacctagtaa
tttgaa**cttcagcatccttatagcc**

Exon3:**actttgccattcatctccag**agaattatgtttttatctttgctttttcctccccccagGTTAGAATATACAGAACACCAAGGAAGGATAAAAAATGCA
AGgtaagcttggaccttattttgtctacaaagcatcctagt**tctggttgcttagagagcag**

Exon4:**gatgcttggttacattttataag**aaatcgtttttcatattgttgttcagGGAAGCTCACAGTCAGATTGAAAAGCGGCGTCGGGATAAAATGAA
CAGTTTTATAGATGAATTGGCTTCTTTGGTACCAACATGCAACGCAATGTCCAGGAAATTAGATAAACTTACTGTGCTA
AGGATGGCTGTTCAGCACATGAAAACATTAAGAGgtgagaccctgggctctattgtcctttatgtccttgcccac**aaatgttaccacccttgcc**

Exon5:**gaggcagcaagttagaatga**gacattttctgaatatcaagtataccaattctttctcttttgcccctaagGTGCCACCAATCCATACACAGAAGCAAACTAC
AAACCAACTTTTCTATCAGACGATGAATTGAAACACCTCATTCTCAGGgtatgttcaattatgggattgttttacaacgtttgtttttataaatttt**caagtaa
gtaccagcatgtgg**

Exon6:**agaaagcacatcctctatttgt**tatcagggtgattacaaattatgtttcctacagtatgagaaattgattatccatttctcctgattagGCAGCAGATGGATTTTTGTTTGT
CGTAGGATGTGACCGAGGGAAGATACTCTTTGTCTCAGAGTCTGTCTTCAAGATCCTCAACTACAGCCAGgtattgttcatgctcct
gttgatggtgggcagcctcac**agcagtcagaagtgtcactc**

Exon7:**gactgtgcatgcttacttgt**tgcataattgattttctgcatgcaattgacttgtcatgtttaacatttcatctccccagAATGATCTGATTGGTCAGAGTTTGTTTGA
CTACCTGCATCCTAAAGATATTGCCAAAGTCAAGGAGCAGCTCTCCTCCTCTGACACCGCACCCCGGGAGCGGCTCATA
GATGCAAAAAgtgagtaccagagaggcctcgcatttcctcagcagcccactcacaggcagcc**aaccctgagtgagcagagg**

Exon8:**aaggctttgctcaaggtcac**actccccctcctgacagacaacactgctctcagtttatcacattttgtgtattgatttgcagCTGGACTTCCAGTTAAAGCAGATAT
AACCCCTGGGCCATCTCGATTATGTTCTGGAGCACGACGTTCTTTCTTCTGTAGGATGAAGTGTAACAGGCCTTCAGTA
AAGGTTGAAGACAAGGACTTCCCCTCTACCTGCTCAAAGAAAAAAGgtaccaatttaacagtccattaaaaccctgtgacaggtgaagcatgctttctgc
agcggagctctcagctgggc**gttggttccatggtttctg**

Exon9:**ctccatggcccaaacctagt**gctgacactaaccacgaactttgctttctagCAGATCGAAAAAGCTTCTGCACAATCCACAGCACAGGCTATTT
GAAAAGCTGGCCACCCACAAAGATGGGGCTGGATGAAGACAACGAACCAGACAATGAGGGGTGTAACCTCAGCTGCC
TCGTCGCAATTGGACGACTGCATTCTCATGTAGTTCCACAACCAGTGAACGGGGAAATCAGGGTGAAATCTATGGAAT
ATGTTTCTCGGCACGCGATAGATGGAAAGTTTGTTTTTGTAGACCAGAGgtaagagtctacatactaccccttgagcaatgat**ggtagaggattttcaa
ccct**

Exon10:**gcaattaatcatctgaatggct**ttttcttctttaaatattcctttattccctttagGGCAACAGCTATTTTGGCATATTTACCACAAGAACTTCTAGG
CACATCGTGTTATGAATATTTTCACCAAGATGACATAGGACATCTTGCAGAATGTCATAGGCAAGgtaagctaggatgtatgaaagat
cttaagttgaaagtgtc**ccttgcttctagactagtc**

Exon11:**ctgtttaatactttggtctgaga**aaacaacaatgtccatgttttctttacattttcagTTTTACAGACGAGAGAAAAAATTACAACTAATTGCTATAA
ATTTAAAATCAAAGATGGTTCTTTTATCACACTACGGAGTCGATGGTTCAGTTTCATGAACCCTTGGACCAAGGAAGTA
GAATATATTGTCTCAACTAACACTGTTGTTTTgtaagtacttttcctatatctgaagctccccttg**cttcaaacagatgcctagg**

Exon12:**gaatggtgcacagttctgag**caggcctgactcacgtttccttattgctgggatgttcacagAGCCAACGTCCTGGAAGGCGGGGACCCAACCTTCCC
ACAGCTCACAGCATCCCCCCACAGCATGGACAGCATGCTGCCCTCTGGAGAAGgtaactatgtgctgctggggccctggggcttgcccgtg**gga
aggtgcttgtggtcaaa**

Exon13:**tccccttcctactctcaga**ttcctttgttgtagGTGGCCCAAAGAGGACCCACCCCACTGTTCCAGGGATTCCAGGGGGAACCCGG
GCTGGGGCAGGAAAAATAGGCCGAATGATTGCTGAGGAAATCATGGAAAT**CCACAG**gcaagtaacaccttctagttcctctgtta**aaccagt**
ggttctcaaccca

Exon14:**caaagcacatacactccactg**aaaaaagaaaaggcagtgtaattctcttttctgacagGATAAGAGGGTCATCGCCTTCTAGCTGTGGCTCCAGCC
CATTGAACATCACGAGTACGCCTCCCCCTGATGCCTCTTCTCCAGGAGGC**AAGAAG**gtaagactgatgattcttagcctaagctagag**aacct**
cttgcccaagatctg

Exon15:**ggcattgctcataatactgatt**caaacttcacacttccctccttttgtttgtagATTTTAAATGGAGGGACTCCAGACATTCCTTCCAGTGGCCTA
CTATCAGGCCAGGCTCAGGAGAACCCAGGTTATCCATATTCTGATAGTTCTTCTATTCTTGgtaagtggcatcattattcgtttccattgcaat
gagcttgcaaaacatcttacataaagtcaattttaaga**actgaactgtgtgaaacaagc**

Exon16:**ggaattgcttacttaatctgaag**atgctttaaaaaagaaatcactgaccagtctttatctcctcccacagGTGAGAACCCCCACATAGGTATAGACATGAT
TGACAACGACCAAGGATCAAGTAGTCCCAGTAATGATGAGGCAGCAATGGCTGTCATCATGAGCCTCTTGGAAGCAGA
TGCTGGACTGGGTGGCCCTGTTGACTTTAGTGACTTGCCATGGCCGCTGTAAacactacatgttgctttggcaacagctatagtatcaaagtgcatt**a**
ctggtggagttttacagtc

BMAL2

Exon1:**ttgttgtactctgctgccca**taggtaaagtgttgagagaggagaaccagtgcattgCTCCTGTGGTTTCCAGCCGCGTGAGTCCAGGGACAAGACC
AACAGCTATGGGGTCTTTCAGCTCACACATGACAGAGTTTCCACGAAAACGCAAAGGAAGTGATTCAGACCCATCCCA
GTaagtgaatttggtcctctaacccagtgagatctttgactttagggagaagaggaaaatattccttttaaaatcattaattatttccaagttcatggtaacatttggagatgggagagtacttatccaccca
tctgctacc**ttgtcggtgactgacttgg**

Exon2:**tctccacttgaggacaggct**tgctgtccattcccagaacatctgggtagggggtgacccaaggcctccttccttccaggtCAGGAATCATGACAGAAAAAGTGG
TGGAAAAGCTTTCTCAGAATCCCCTTACCTATCTTCTTTCAACAAGGATAGAAATATCAGCCTCCAGTGGCAGCaggtaagtc
ctggactgtctttgacatactctctcccctacttgaagagggcatagagtgggagtgaaaacatgatacacg**tcccactgatttgctcatca**

Exon3:**agaacagtgtgtgcctgctg**ggctcagcatctgctccagtgagcaacacgggggtgactgggggtctgctgaatgttaaatataaaggaagttccttttccctcttAGAGAAGCT
CATAGCCAAACTGAAAAGCGGAGGAGAGATAAAATGAATAACCTGATTGAAGAACTGTCTGCAATGATCCCTCAGTGC
AACCCCATGGCGCGTAAACTGGACAAACTTACAGTTTTAAGAATGGCTGTTCAACACTTGAGATCTTTAAAAGgtgagtttga
cgat**ggcttccacacttcggtaag**

Exon4:**gccaaagagcaaataccagc**agcagcagcattgctaatgttcattaagcattttgccctctctactatatttccaataactcttgatgcctttctttttagGCTTGACAAATTCTT
ATGTGGGAAGTAATTATAGACCATCATTTCTTCAGGATAATGAGCTCAGACATTTAATCCTTAaggtaactaaagatatatttgtctaagtt
gtgta**tgtgctttcattgctgtttga**

Exon5:**tgccacagtaatttcctcagaa**tctgaatgtgtgtgtgtgtgcgtgtgtataagagacagacaatattttaaaatattcacttttttttttaaatcctAGACTGCAGAAGGCTTC
TTATTTGTGGTTGGATGTGAAAGAGGAAAAATTCTCTTCGTTTCTAAGTCAGTCTCCAAAATACTTAATTATGATCaggtatc
caaaaatgaggatattttccatacaatgtttaatttttgaacaaacacatatttttaagctcttttctgaaca**ccttctccccactgggatat**

Exon6:**cgtggacatatctttgagcttg**agaaaaatcaatcaaaaatcaaaaaagaacatttattgtatgcatcaagaaatgtagaaaaagcatggtactgattttaaatgaatgtctaccttatgaat
AGGCTAGTTTGACTGGACAAAGCTTATTTGACTTCTTACATCCAAAAGATGTTGCCAAAGTAAAGGAACAACTTTCTTC
TTTTGATATTTCACCAAGAGAAAAGCTAATAGATGCCAAAAgtaagtgtccatttccgcatgcttattattttatgtaaatgt**aatgatcacctaaaagtttagc**
taca

Exon7:**ctattctctcgcccccttct**gcacgaaagCTGGTTTGCAAGTTCACAGTAATCTCCACGCTGGAAGGACACGTGTGTATTCTGGCT
CAAGACGATCTTTTTTCTGTCGGATAAAGAGTTGTAAAATCTCTGTCAAAGAAGAGCATGGATGCTTACCCAACTCAAA
GAAGAAaggtatcattttgaaatgtc**aagtgatgcaaagcatggct**

Exon8:**ggaataccattcccctttca**tattttagcatatttaaagagcattttatagcacaattataactattatagatgtcaatataagaaatttaatgacttatttataatgatccaaatgtccttttttaaaaat
ctttgaattAGAGCACAGAAAATTCTATACTATCCATTGCACTGGTTACTTGAGAAGCTGGCCTCCAAATATTGTTGGAATGG
AAGAAGAAAGGAACAGTAAGAAAGACAACAGTAATTTTACCTGCCTTGTGGCCATTGGAAGATTACAGCCATATATTG
TTCCACAGAACAGTGGAGAGATTAATGTGAAACCAACTGAATTTATAACCCGGTTTGCAGTGAATGGAAAATTTGTCTA
TGTAGATCAAAGGtaaacatttacatgttataatgattagaat**tcaatgggatatttgaagctattaaa**

Exon9:gtgggcctacagtcttctggggagggagtacactcaccacttctgaagtttattttcaattttgaaaccaggGCAACAGCGATTTTAGGATATCTGCCTCAGGA
ACTTTTGGGAACTTCTTGTTATGAATATTTTCATCAAGATGACCACAATAATTTGACTGACAAGCACAAAGCaggtaggtatgc
attgagcagaatacattttgggga

Exon10:tcttaatttcccattcctgtgaaatttgaagtttgaattaatcttcacaacattgatttttatagtcattgactattatgctgataattatctttctcgttaAGTTCTACAGAGTAAG
GAGAAAATACTTACAGATTCCTACAAATTCAGAGCAAAAGATGGCTCTTTTGTAACTTTAAAAAGCCAATGGTTTAGTT
TCACAAATCCTTGGACAAAAGAACTGGAATATATTGTATCTGTCAACACTTTAGTTTTGtaagtaatttttatgttaagacctttatattgatttc
aaatgagtctctttgctttctcctctcatcttgctaaacca

Exon11:ccttcaccttagaaagtaaatcacctatggtgtttttaattctaggGGACATAGTGAGCCTGGAGAAGCATCATTTTTACCTTGTAGCTCTC
AATCATCAGAAGgtaagcttacttttagatgatggaagacttattactaagacatattattaagactattactatcttttttctgtcctggagaggg

Exon12:AAAGTCCTCAACTGAATTTCTCCttttgctgttacttAGAATCCTCTAGACAGTCCTGTATGAGTGTACCTGGAATGTCT
ACTGGAACAGTACTTGGTGCTGGTAGTATTGGAACAGATATTGCAAATGAAATTCTGGATTTACAGaggtaatgttttattgctgcaaa
tattttcaaaagtaaaaatatcatatttataaaatcaatatacaaaaatcagtagccttcc

Exon13:cagtttcaagttcctcactgtatttttattagtagattattatgtatttagaggagaaaatttccttctaaaatatgtaaaattaaaaatgttttatgtatcacttttaaAGGTTACAGTC
TTCTTCATACCTTGATGATTCGAGTCCAACAGGTTTAATGAAAGATACTCATACTGTAAACTGCAGGAGTgtaagtatacttgtaa
atgataatattcatgaaataaatgaacaataaaatttgcccc

Exon14:cacagcgagcctccatctcaaaaaaataaaaaataaaaagtaaaaataaataaataaagagtgtccttattctagtaggaacctcactgtttgttactctggctgtcttttcagATGTC
AAATAAGGAGTTGTTTCCACCAAGTCCTTCTGAAATGGGGGAGCTAGAGGCTACCAGGCAAAACCAGAGTACTGTTGC
TGTCCACAGCCATGAGCCACTCCTCAgtaagttttcttttgggaactgctgaccat

Exon15:cctcaaaatgtgtgaaatgtatgactttactgatcacctttacttacacaggcctgtattttaattcatagGTGATGGTGCACAGTTGGATTTCGATGCCCTA
TGTGACAATGATGACACAGCCATGGCTGCATTTATGAATTACTTAGAAGCAGAGGGGGGCCTGGGAGACCCTGGGGAC
TTCAGTGACATCCAGTGGACCCTCTAGcctttgattttttaactccaaaaatgagaaaca

CRY1

Exon1:ggaagcgaaggtgtcggctatgagccggagcctccttccttgaatttctccgtggaggacccgccgcgccccccggcATGGGGGTGAACGCCGTGCACTGGT
TCCGAAAGGGGCTCCGGCTCCACGACAACCCCGCCCTGAAGGAGTGCATTCAGGGCGCCGACACCATCCGCTGCGTCT
ACATCCTGGACCCCTGGTTCGCCGGCTCCTCCAATGTGGGCATCAACAGGTGGCGgtgagtcacaagcccgtgggaaatggatttgggtgttta
atgagtctgatgttaatgaattccatgcgatccgccaaatctg

Exon2:gtatggtttttggaaaaagtatatatcaataggaggtaataagatgataggttggcatttcaacttttagaataacatgactttgtaataatttatgtcttctaaatatgtatttttttaataatttaaat
aatactttcttctctctaGATTTTTGCTTCAGTGTCTTGAGGATCTTGATGCCAATCTACGAAAATTAAACTCCCGTCTGTTTGTGATT
CGTGGACAACCAGCAGATGTGTTTCCCAGGCTTTTCAAGgtaatttgaaaaatatttgcataaaacaatcttttctcagataatattacatatttggtaaataaagttttt
tgactaattgaaaatgtagcgaatataagtattttcaag

Exon3:ctttgctagattgttgcctagcataatgcctagaatctaatgggttatgcattcattacttatgtatttttaattgataaattgtttacttttcctgcatattcaaagtttgatttatgtataatcctttga
tatgtagattttcagctttttcacttttcgttataatagaaaaaataactattacaattggtgtacattgttccccttctcttacttttagGAATGGAACATTACTAAACTTTCAATTGA
GTATGATTCTGAGCCCTTTGGAAAGGAACGAGACGCAGCTATTAAGAAACTGGCAACTGAAGCTGGAGTAGAAGTCAT
TGTAAGAATTTCACATACATTATATGACCTAGACAAgtgagtcc

Exon4:caccctcaaagacttcagtgattaattttattttctgcttttaagccttttgggagcttattagccaaaatgtattgtctttttaatactaactacattttactaactcttgttatagGATCATA
GAACTCAATGGTGGACAACCGCCTCTAACTTATAAAAGATTCCAGACTCTCATCAGCAAAATGGAACCACTAGAGATA
CCAGTAGAGACAATTACTTCAGAAGTGATAGAAAAGTGCACAACTCCTCTGTCTGATGACCATGATGAGAAATATGGA
GTCCCTTCACTGGAAGAGCTAGgtgagtgtaaactgtagtcagtgtgagg

Exon5:gttctcccagttattggggttaaataaaaattagtttcggaagaatgatgtttttttctttttctttcttgtagGTTTTGATACAGATGGCTTATCCTCTGCAGTGTG
GCCAGGTGGAGAAACTGAAGCACTTACTCGTTTGGAAAGGCATTTGGAAAGAAAAgtatgataatgtagattatatagctatgcttgtatttccaa
actgcc

Exon6:**gacaattagttaatataattttctctgtgtg**ttttcagGCTTGGGTGGCAAATTTTGAAAGACCTCGAATGAATGCGAATTCTCTGCTTG
CAAGCCCTACTGGACTTAGTCCTTATCTCCGATTTGGTTGTTTGTCATGTCGACTGTTTTACTTCAAACTAACAGATCTCT
ACAAAAAGgtattctctaaaattagagcttattgtttaatactttaaaaaaaaattctgataatacttctttg**ctttttaaccataggtaaagaagaacag**

Exon7:**gactgttttacttcaaactaacagatc**tctacaaaaaggtattctctaaaattagagcttattgtttaatactttaaaaaaaaattctgataatacttctttgctttttaaccatagGTAAAGA
AGAACAGTTCCCCTCCCCTTTCCCTTTATGGGCAACTGTATGGCGTGAATTTTTCTATACAGCAGCAACAAATAATCCAC
GCTTTGATAAAATGGAAGGAAACCCTATCTGTGTTCAATTCCTTGGGATAAAAATCCTGAGGCTTTAGCCAAATGGGCG
GAAGGCCGGACAGGCTTTCCATGGATTGATGCCATATGACACAGCTTCGTCAGGAGGGTTGGATTCATCATCTAGCCAG
GCATGCAGTTGCTTGCTTCCTGACACGAGGGGACTGTGGATTAGTTGGGAAGAAGGAATGAAGgtaagtgttctaa**ctgatatagcat**
gccttattttg

Exon8:**ttgccttgactttg**gctctactgtgaccttgaaaatgcttgctttgcgaattatgtgtgtgcaaactaattggttactgttacttctgaagGTATTTGAAGAATTATTGCTTG
ATGCAGATTGGAGCATAAATGCTGGAAGTTGGATGTGGCTGTCTTGTAGTTCCTTTTTTCAACAGTTTTTTCACTGCTAT
TGCCCTGTTGGTTTTGGTAGGAGAACAGATCCCAATGGAGACTATATCAGgtaaatcaagggtgattactactcagtttggaatagttaattcaagaag
agcttttcatgtttaat**caatgcttaaagtattccccac**

Exon9:**gatgggcagcagagatgag**aagggtaaacagatcatttaaatggtcttgatttgattttggtctgtcatagctagtagttatagtttgcttagagtgcattttattagtaatctttctttttctccca
aagGCGTTATTTGCCTGTCCTAAGAGGCTTCCCTGCAAAATATATCTATGATCCCTGGAATGCACCAGAAGGTATCCAAA
AGGTAGCCAAATGTTTGATAGGAGTTAATTATCCTAAACCAATGGTGAACCATGCTGAGGCAAGCCGTTTGAATATCGA
AAGGATGAAACAGATCTATCAGCAGCTTTCACGATATAGAGGACTAGgtatgttaagaactgtctttgtttctttggcagctgtttatgtacttatctttgaatt
ttatcttgatcataatttaaaagaaaattttttt**gtcctttaggtcttctggc**

Exon10:**gaggactaggtatgttaagaactgtc**tttgtttctttggcagctgtttatgtacttatctttgaattttatcttgatcataatttaaaagaaaattttttttgtgctttagGTCTTCTGGCAT
CAGTACCTTCTAATCCTAATGGGAATGGAGGCTTCATGGGATATTCTGCAGAAAATATCCCAGGTTGTAGCAGCAGTGG
AAgtaagtgaaaaggaaatttctgcacttagtaacatgaagaggttattaaacaaatatatttgttattgatcctcactaacatattttataaaaat**ctgtctttgaaattagcttaatag**

Exon11:**tggttcataggaagattgagatttagt**cttaaaagcatataaatgaccttaagtacaagcgctaaaagttggatttgtagacttaataatacatacatcttggatttgattttaagtaattttact
gtgttttaaatactaacagGTTGCTCTCAAGGGAGTGGTATTTTACACTATGCTCATGGCGACAGTCAGCAAACTCACCTGTTGAAG
CAAGgtaagaatgaagcattggagcatactgttctttttccttttcctatcttaaacatacatttttaaatgtgca**ggaagaagctccat**

Exon12:**gctcatggcgacagtcag**caaactcacctgttgaagcaaggtaagaatgaagcattggagcatactgttctttttccttttcctatcttaaacatacatttttaaatgtgcagGAAGAA
GCTCCATGGGCACTGGTCTCAGTGGTGGGAAACGTCCTAGTCAGGAAGAGGACACACAGAGTATTGGTCCTAAAGTCC
AGAGACAGAGCACTAATTAGgtaaatattttagagctgtatttcttgctttagaagagtatataattaacataaattaagataatttcaaaaatggagcaaatctctatttt**caaaccaga**
aaatcttgaggc

CRY2

Exon1:**gtggctggagcagtctg**gacagtcATGGCGGCGACTGTGGCGACGGCGGCAGCTGTGGCCCCGGCGCCAGCGCCCGGCACGG
ACAGCGCCTCTTCGGTGCACTGGTTCCGCAAAGGGCTGCGACTCCACGACAACCCGGCGTTGCTGGCGGCCGTGCGCG
GGGCGCGCTGCGTGCGCTGCGTTTACATTCTCGACCCGTGGTTCGCGGCCTCCTCCTCAGTCGGGATCAACCGATGGAG
gtgaggggacccggggctgggtggcggggacgcagc**caggaccctgaccctg**

Exon2:**cagcgaaccagtttctccc**tgctttgttaggaaagagagccactcttcatgatgttatcactaacaaggcctgtgtggactccacagGTTCCTACTTCAGTCTCTGGAA
GATTTGGACACAAGTTTAAGGAAACTGAACTCCCGCCTGTTTGTAGTCCGGGGACAGCCAGCCGACGTGTTCCCAAGGC
TGTTCAAGgtaagcgtgcagagccccagagaagacagtgagattctgtccctgacggtttcc**ccacagcctgagtgatatg**

Exon3:**cccaaacacagtgttgagc**ataacagatcctctccccacagGAATGGGGAGTGACCCGCTTGACCTTTGAATATGACTCTGAACCCTTTG
GGAAAGAACGGGATGCAGCCATCATGAAGATGGCCAAGGAGGCTGGTGTGGAAGTAGTGACGGAGAATTCTCATACC
CTCTATGACCTGGACAGgtaagagatggggcccagggatcaggttaccaattgtgagagttagtaatttg**ggcccctgctgagcggaac**

Exon4:**gccatgtgggtaacactagc**tatgctttgggctccccagGATCATTGAGCTGAATGGGCAGAAGCCACCCCTTACATACAAGCGCTTTC
AGGCCATCATCAGCCGCATGGAGCTGCCCAAGAAGCCAGTGGGCTTGGTGACCAGCCAGCAGATGGAGAGCTGCAGG
GCCGAGATCCAGGAGAACCACGACGAGACCTACGGCGTGCCCTCCCTGGAGGAGCTGGgtgcgtacttcctg**cccagagccacttgtgct**
gg

Exon5:**cagaacagccgtgccggg**ctatcactgaaatggtcaaacctcctgtcttgtgacctttccttctcttcagGGTTCCCCACTGAAGGACTTGGTCCAGCTGTCT
GGCAGGGAGGAGAGACAGAAGCTCTGGCCCGCCTGGATAAGCACTTGGAACGGAAGGtatgggccgtttctgagacacagagctgcagat
actgatatccacaca**gcaggagatacaggtcatg**

Exon6:**ggctgttctgtgaccgtagg**cagattccttaaccacccaatgcctccatttttcctctgttacatccaagcctttccttttgccaccttctctttctgctgtagGCCTGGGTTGCCAA
CTATGAGAGACCCCGAATGAACGCCAACTCCCTCCTGGCCAGCCCCACAGGCCTCAGCCCCTACCTGCGCTTTGGTTGT
CTCTCCTGCCGCCTCTTCTACTACCGCCTGTGGGACCTGTATAAAAAGgtaaggggacatacctgcccacattgca**cctaaggcctgcagccag**

Exon7:**cctttgtagaagagacctgag**aggcaccatgctaagagctgggcgagtgtttgtatccatgtgccacccctacctctcagGTGAAGCGGAACAGCACACCTCCC
CTCTCCCTATTTGGGCAACTCCTATGGCGAGAGTTCTTCTACACGGCAGCTACCAACAACCCCAGGTTTGACCGCATGG
AGGGGAACCCCATCTGCATCCAGATCCCCTGGGACCGCAATCCTGAGGCCCTGGCCAAGTGGGCTGAGGGCAAGACAG
GCTTCCCTTGGATTGATGCCATCATGACCCAACTGAGGCAGGAGGGCTGGATCCACCACCTGGCCCGGCATGCCGTGGC
CTGCTTCCTGACCCGCGGGGACCTCTGGGTCAGCTGGGAGAGCGGGGTCCGGgtgagtgctctctcaacgaaaagctggcctgtaccctctggtca
ggcccgtcaaagggcagccc**ccttctgggctgagggatg**

Exon8:**gggcactgtggtgacttg**ggaaaaaacatggctgcatgtccccaaggaggctgatcatcccctcccctatctagGTATTTGATGAGCTGCTCCTGGATGCAG
ATTTCAGCGTGAACGCAGGCAGCTGGATGTGGCTGTCCTGCAGTGCTTTCTTCCAGCAGTTCTTCCACTGCTACTGCCCT
GTGGGCTTTGGCCGTCGCACGGACCCCAGTGGGGACTACATCAGgtgaggatacagaccaggctctctggcctctgaccactgtg**gcctcctactagga
tggg**

Exon9:**gaccactgtggcctcctac**taggatgggataccctgggccttttgaaggagggtctgggtatgctgatgggtcatctggtgtatcttatttcagGCGATACCTGCCCAAAT
TGAAAGCGTTCCCCTCTCGATACATCTATGAGCCCTGGAATGCCCCAGAGTCAATTCAGAAGGCAGCCAAGTGCATCAT
TGGTGTGGACTACCCACGGCCCATCGTCAACCATGCCGAGACCAGCCGGCTTAACATTGAACGAATGAAGCAGATTTA
CCAGCAGCTTTCGCGCTACCGGGGACTCTgtaaggagacaaacacctagctcactgaagggaagga**cagcacctacaggctcagg**

Exon10:**cctctgcaatcctgcgaga**cggcactctgattactcctcgcctctctcccagGTCTACTGGCATCTGTCCCTTCCTGTGTGGAAGACCTCAGTC
ACCCTGTGGCAGAGCCCAGCTCGAGCCAGGCTGGCAGCATGAGCAGTGCAGgtgagcagcagcaaccaacctcctgtggcctcctgtg**gcctgt
gccaccacttcag**

Exon11:**gacacgcttccctacagg**CCCAAGACCACTACCCAGTGGCCCAGCATCCCCCAAACGCAAGCTGGAAGCAGCCGAGGAA
CCACCTGGTGAAGAACTCAGCAAACGGGCCCGGGTGGCAGAGTTGCCAACCCCAGAGCTGCCGAGCAAGGATGCCTG
AGagtgagtgacagcagcctagattcaacctcaggaaggaagttgggagtgggggggcctactgccctgccagctgcaggttgaaacatagcaaactagatgaaaatctggtgg**gaccaccca
atgctcagcc**

CLOCK

Exon1:**ctcaagataagtttgtggaag**taacatttttagaaaactaatgaccatttatttttcttttcacctaaggagaagtacaaatgtctactacaagacgaaaacgtagtatgttATGTTGTT
TACCGTAAGCTGTAGTAAAATGAGCTCGATTGTTGACAGgtatgtttttgaagacttattttaagttatatataattattttaaaa**tgcactattagaataatggtct**

Exon2:**ctgagttgatttacatgtcact**ttagtattgctgttgcttagtgagtctgctcttactttctctatccgctttcttttagAGATGACAGTAGTATTTTTGATGGGTTGGT
GGAAGAAGATGACAAGGACAAAGCGAAAAGgtagtttgattagagatataaaatagtaaatgaatgaataatagataaatataatggtaaataaatagtgaataaatgatt
tccaaaagctatgtgctttag

Exon3:**gtatattggtaacctgggag**atatttgttaccatctatgttgatagaagtacatgctgtgtcatgtctaaattaacattgtattaaactacttgtgtaattaaatggattgtttaaaaaatgcatatttt
tcatttcatcagAGTATCTAGAAACAAATCTGAAAAGAAACGTAGAGATCAATTTAATGTTCTCATTAAAGAACTGGGATCCAT
GCTTCCTGGTAATGCTAGAAAGATGGACAAATCTACTGTTCTGCAGAAAAGCATTGATTTTTTACGAAAACATAAAGgta
aatttttaactctgtaaaatggaacagactctcaaagcattagt**tagaatcttggcagagatgc**

Exon4:**gtagggctttttgtactcctc**cggtggttggagtatgccactaatatgtcaatctgtttacagAAATCACTGCACAGTCAGATGCTAGTGAAATTCGACA
GGACTGGAAACCTACATTCCTTAGTAATGAAGAGTTTACACAATTAATGTTAGAGgtatgtccagatttaatttttgaaagttttatttttcctcaaaaa
agaaatcacagggtgacttaatatccaggtgtaccttggcgatattgcgagttgagttccagaccactgcaataaagctaatatttca**gtaaaatgagtcacatgaattg**

Exon5:**tatttctgtcctgcaaaatact**tttttctttttcatttaacatatcattatgtttaatttcagGCTCTTGATGGTTTTTTTTTAGCAATCATGACAGATGGAAG
CATAATATATGTGTCTGAGAGTGTAACTTCATTACTTGAACATTTACCAgtaagtataaagatcctacaatctacttcgtattaaaatgcctattttaaatat
tctaaag**cactgggaagtggactttga**

Exon6:**gcaattgtctcttgaatcattg**aagttattttacttttaacaattttcttttcagTCTGATCTTGTGGATCAAAGTATATTTAATTTTATCCCAGAAGG
GGAACATTCAGAGGTTTATAAAATACTCTCTACTCATCTGCTGGAAAGTGATTCATTAACCCCAGAATATTTAAAATgtaa
gtagtagctgttaagcaaaaaagtcaaatgttgtattcag**tagcactatccttttgcaag**

Exon7:**gatcttactttatgtggtatatc**aatcattgttttatatcagaaatatgtgatttttaaaatctctttttatttcagCAAAAAATCAGTTAGAATTCTGTTGTCACATG
CTGCGAGGAACAATAGACCCAAAGGAGCCATCTACCTATGAATATGTAAAATTTATAGGAAATTTCAAATCTTTAAAC
AGTGgtgagttaaaatgcttctctcacaatgtgttttaacttgttatttt**tctgtgctcttaaagacatag**

Exon8:**ctgtgctcttaaagacataga**tgtttgaatatcagtgacaattaggttttgctggcataactgatgatacatatttccctattgttttagTATCCTCTTCAGCACACAATGG
TTTTGAAGGAACTATACAACGCACACATAGGCCATCTTATGAAGATAGAGTTTGTTTTGTAGCTACTGTCAGGTTAGCT
ACACCTCAGTTCATCAAGgtatgtttttaattttatttcccaaaggggatttcagttcatatgctgagagctgcctgaa**acttcctgcagacattgagg**

Exon9:**gattacaggtgtgagccact**gcacctggccatgacttatttttatatgtagcaatatttaatattcttaaggacacaaagtatttataaattttaattatttatttgtagGAAATGTGCAC
TGTTGAAGAACCCAATGAAGAGTTTACATCTAGACATAGTTTAGAATGGAAGTTTCTGTTTCTAGATCACAGgtaattccatttttt
aaattccatgaaaaggtaatagtcatgttatataattcttgaa**attaatggatcaagggcaaac**

Exon10:**ggactttgaaacctgttccca**ttttttgaaaaataaagccccccccccaaagtttatttctagttgaaatatttcttattatggaaaaacttataataatgattgttttctgtgtaatttagGGCA
CCACCCATAATAGGGTATTTGCCATTTGAAGTTCTGGGAACATCAGGCTATGATTACTATCATGTGGATGACCTAGAAA
ATTTGGCAAAATGTCATGAGCACTgtaagtagattttaacatttctggtgataataactgttttataagcagaagtcctgtcctgaa**atgataggtagtaagacacag**

Exon11:**atgtaaatgatagcttttggtta**aaaaacaatctttatataatatgaattaaagaaaaaatatttctctattttccttttagTAATGCAATATGGGAAAGGCAAATCA
TGTTATTATAGGTTCCTGACTAAGGGGCAACAGTGGATTTGGCTTCAGACTCATTATTATATCACTTACCATCAGTGGAA
TTCAAGGCCAGAGTTTATTGTTTGTACTCACACTGTAGTAAGgtaataattcttttagagaatttctgaattagggtaacatcctatgatgattttggcattgtaact
ttt**atgcgtaagttgttaaagagc**

Exon12:**gaatagttacagctgtgcact**attttaaacgaatgaccagacactaaaatttgattatttttccatttgtagTTATGCAGAAGTTAGGGCTGAAAGACGACG
AGAACTTGGCATTGAAGAGTCTCTTCCTGAGACAGCTGCTGACAAAgtatgtttcttataattaaaaaaaattatttttaatttctccccaataaaagatgaaa
ctcaataattaataggaaaactatttttcaaaaatactttatttc**ctcacttataacagggatgtg**

Exon13:**ttgtgaatttgagatctctg**aactgaaccacaagaaaacatttattttactctgtctccataga**GCCAAGATTCTGGGTCAGATAATCGTATAAACACA**
GTCAGTCTCAAGGAAGCATTGGAAAGGTTTGATCACAGCCCAACCCCTTCTGCCTCTTCTCGGAGTTCAAGAAAACCAT
CTCACACGGCCGTCTCAGACCCTTCCTgtgagtacccttgcttcaaagcagacttccttaaagtaactaactaaacttttagttacttata**tcagcatttctcatcaaacgc**

Exon14:**cactttcattgaatggtttgga**aaaataattcaaaagccatttttattaactgaaatacattttgagattaatctttaaaaactatattttataaagtactaatgctcttctgattttgttgacttcag
CAACACCAACCAAGATCCCGACGGATACGAGCACTCCACCCAGGCAGCATTTACCAGCTCATGAGAAGATGGTGCAAA
GAAGGTCATCATTTAGTAGTCAGgtaagctctttagtggatattcttctgaataaagatttattaagaggggaaaaatgatctaaatcttcagaaat**tcatctatttgtcacccctc**

Exon15:**ctgctggaagtactcatgta**tgggaatgagaatcacttcagtgttatttttttattttgctctagTCCATAAATTCCCAGTCTGTTGGTTCATCATTAACAC
AGCCAGTGATGTCTCAAGCTACAAATTTACCAATTCCACAAGGCATGTCCCAGgtacttttggtttttgtttcagttgcgtatttgaatatgataaattg
cttttaagctaatgtaatttttttaaaaatccaggcttgctggca**agcacctgtagccacagcta**

Exon16:**gttgtgcaattataaggagtaa**gtaattctaaaatatattacacttttccgtacatggtacttcagTTTCAGTTTTCAGCTCAATTAGGAGCCATGCAAC
ATCTGAAAGACCAATTGGAACAACGGACACGCATGATAGAAGCAAATATTCATCGGCAACAAGAAGAACTAAGAAAA
ATTCAAGAACAACTTCAGATGGTCCATGGTCAGGGGCTGCAGgtaattgttatatttgaata**caaacaaagcatcccattcac**

Exon17:**ctttgtagcttgattttgcctt**cttttaatgctcattcttcttttcaatctacaaagctcattttaacataatctttatttttaaagATGTTTTTGCAACAATCAAATCCTGG
GTTGAATTTTGGTTCCGTTCAACTTTCTTCTGGAAATTCATCTAACATCCAGCAACTTGCACCTATAAATATGCAAGGCC
AAGTTGTTCCTACTAACCAGATTCAAAGTGGAATGAATACTGGACACATTGGCACAACTCAGCACATGATACAACAAC
AGACTTTACAGAGTACATCAACTCAGgtaatgttactgagcacagcgggctatggagtgatcagtggttggaagg**cacactattgctgaagcaga**

Exon18:**gaattctagcatacttcccaa**ataattattttcagttaatctgtctataaaatctctttatttttaacagAGTCAACAAAATGTACTGAGTGGGCACAGTCAG
CAAACATCTCTACCCAGTCAGACACAGAGCACTCTTACAGCCCCACTGTATAACACTATGGTGATTTCTCAGCCTGCAG
CCGGAAGCATGGTCCAGATTCCATCTAGTATGCCACAAAACAGCACCCAGAGTGCTGCAGTAACTACATTCACTCAGG
ACAGGCAGATAAGgtagttgtcatatttcatttgttatttttaaaattgtaaaccgattgattagaaaacaataatttgatttcttaatcaaatttttttaatgtgattttaa**tgagatgctcactgcagc**
c

Exon19:**actccactgcgttttatgatg**tataccttgtactttggactccaatttttttccttctttcttctaacagATTTCTCAAGGTCAACAACTTGTGACCAAATTAGT
GACTGCTCCTGTAGCTTGTGGGGCAGTCATGGTACCTAGTACTATGCTTATGGGCCAGGTGGTGACTGCATATCCTACTT
TTGCTACACAACAGCAACAGTCACAGACATTGTCAGTAACGCAGCAGCAGCAGCAGCAGAGCTCCCAGGAGCAGCAG
CTCACTTCAGTTCAGCAACCATCTCAGGCTCAGCTGACCCAGCCACCGCAACAATTTTTACAGgtaattctccccatggggaagctgctt
caaactcatttactttcatgtaatgaaattaagcatt**aagtgaacagatttgtgagtga**

Exon20:**gacaggggagagtgtgagta**actattatgtgggtgccataaagggagtaaagcaatgctgcataatccatttgtttttagaCTTCTAGGTTGCTCCATGGGAATC
CCTCAACTCAACTCATTCTCTCTGCTGCATTTCCTCTACAACAGAGCACCTTCCCTCAGTCACATCACCAGCAACATCAG
TCTCAGCAACAGCAGCAACTCAGCCGGCACAGGACTGACAGCTTGCCCGACCCTTCCAAGGTTCAACCACAGTAGCAC
ACGTGCTTCCTCTCTTGACATCAAGGGAGGAAGGGGATGGCCCATTA**agagttactcagatgacctg**

NPAS2

Exon1:**caggaaaaactgcatagaaaatc**taATGGATGAAGATGAGAAAGACAGAGCCAAGAGgtaagatgcagctgtccccctgctcagcagagctctctgg
ccccgggggg**tctgcctggcagaatctcg**

Exon2:**cctttgtgacgtggaatgttc**cagtaacctgctcgttttgtgtttcagagCTTCTCGAAACAAGTCTGAGAAGAAGCGTCGGGACCAGTTCAAT
GTTCTCATCAAAGAGCTCAGTTCCATGCTCCCTGGCAACACGCGGAAAATGGACAAAACCACCGTGTTGGAAAAGGTC
ATCGGATTTTTGCAGAAACACAATGgtaaaggtcaccttctctct**gttttttttccaccctgcc**

Exon3:**catagaagtaacatgtgc**ttcatttgttaattccaatttctaggtgccattgaatataaaggcttatttgtgtctcttttctagAAGTCTCAGCGCAAACGGAAATCTGT
GACATTCAGCAAGACTGGAAGCCTTCATTCCTCAGTAATGAAGAATTCACCCAGCTGATGTTGGAGGtgaaatgcactttcaaaata
gcttaaacagttgccagttaaaatggtag**ctacttgttgcagataagtc**

Exon4:**aacgcattgctaaggagct**ttcaaatgttgcattttccacaggCATTAGATGGCTTCATTATCGCAGTGACAACAGACGGCAGCATCATCT
ATGTCTCTGACAGTATCACGCCTCTCCTTGGGCATTTACCGgtgagtttccactccaatggcctttt**accggttcacgttaccatg**

Exon5:**ttcatcttcgttgagggtgt**accttgtccttttattttcttttcagTCGGATGTCATGGATCAGAATTTGTTAAATTTCCTCCCAGAACAAGAAC
ATTCAGAAGTTTATAAAATCCTTTCTTCCCATATGCTTGTGACGGATTCCCCCTCCCCAGAATACTTAAAATgtaagtttaatttttc
tggttttacaagctagaaagataagaattt**tgcttttgaaaggaggttag**

Exon6:**agtctgtgcaatgctcacga**ccccttctctcctcttcttcctttaacggcccagCTGACAGCGATTTAGAGTTTTATTGCCATCTTCTCAGAGGCA
GCTTGAACCCAAAGGAATTTCCAACTTATGAATACATAAAATTTGTAGGAAATTTTCGCTCTTACAACAATGgtaagctttaatt
gtcatataattgtgacagtgtctttt**ctcatgcaaacgtgcacag**

Exon7:**cagacagggctaacctatgt**gtcctcttcttcccaacccccagTGCCTAGCCCCTCCTGTAATGGTTTTGACAACACCCTTTCAAGACCTT
GCCGGGTGCCACTAGGAAAGGAGGTTTGCTTCATTGCCACCGTTCGTCTGGCAACACCACAATTCTTAAAGGcaagtacctga
gaggcagttcattgtgcg**gagctgttatgattgactcac**

Exon8:**agcatctggcacccaagcaa**cttttttttttttctgcttccaatacaggAAATGTGCATAGTTGACGAACCTTTAGAGGAATTCACTTCAAGGC
ATAGCTTGGAATGGAAATTTTTATTTCTGGATCACAGgtttgagaaaagaaaaacatatttgggttgggccc**ttctcaagtcttgtttgcgt**

Exon9:**gttgatcattatggaaaggcat**ggccaccagggtgagccctgcagggtgtctcctccctgatgacaagtcctccttgtccttgtgcagAGCACCTCCAATCATAGGAT
ACCTGCCTTTTGAAGTGCTGGGAACCTCAGGCTATGACTACTACCACATTGATGACCTGGAGCTCCTGGCCAGGTGTCA
CCAGCACCgtgagtaccactgcccagcccaggcatgggggcc**ttgcgttcactccactggg**

Exon10:**caagccatgtttggtattgtc**ttttttttgaaagcttatctttacaataactcttggggaaaagatcattttcatattaacattggttatatgcggaatccattttctaccgacagTGATGC
AGTTTGGCAAAGGGAAGTCGTGTTGCTACCGGTTTCTGACCAAAGGTCAGCAGTGGATCTGGCTGCAGACTCACTACTA
CATCACCTACCATCAGTGGAACTCCAAGCCCGAGTTCATCGTGTGCACACACTCGGTGGTCAGGtaccgcgcacgggcaggggtgc
ggctgcgtccttgtcgcacctgggggaggggtgcaggatggcgtggcccc**tgatggccaaggcagatcag**

Exon11:**gtaccttgctgtctgttcag**gtggtgtcatcccttcctggaatgccccatctccactgtggtctcttaatttcctgtacagTTACGCAGATGTCCGGGTGGAAAGG
AGGCAGGAGCTGGCTCTGGAAGACCCGCCATCCGAGGCCCTCCACTCCTCAGCACTAAAGGtacgcccatccctgccagatggatacgg
caaaggttggctaggaagaaaatgcagccaaccagtctctgaaacaagggtttcttttcatcaatggaagggtacaaccaagctattcaggaggctgaggtgggaggatccttgag**gccgtcacat**
tgaggctgt

Exon12:**actaaagtcacgcccactga**ttctttcctcttgatgctgacatgaggactgtttgatgtgtgtgtttcaggACAAGGGCTCAAGCCTGGAACCTCGGCAGCA
CTTTAACACACTCGACGTGGGTGCCTCGGGCCTTAATACCAGTCATTCGCCATCGGCGTCCTCAAGAAGTTCCCACAAA
TCCTCGCACACAGCCATGTCAGAACCCACCTgtgagtgcgagtccatggatggggagtgg**gatgtccacatcagaccaga**

Exon13:**cttcggatgagtacatgctaa**gtacatggaagttagaaggtcattcgttgctttcttacagCCACTCCCACCAAGCTGATGGCAGAGGCCAGCACCC
CGGCTTTGCCAAGATCAGCCACCCTGCCCCAAGAGTTACCTGTCCCCGGGCTCAGCCAGGCAGCCACCATGCCGGtaagtgt
gtgaccccaaactcctccacgg**gtgtccgctacaatgtggtg**

Exon14:**ctggaatggcagaagcagt**ggtaacaaagccccttttctctcccacaggCCCCTCTGCCTTCCCCATCGTCCTGCGACCTCACACAGCAGCTC
CTGCCTCAGACCGTTCTGCAGAGCACGCCCGCTCCCATGGCACAGgtgagtctgggacccaggaaagggcagcccc**tctcaagccagaagtccgca**

Exon15:**gaagtgtacagaccgagcag**cagcaagatctgcctgcaaggctgaaataactctttcatctgattatgtttttggctccaccttgaagTTTTCGGCACAGTTCAGCAT
GTTCCAGACCATCAAAGACCAGCTAGAGCAGCGGACGCGGATCCTGCAGGCCAATATCCGGTGGCAACAGGAAGAGC
TCCACAAGATCCAGGAGCAGCTCTGCCTGGTCCAGGACTCCAACGTCCAGgtgatccccttcccgggctggcctctgtcc**ctgctgctgtgtggga**
agg

Exon16:**ccagtggagtaaatgaactatt**tctaggcagctcagagcaagaaagttcttactggcacagggaatgcaaaggaggtgcacactggtgaggtacccatgaccccaacttcacaggg
catttctattctgctcccagATGTTCCTGCAGCAGCCAGCTGTATCCCTGAGCTTCAGCAGCACCCAGCGACCTGAGGCTCAGCAGC
AGCTACAGCAAAGGTCAGCTGCAGTGACTCAGCCCCAGCTCGGGGCGGGCCCCCAACTTCCAGGGCAGATCTCCTCTG
CCCAGGTCACAAGCCAGCACCTGCTCAGAGAATCAAGTGTGATATCAACCCAGGtaaatgtgctccttgccagcttcactccttgcctctagagc
agacaccctcttgcagtttggg**acatacttgattcctgcagcc**

Exon17:**agacactgggaggtttcct**ggagagatggcccagggttgagtccaagtcttacctttctcattgaatcattgaaatgatgctccaggGTCCAAAGCCAATGAGAAGC
TCACAGCTAATGCAGAGCAGCGGCCGCTCTGGAAGCAGCCTAGTGTCCCCGTTCAGCAGCGCCACAGCTGCGCTCCCG
CCAAGTCTGAATCTGACCACACCTGCTTCCACCTCCCAGGATGCCAGCCAGTGCCAGCCCAGCCCAGACTTCAGCCATG
ATCGGCAGCTCAGGtacgagactgcccttgtttaaaggataacccaggcatcattttaccccattcatttcagctctactttc**tgctttagacggaggcagag**

Exon18:**ggattagagtcaaccataaag**ggtccagccaggctgagcaagtgctgccacgaccagtgggtctgtggttcaggtgctgatcagtttcctatttccccacctctgcttaaaggCTG
TTGCTGAGCCAGCCCATCCAGCCCATGATGCCCGGGTCCTGTGACGCAAGGCAGCCCTCGGAAGTCAGCAGGACGGGA
CGGCAAGTCAAGTACGtggaccctggcgggaggcaggaggcaagcgctggt**ggaatggttccaggctgg**

Exon19:**ggtgtcgtatcaatactgct**ttcttaaaggacctgttttctccttcccacgtgaaacaggtacgCCCAGAGCCAGACCGTGTTTCAAAATCCAGACGCA
CACCCCGCCAACAGCAGCAGCGCCCCGATGCCCGTCCTGCTGATGGGGCAGGCGGTGCTCCACCCCAGCTTCCCTGCCT
CCCAACCATCGCCCCTGCAGCCTGCACAGGCCCGGCAGCAGCCACCGCAGCACTACCTGCAGGTgggtgccacggcccaggggggc
ccccgtgcaggcctgggagccgggccacgctccacacccgaagtctcagagatattttat**tcccttgctttcaaggttg**

Exon20:**actgccttgtaagacagttga**ggagcggacatcagaaccacctctgaagccctttgttcttttttttctaggtACAGGCACCAACCTCTTTGCACAGTGAGCA
GCAGGACTCGCTACTTCTCTCCACCTACTCACAACAGCCAGGGACCCTGGGCTACCCCCAACCACCCCCAGCACAGCCC
CAGCCCCTACGTCCTCCCCGAAGGGTCAGCAGTCTGTCTGAGTCGTCAGGCCTCCAGCAGCCGCCCCGATAAtgccccggcac
tgaagtcgggacacaatcagctttaaccaatggatgaggggggtggccacaggagatggggagaggagtctgaactaaaccccctggct**ttgtgcacactgcatacgt**

PER1

Exon1:**tgcctgctcacaagaccatt**cctagacccaacataccacatcccatacacaCCTCTTGCTGCTCTCAGTGGTCTCCAGCAGGGCTGAGTCCTTG
CCGTTGCCTGAGGAGGAGCTGTGTGAGCTCCGCTGAGATGCGCCTCTAGACTCATGCCCGTTGGACTCATTGCCACTTG
AACCATTGCTGTTGGCATCGGTGTCATCGGCCAGGCTGGGGCCTGGGCAAGGCCGGTGCTGTGGGGGCCCAGGGGATG
GGACGCCCCCAGGACAAAATGATTCCCCAGGCCTGGGGTCCCCTCCCCCATCAGCCCCTTCTAGGGGGCCACTCATGTC
TGGGCCATGgggagaa**cagaacagagaaggcag**

Exon2:**agacattagtcccagagtgt**ggcctgggcccccagacctctcctccagcctcacccgacgtacCTGCAGCCACTGGTGGACGGGTTGTCCTGCTCTG
AGCTGGCACTCAGGAGGCTGTAGGCAATGGAACTGCTGGGTGGGGATGGGCTCTGAGAGTTTGTgctaggagacagcaacaggccc
agttacaggtagggccagcagtgcgaggctgtcacccagct**ctgcctgctcacaagac**

Exon3:**gtgaggcattcagtaaggag**gctgcctcttctcgggagcccaggcccaggcattccctcttgggacacaccacttaCCTGCACCTGCTTGACACAGGCCAGT
GCGTACTGCAGCGTGGCCAGGGTCCCAGARCGGCCCTTGCCCCGGCGCTCTGGCGGCAGTCGAAGCTTGAGCTCTCGA
AGTGCTGTCATGAGTTCCTTCTGAGTCCTTGCCCGGGCTGACTGTTCACTGctgcggggccacaggaagaa**agagataaagacattagtccag**

Exon4:**agctgtgggagaaggagta**gggatagggtgcgtcgggatgcagaggccaggccgccgctgacCTGGTTCTGAAGTGTGTACTCAGACGTGATGTG
CTCCAGCTCCTCCAGGGTATAGGTGGACATGTCCATGGAGCAAGGCTCGCCCTCCTCCAGGCTCCACTGCTGGTAGTAT
TCCTGGTTGGctgcagagtggaggcagtgaggcattcag**taaggaggctgcctcaacac**

Exon5:**ctcacagcaggaatttcct**gggactgctcatgcctccccacagcgcttgggcacctcacCTGCTGAGGCCCCTGTGCCCCAGGTGGGCAGGCGAGA
TGGAGCAGTGGAACCATAGAAGACTCCCACATCCTGGGGAGCCAGGAGCTCAGAGAAGCGGGTACCCCGGAACACGT
CCCGCTTGCAACGCAGCAGGACGGCTGCCTGCTCCGAAATGTAGACGATTCGGCCCGTCAGGAAGGAGACAGCCACTG
AGAAGGTATCctggcaggaggggagagcaagagcagattcaagagctgtgggagaaggagtaggggtgcg**tcgggatgcagaggccag**

Exon6:**ggcagaggtcttctccagtt**cccctcacctacCTGATACGGCAGAAGACGGACTTCTCCTGGGTAAAGTCCCTGAGGCCTGAACctgg
gacagacaggagaggagtgagcacagcttcctgccccttccctaggctgcgaagaatccactaagggaaagtctgggttccccggcccct**cacagcaggaatttcctg**

Exon7:**t**tgaaagtccctaatgctcct**c**tctcctttgctagAGGAGGTCCTGACCGGGATCCAGGGCCTCGGTACCAGCCATTCCGCCTAACCCC
GTATGTGACCAAGATCCGGGTCTCAGATGGGGCCCCTGCACAGCCGTGCTGCCTGCTGATTGCAGAGCGCATCCATTCG
GGTTACGAAGgtgggcagttcagggccctggcctggtgggggctgggagaaaggg**acatttcctcatggccaga**

Exon8:**gttgggcattctggacgaaa**cccagtgaccacactctctgtgcctcagCTCCCCGGATACCCCCTGACAAGAGGATTTTCACTACGCGGCAC
ACACCCAGCTGCCTCTTCCAGGATGTGGATGAAAGgtgaggataggacctagaggagacgagggcagccagggctgaggccacggccactct**gatgcctcct
tcccgttcag**

Exon9:**tgaggccacggccactctg**atgcctccttcccgttcagGGCTGCCCCCCTGCTGGGCTACCTGCCCCAGGACCTCCTGGGGGGCCCCAGT
GCTCCTGTTCCTGCATCCTGAGGACCGACCCCTCATGCTGGCTATCCACAAGAAGAgtgagttcctctcgccctgctcgcccttcccactgtcct
gggcttttg**agtggctgcccttgtggtt**

Exon10:**tggcatggcctccctctta**ctcagctctccctccctttgaccgctcctcctttcccacttccatcagttCTGCAGTTGGCGGGCCAGCCCTTTGACCACTCC
CCTATCCGCTTCTGTGCCCGCAACGGGGAGTATGTCACCATGGACACCAGCTGGGCTGGCTTTGTGCACCCCTGGAGCC
GCAAGGTAGCCTTCGTGTTGGGCCGCCACAAAGTACGCACgtaagtgggccatgcccccgagctggcgttggggatagggcagtgcggtgggggacagg
accgggccagg**gctggattcactcttcactc**

Exon11:**gagctggcgttggggata**gggcagtgcggtgggggacaggaccgggccagggctggattcactcttcactctacagGGCCCCCCTGAATGAGGACGTGTT
CACTCCCCCGGCCCCCAGCCCAGCTCCCTCCCTGGACACTGATATCCAGGAGCTGTCAGAGCAGATCCACCGGCTGCTG
CTGCAGgtgagagtagcggagagggagcctgggag**gtgagaaaaggtgtgggaag**

Exon12:**gtgagaaaaggtgtgggaag**cggggtcaagccatctaacctgccctctccctgctgcagCCCGTCCACAGCCCCAGCCCCACGGGACTCTGTGGA
GTCGGCGCCGTGACATCCCCAGGCCCTCTCCACAGCCCTGGGTCCTCCAGTGATAGCAACGGGGGTGATGCAGAGGGG
CCTGGGCCTCCTGCGCCAgtgagtgacctgcttcctacctaccctctaatcgccctttccccctcttctt**cttggaaccagcacttgcag**

Exon13:**cttctcaagctcacatgga**aaaaaacagcaaatgggttgggggtgaaggtcaggggacccccccaggtctgtctcttcacccacacatcatcatcaactcacCAGGGAGGCG
GGGCCGGGACTGAGGCCGGGCCCGAGACTCAATAAAAAGCTGCTGGCCCTGGTGCTTCACCAGATGCACATCCTTACA
GATCTGCTGGAAAGTCACctgtgggacacagcaccacagtgagcagaaccaggggggtgtcgccagtgtcaggggccaagggcacaataaaacaagaaggtaccagtgggga
ggcacagacgccttg**atgggagcaggacaagaag**

Exon14:**tgctgtttttttccatgtgag**ctttagaaggctattttcctctttctctctttgccccagCTACAGGCACGTTCAAGGCCAAGGCCCTTCCCTGCCAATC
CCCAGACCCAGAGCTGGAGGCGGGTTCTGCTCCCGTCCAGGCCCCACTAGCCTTGGTCCCTGAGGAGGCCGAGAGGAA
AGAAGCCTCCAGCTGCTCCTACCAGCAGATCAACTGCCTGGACAGCATCCTCAGgtaaggcctgccaggcatcttctccacctcgggctctaac
cctgcccaccccaagccctgct**ctgatgccctgtgctgtgt**

Exon15:**atgccctgtgctgtgtccat**ccccagGTACCTGGAGAGCTGCAACCTCCCCAGCACCACTAAGCGTAAATGTGCCTCCTCCTCC
TCCTATACCACCTCCTCAGCCTCTGACGACGACAGGCAGAGGACAGGTCCAGTCTCTGTGGGGACCAAGAAAGgtaaagatc
caatgcaccctgctcccactgccccgtcctggcctggtggccctgtgtcttttcccttctgcttctgggccc**tcttgctctgccctgctc**

Exon16:**gatcctctctcctgacttcc**cagtgggggtggggatggtaactggcaccatctctctgcacagATCCGCCGTCAGCAGCGCTGTCTGGGGAGGGGGC
CACCCCACGGAAGGAGCCAGTGGTGGGAGGCACCCTGAGCCCGCTCGCCCTGGCCAATAAGGCGGAGAGTGTGGTGTC
CGTCACCAGTCAGTGTAGCTTCAGCTCCACCATCGTCCATGTGGGAGACAAGAAGCCCCCGGAGTCGGgtatgggtgtggaattg
gggggcag**tgcttgggctccaccggtct**

Exon17:**ccaacaatccagtcctagact**gggcagagggcaggctccaggaggccccaggtggctacCTCGCTCGCCAAGGGCTGAGGGAGCTGTGGAAGA
GCTGTCGAGTCCACGCAGCCTGCCCAGGTCTCGGAAGCGGCTGAGGAAGGCTTGCTCTTCCTTCTGYGTGTGCAGGGAC
AGCACGGCCTTGGTCAGCCCCACTGGACGGTAGGCGTCTGGGGCTGGGTCAGGGGCTACTGTGGGGCTGGGGGCTGGG
CTGGGGGCTGGGCCTGGGGCTAGGCCAGGCAGGTCCTCCATCATGATGATGTctgaggagagtgagatagggaaaggtcatcagaaccacttca
ggggtcaacacatccataccacaccc**tccctgtctgatagcctag**

Exon18a:**tactaaccccaggttgaggt**ccttgctaaccctagtctctccccacagGCTGCCACCACGGCCCCGCACCCCCAAGCCGCCGACACCACTG
CCGATCCAAAGCCAAGCGCTCACGCCACCACCAGAACCCTCGGGCTGAAGCGCCCTGCTATGTCTCACACCCCTCACCC
GTGCCACCCTCCACCCCCTGGCCCACCCCACCAGCCACTACCCCCTTCCCAGCGGTTGTCCAGCCCTACCCTCTCCCAGT
GTTCTCTCCTCGAGGAGGCCCCCAGCCTCTTCCCCCTGCTCCCACATCTGTGCCCCCAGCTGCTTTCCCCGCCCCTTTGG
TGACCCCAATGGTGGCCTTGGTGCTCCCTAACTATCTGTTCCCAACCCCATCCAGCtatccttatggggcactccagaccctgctgaagggcc
tcc**cactcctgcctcgcactc**

Exon18b:**tggtgctccctaactatctgttcc**caaccccatccagcTATCCTTATGGGGCACTCCAGACCCCTGCTGAAGGGCCTCCCACTCCTGC
CTCGCACTCCCCTTCTCCATCCTTGCCCGCCCTCCCCCCGAGGTCCTCCTCACCGCCCGGACTCTCCACTATTCAACTCG
AGATGCAGCTCTCCACTCCAGCTCAATCTGCTGCAGCTGGAGGAGCTTCCCCGTGCTGAGGGGACTGCTGTTGCAGGAG
GCCCTGGGAGCAGTGCCGGGCCCCCACCTCCCAGTGCGGAGGCTGCTGAGCCAGAGGCCAGACTGGtgagcactgacccctgcgt
ctgcctgccagccccccaccccagccccgcccctctgccaccc**tgtgctgcctgctgtctct**

Exon19:**agcagttgaagggaggccta**ggtgctgacccctccatccctccttgccccccctccctcctccagg**CGGAGGTCACTGAGTCCTCCAATCAGGACGC**
ACTTTCCGGCTCCAGTGACCTGCTCGAACTTCTGCTGCAAGAGGACTCGCGCTCCGGCACAGGCTCCGCAGCCTCGGGC
TCCTTGGGCTCTGGCTTGGGCTCTGGGTCTGGTTCAGGCTCCCATGAAGGGGGCAGCACCTCAGCCAGCATCACTCgtgag
taccccgcctccagcatctcccagggtagggcagtgattggggagccgggagcccaggccccg**tcttggcggagcttcctaag**

Exon20:**cttgtgaggtcccaggagt**gggcatgcagccggcctgactcccattggtctgccccccacttcacagGCAGCAGCCAGAGCAGCCACACAAGCAAAT
ACTTTGGCAGCATCGACTCTTCCGAGGCTGAGGCTGGGGCTGCTCGGGGCGGGGCTGAGCCTGGGGACCAGGTGATTA
AGTACGTGCTCCAGGATCCCATTTGGCTGCTCATGGCCAATGCTGACCAGCGCGTCATGATGACCTACCAGGTGCCCTC
CAGgtgaggcatttcagaggccttcttggcc**ttcctttcagaggtagtagtg**

Exon21:**aaagctgtggtagagaaaggaa**tgccagcttcatgggtagtgccccgggtcctggatcccagcctctgccttctgaaccccttcttgggcagGGACATGACCTCTGTG
CTGAAGCAGGATCGGGAGCGGCTCCGAGCCATGCAGAAGCAGCAGCCTCGGTTTTCTGAGGACCAGCGGCGGGAACTG
GGTGCTGTGCACTCCTGGGTCCGGAAGGGCCAACTGCCTCGGGCTCTTGATGTGATGgtgagagaagcctgggacggggagaaaaaagaa
ttgagctcaagttcaaggggg

Exon22:**agttctgagaattgggacata**GgagaagaaagcctctcatggactcctggagatggtcccagaatggagtCTAGCTGGTGCAGTTTCCTGCTGTAGGTA
AGGCTGGACTGGATGAGCTCCTGCCTTCTTCCTCCTCCTCCATAGCCAAGTCCTGAGAGCTTGAAGCCTTGGCCCCGCCT
TGGGCCTCCTCGCAGCCCTCTCCCTCACCACTGCCGCCACCGCTGCTGCCCTGCTCGCCTCCACCCTCTTCCATGGGCTC
CAGCCCCAGTCCATCCAGCTCTGAGAAGAGTGGGTCATCAGGGTGACCAGGATCTTGGGTGCTGCTCCCACAGTCCAC
ACAGGCcttggtgagagaaatggacatgagagagt**tcagacagggttctcactg**

PER2

Exon1:ccttgtgcgtgtgcttgttaatgcgtgacagcatccctctgtttgccagcttcgttccagagcccagcATGAATGGATACGCGGAATTTCCGCCCAGCCCC
AGTAACCCCACCAAGGAGCCCGTGGAGCCCCAGCCCAGCCAGGTCCCACTGCAGGAAGATGTGGACATGAGCAGTGG
CTCCAGTGGACATGAGACCAACGAAAACTGCTCCACGGGGCGGGACTCGCAGGGCAGTGACTGTGACGACAGTGGGA
AGGAGCTGGGGATGCTGGTGGAGCCACCGGATGCCCGCCAGAGgtgagttcagcctctggccagatggaggctgggcaggttgttttctcagtggctcatt
tctgctgtgatttgattgcttttgcaatctttaaatcatgattaccaagtttttcaag

Exon2:ttttctgatgtctgaaggtttatattccagttttatcttaaccttgtatttttaaaaaattgtcttaccatggtattatctagcctgttatcactggtaggatggcaggggaagatgtgtctggagc
atacaattgtctaaattttgcttttatttttttgttttcatagTCCAGATACCTTTAGCCTGATGATGGCAAAATCTGAACACAACCCATCTACAAGTGG
CTGCAGgtaaggccaattagaacttcatacatagaggttttagagaaattgaaagacttcttattggaggttagttttctgggagtgacgtggctttttttaagctgtgctaaaacccatctgtgtggct
atgtgggtacgaacccagcctcactctggcctttcagacac

Exon3:tgggcaagaggcacgtttctttcaggaaaggacacctaggaagctaacatttggctgcctctttcttgaatcctgcagTAGCGACCAGTCTTCGAAAGTGGACAC
ACACAAAGAACTGATAAAAACACTAAAGGAGCTGAAGGTCCACCTCCCTGCAGACAAGAAGGCCAAGGGCAAGGCCA
GTACGCTGGCCACCTTGAAGTACGCCCTCAGGAGCGTGAAGCAGGTGAAAGgtacgtcggcctcgcacatctgctccaaacctatagaaatatgttt
taaatccccccaaattatagcttggattgtgttgactttctaaaactcgaggctcatcgc

Exon4:gtaagagctagtgactgtctccggccaagcgctgggttctgcccactgagtgaacactgtctctcctgcagCCAATGAAGAGTATTACCAGCTGCTGATGT
CCAGCGAGGGTCACCCCTGTGGAGCAGACGTGCCCTCCTACACCGTGGAGGAGATGGAGAGCGTTACCTCTGAGCACA
TTGTGAAGAATGCCgtaagcctctttccgcaaagtttctttctaaaatggcaggagttcctc

Exon5:gtccgacaccatctgacctttgtcatcagagcccgactcttccttttcagGATATGTTTGCGGTGGCCGTGTCCCTGGTGTCTGGGAAGATCCTG
TACATCTCTGACCAGGTTGCATCCATATTTCACTGTAAAAGAGATGCCTTCAGCGATGCCAAGTTTGTGGAGTTCCTGG
CGCCTCACGATGTGGGCGTGTTCCACAGTTTCACCTCCCCGTACAAGCTTCCCTTGTGGAGCATGTGCAGTGGAGCAGgt
gcagtggagcaggtgagtatatcgaggtggtgccttgttccctctggggtcgggaaaggggccaggagctgggcccaacccagatgtggtgcaggcgccctgcctcacctttcagagcc

Exon6:gtttcaccttgaatcttgcttgattctgctgctcctcttttgtttgtgagaaatgaggaacactgtatttagttgttggtttggatgaatgactttgggctctctcttttagATTCTTTTACT
CAAGAATGCATGGAGGAGAAATCTTTCTTTTGCCGTGTCAGgtaagcctggttcccagttttcttaaattagaaaaccgtataaacatttcaccccagcactggtc

Exon7:agggaacagaacaggggactgttcctgtgtcacagttcccaacttagagcgaggctcttcaccgcagTGTCCGGAAAAGCCACGAGAATGAAATCCGC
TACCACCCCTTCCGCATGACGCCCTACCTGGTCAAGGTGCGGGACCAACAAGGTGCTGAGAGTCAGCTTTGCTGCCTTC
TGCTGGCAGAGAGAGTGCACTCTGGTTATGAAGgtaacagccaagcccagggcgagggcagatgttgtctctggctccccctcagttactcctgtggttc

Exon8:tacagggtgttttctggtagtttaatataacatcaaatatgcatttcttaggatcacaaatgtgtgcaatattctgttctttcagCCCCTAGAATTCCTCCTGAAAAGAG
AATTTTTACAACCACCCATACACCAAATTGTTTGTTCCAGGATGTGGATGAAAGgtacgtggtcttgacccacccccttttttcatgtttttgatataaa
agctatttagccaaagccaagactgcatcttggttttataatttacatgataatggacaaaaacatg

Exon9:ggttcttagtgacaatctcctcatctgtttggatgccaatcctagcgtgtgtctgcttgccttccagGGCGGTCCCTCTCCTGGGCTACCTACCTCAGGACC
TGATTGAAACCCCAGTGCTCGTGCAGCTCCACCCTAGTGACAGGCCCTTGATGCTGGCCATCCACAAAAAGAgtaggtcccctt
ttcatggtacatcctgaagtgtttggcggaagttcctgtgtccttggggctgcttcttgggaccagtctagctc

Exon10:ctgagtgactcttgacttgtctctctctactataaatcctgtttgctccccttttccccctgaatgctggcttttgctctcctagTCCTGCAGTCAGGCGGGCAGCCTTTC
GACTATTCTCCCATTCGGTTTCGCGCCCGGAACGGAGAGTACATCACGTTGGACACCAGCTGGTCCAGCTTCATCAACC
CATGGAGCAGGAAAATCTCCTTCATCATTGGGAGGCACAAAGTCAGGGTgtgagtgctccaagggcccgaggtggctcaggggtcttgggcggg
ggtctcgggctgtcctcacctcccagcaacagatggcataggga

Exon11:gctatacagtcacgccagagaggtcctcctgtggggccccatctaacaagatgaattaaaaccacgcagGGGCCCTTTGAATGAGGACGTGTTTGCAGC
CCACCCCTGCACAGAGGAGAAGGCCCTGCACCCCAGCATTCAGGAGCTCACAGAGCAGATCCACCGGCTCCTGCTGCA
Ggtgggtgtggtgcctgcatgtcctcctcccaggtagc

Exon12:cgaaacagggtgtgttggcaggggccacatgcatagctcagcagCCCGTCCCCCACAGCGGCTCCAGTGGCTACGGGAGTCTGGGCAG
CAACGGGTCCCACGAGCACCTTATGAGCCAGACCTCCTCCAGCGACAGCAACGGCCATGAGGACTCACGCCGGAGGAG
AGCCgtacgtctccttccattctccctgagaaaatgagtttgtggatgtccctccagagttaaaaagcacactcaagacaacctttt

Exon13:**tcctctgttctcactttgcc**ggacagactgaaggaggtctcctagaatgaataatgtgttcattttgtttttcttcaagGAAATTTGTAAAAATGGTAACAAGACC
AAAAATAGAAGTCATTATTCTCATGAATCTGGAGAACAAAAGAAAAAATCCGTTACAGgtaaaaaaaaaaatattcaacatttccttactgaa
actagagtatggccacatgagaagagggaacctgggttaaatgctgactctggctggcagggagtctaccttgtagccgtg

Exon14:**cctgtcttcaggtagaacga**aaatgctttgtaaatacacagcgttttctgtgggagaaaaatgaatgaaagaacaattttgccattccttcagAAATGCAAACTAATCCC
CCAGCTGAGAAGAAAGCTGTCCCTGCCATGGAAAAGGACAGCCTGGGGGTCAGCTTCCCCGAGGAGTTGGCCTGCAAG
AACCAGCCCACCTGCTCCTACCAGCAGATCAGCTGCTTGGACAGCGTCATCAGgtatgccggcatttccagccgagtctccaccatctcacacac
cttccctcctgtcatgttgtgtggccttaccagtggttcatgcctttcacacaggtac

Exon15:**ccatctcacacaccttccct**cctctcatgttgtgtggcctcaccagtggttcatgcctttcacacagGTACTTGGAGAGCTGCAATGAGGCTGCCACCCT
GAAGAGGAAATGCGAGTTCCCAGCAAACGTCCCAGCGCTAAGGTCCAGTGATAAGCGGAAGGCCACAGTCAGCCCAG
GGCCACACGCTGGAGgtatctaatctgtgtagagccatgtacatgtgaaataatgtaaatcctctggagtagagtcagacgtccc**catggcttctgtggacacag**

Exon16:**gggtgtcggtttctcatctg**cacagtgcattgtaatgacacactaatgtttgttccccttcctctcatgaagAGGCAGAGCCGCCCTCCAGGGTGAACAGCC
GCACGGGAGTAGGTACGCACCTGACCTCGCTGGCACTGCCGGGCAAGGCAGAGAGTGTGGCGTCGCTCACCAGCCAGT
GCAGCTACAGCAGCACCATCGTCCATGTGGGAGACAAGAAGCCGCAGCCGGAGTTAGgtatgactatgggctcttggatcagagagcagttt
gatttttaaccatgaaaacaagaagtttgccatcttaaatttt**ctaagtgcagaagaactcc**

Exon17:**gaatgatttgtcttgttcgtg**aatatagtgtggccttaaaataataaacagggcacgtgtggaccagagccctgggttcttgtgttacAGATGGTGGAAGATGCTGCG
AGTGGGCCAGAATCCCTGGACTGCCTGGCGGGCCCTGCCCTGGCCTGTGGTCTCAGCCAAGAGAAGGAGCCCTTCAAG
AAGCTGGGCCTCACCAAGGAGGTACTCGCTGCACACACACAGAAGGAGGAGCAGAGCTTCCTGCAGAAGTTCAAAGA
AATAAGAAAACTCAGCATTTTCCAGTCCCACTGCCATTACTACTTGCAAGAAAGATCCAAGGGGCAGCCAAGTGAACG
AAgtaagtgatacccgaattaaaagtgcgttttaaaaaactttattcctgtt**tggtactgagtccagtgctg**

Exon18A:**ccaggactgttgaagcaaga**ggtgtcttcaaatttggagttaaaattttaactccgagtatttctttttctgcattagCTGCCCCTGGACTAAGAAATACTTCCG
GAATAGATTCACCTTGGAAAAAAACAGGAAAGAACAGAAAATTGAAGTCCAAGCGGGTCAAACCTCGAGACTCATCT
GAGAGCACCGGATCTGGGGGGCCCGTGTCCGCCCGGCCCCCGCTGGTGGGCTTGAACGCCACAGCCTGGTCACCCTCA
GACACGTCCCAGTCCAGCTGCCCAGCCGTGCCCTTTCCCGCCCCAGTGCCAGCAGCTTATTCACTGCCCGTGTTTCCAGC
GCCAGGGACTGTGGCAGCACCCCCGGCACCTCCCCACGCCAGCTTCACAGTGCCTGCTGTGCCCGTGGACCTCCAGCAC
CAGTTTGCAGTCCAGCCCCCACCTTTCCCTGCCCCTTTGGCGCCTGTCATGGCATTCATGCTACCCAGTTATTCCTTCCCC
TCGGGGACCCCAAACCTGCCCCAGGCCTTCTTCCCC**agccagcctcagtttccgag**

Exon18B:**cctgtcatggcattcatgct**ACCCAGTTATTCCTTCCCCTCGGGGACCCCAAACCTGCCCCAGGCCTTCTTCCCCAGCCAG
CCTCAGTTTCCGAGCCACCCCACACTCACATCCGAGATGGCCTCTGCCTCACAGCCTGAGTTCCCCAGCCGGACCTCGA
TCCCCAGACAGCCATGTGCTTGTCCAGCCACCCGGGCCACCCCACCATCGGCCATGGGTAGGGCCTCCCCACCGCTCTT
TCAGTCCCGCAGCAGCTCGCCCCTGCAGCTCAACCTGCTGCAGCTGGAGGAAGCCCCTGAGGGTGGCACTGGAGCCAT
GGGGACCACAGGGGCCACAGAGACAGCAGCTGTAGGGGCGGACTGCAAACCTGGCACTTCTCGGGACCAGCAGCCGA
AGGCGCCTCTGACCgtaaggattttctgatgctctttccccaaagcaggcagcaaacagcacacctggcaggccggccgc**acatcctcagttcagacatg**

Exon19:**tatagctgtgtcctgactgag**cccctgaacagcagtatctgcttcctgtccctaaagCGTGATGAACCCTCAGACACACAGAACAGTGACGCCCT
TTCCACGTCAAGCGGCCTCCTAAACCTCCTGCTGAATGAGGACCTCTGCTCAGCCTCGGGCTCTGCTGCTTCGGAGTCTC
TGGGCTCCGGCTCACTGGGCTGCGACGCCTCCCCGAGTGGGGCAGgtatgttggccctggcggggtgttaggcacttgggaggttcctgcagg**atgcac
tgctccagagtcac**

Exon20:**gaggaagcacattatgcaag**gtttaatttcatatgtcaatgttttgacgcaccacgttttttgtttttaaagGCAGTAGTGACACAAGTCATACCAGCAAATA
TTTTGGAAGCATTGACTCCTCAGAGAATAATCACAAAGCAAAAATGAACACTGGTATGGAAGAAAGTGAGCATTTCAT
TAAGTGCGTCCTGCAGGATCCCATCTGGCTGCTGATGGCAGATGCGGACAGCAGCGTCATGATGACGTACCAGCTGCCT
TCCCGgtaaccacccagcgttttcctaggcacctggggagggatggggttcaggagctcccagaaa**caacaaggtcaaggtcattc**

Exon21:**catctaaaactacattattctgaa**agaataaaaatagataccttaagacatttgaaagcttaccgatttctaaatatcttgcgaagAAATTTAGAAGCGGTTTTGAA
GGAGGACAGAGAGAAGCTGAAGCTCCTACAGAAACTCCAGCCAGGTTCACGGAGAGTCAGAAGCAGGAGCTGCGCGA
GGTCCACCAGTGGATGCAGACGGGCGGCCTGCCCGCAGCCATCGACGTGGCAgtaagctcacgggactcgatttctgatatggccctaaa**aggct
ctgtgatggggatt**

Exon22:**ggccaatttgaatgacttttgt**AacaactcagatctcaagtttgttactgatttctctttttttttctttaagGAATGTGTTTACTGTGAAAACAAGGAAAAAG
GTAATATTTGCATACCATATGAGGAAGATATTCCTTCTCTGGGACTCAGCGAAGTGTCGGACACCAAAGAAGACGAAA
ATGGATCCCCCTTGAATCACAGGATCGAAGAGCAGACGTAACCCCTGCCCCACCTCAGCCCGGCAGCCAGCG**AGGTAC**
ACCAGGTGGTGCTT

PER3

Exon1:**caaagtgagcgagaagcagg**ctgcgggccgtcccagcacgacgtggagccccgcggagacctcgagATGCCCCGCGGGGAAGCTCCTGGCCCCGGG
AGACGGGGGGCTAAGGACGAGGCCCTGGGCGAAGAATCGGGGGAGCGGTGGAGCCCCGAGTTCCATCTGCAGAGGAA
ATTGGCGGACAGCAGCCACAGgtgacgcgctggcttcaggccgagggccc**catgcgttcgttgtccttcc**

Exon2:**gtgttccctaagccgcaag**atgctgttgtcttcagaggatgaagttgtaatttttttttatcttccagTGAACAGCAAGATCGAAACAGAGTTTCTGAAGAA
CTTATCATGGTTGTCCAAGAAATGAAAAAATACTTCCCCTCGGAGAGACGCAATAAACCAAGCACTCTAGATGCCCTCA
ACTATGCTCTCCGCTGTGTCCACAGCGTTCAAGgtaaacaagccggagagaaatttcatcctacgaatgcaccaggactcata**caagcagccagaggagtg**

Exon3:**ccagcttgatagtgatgaaat**ggtttcctaaagatactgttgtcactggactacctgtttatctccctgtgtttcttagCAAACAGTGAGTTTTTCCAGATTCTCAG
TCAGAATGGAGCACCTCAGGCAGATGTGAGCATGTACAGTCTTGAGGAGCTGGCCACTATCGCTTCAGAACACACTTCC
AAAAACACAgtaagaattcatgcattttgccatatcaac**ctgggtgacttttcctaagg**

Exon4:**:cctttcagggaatattgctag**tgagtatctcaatatttgcatttattttaaatgtttttcatagGATACCTTTGTGGCAGTATTTTCATTTCTGTCTGGAAGG
TTAGTGCACATTTCTGAACAGGCTGCTTTGATCCTGAATCGTAAGAAAGATGTCCTGGCGTCTTCTCACTTTGTTGACCT
GCTTGCACCTCAAGACATGAGGGTATTCTACGCGCACACTGCCAGAGCTCAGCTTCCTTTCTGGAACAACTGGACCCAA
AGAgtaacaggaccaatgttcagatgtctatctttcctcatcaagatcagtttcattcttacaggaatagtacagaaattaacatattatttagaacatgcacactatctggttttt**cttattcctgttatag**
aaagtca

Exon5:**cactgagaaagacctggata**agagggagtgactgaccaggcatctttctttctagGCTGCACGGTATGAATGTGCTCCGGTGAAACCTTTTTTCT
GCAGGATCCGgtaagtatagtggctcg**tggaagccagcaacagtgga**

Exon6:**cccagccttgtttcgcc**atgggccagtagggtgcgtcaggaccagcactaatatctttaatctcctcagtGGAGGTGAAGACAGAAAGCAAGAGAAGTGTC
ACTCCCCATTCCGGATCATCCCCTATCTGATTCATGTACATCACCCTGCCCAGCCAGAATTGGAATCGGAACCTTGCTGT
CTCACTGTGGTTGAAAAGATTCACTCTGGTTATGAAGgtaagtcagtagataagatgcagaaatgtcagcaatcag**ataggaacatgggaaagtctg**

Exon7:**agtggttagttaggtgg**ataattaattagatatttgcctttaaatgggtctttgtttttttttccttagCTCCTCGGATCCCAGTGAATAAAAGAATCTTCACCA
CCACACACACCCCAGGGTGTGTTTTTCTTGAAGTAGATGAAAAgtaagtacttctttaagcctaaaagaaatttgtttctgaaaataaatataaatgtgaagaa
gattacattatgttt**gcatgtttatacattatgtaattg**

Exon8:**gaattacctgatgagtatgcc**acctgtgttgtgtatctgtatcccagAGCAGTGCCTTTGCTGGGTTACCTACCTCAGGACCTGATTGGAACA
TCGATCCTAAGCTACCTGCACCCTGAAGATCGTTCTCTGATGGTTGCCATACACCAAAAAGgtcaggacctactcctttataggaggaaat
atttttctctcattgatttgttctaatttttctttttcatctcatta**gagcgcaacctttaaccaga**

Exon9:**ggcaacagagcgagactcaatctc**aaaaaaaaccactaaaacatttacaaataaatggcttaaaaaggacatttgtaatcagtatctgtgttaagtaaatcctatttttgtcttattattttatata
gTTTTGAAGTATGCAGGGCATCCTCCCTTTGAACATTCTCCCATTCGATTTTGTACTCAAAACGGAGACTACATCATACT
GGATTCCAGTTGGTCCAGCTTTGTGAATCCCTGGAGCCGGAAGATTTCTTTCATCATTGGTCGGCATAAAGTTCGAACgta
agccagtcagttttcatattttctaaaacatctcttgtatcaaataata**ttccttagcttattgactgcc**

Exon10:**:tgtttgactcagtctctcac**tgggcattttctagGAGCCCACTAAATGAGGATGTTTTTGCTACCAAAATTAAAAAGATGAACGATA
ATGACAAAGACATAACAGAATTACAAGAACAAATTTACAAACTTCTCTTACAGgtaaggtgagattgttaaaaat**gcaaagttccctgaattgt**
g

Exon11:**:ttcgtgtcagcatcagcatt**aaaagtaccaacctgcacacacctaatttagtatttcaggaattgtcatcttaatttttacatgattctagatgagctctgcggtggctgcatttgaacaccca
gcaattctggacttgttcctctttgtccttccagCCAGTTCACGTGAGCGTGTCCAGCGGCTACGGGAGCCTGGGGAGCAGCGGGTCGCAGGA
GCAGCTTGTCAGCATCGCCTCCTCCAGTGAGGCCAGTGGGCACCGTGTGGAGGAGACGAAGGCGGAGCAGgtgcatgggctta
tgtcacattcttatacaggcatcgtgttttctgtactacctcggttctgaatgtggtgacatcttagtatatattcctgactt**gaagacctcaactgataacag**

Exon12:**attagcatattgtgaacagattta**tttagaatttgttggtaccagtatactgtggcatggtgcaggaaactggattaaagtgattactgtgcttcagtcattatatcttcaaagaaacagaag
ctaagtgtattttgtttatgtatcttttagtggacatttttataatttttgaaacatattttatcattcctttccctaagATGACCTTGCAGCAGGTCTATGCCAGTGTGAACAAA
ATTAAAAATCTGGGTCAGCAGCTCTACATTGAGTCAATGACCAAATCATCATTCAAGCCAGTGACGGGGACACGCACA
GAACCGAATGGTGGTGGTGAGgtgagtcagcgaatggtggtggtgagtcagccggcagccccaaggatctccttccatgggctgtcac**tctctgcatagacgtcatgta**

Exon13:**tatatacatgataaagtgccatg**atttaattttggtaagaaagtatatgttcttaattacatgctgggtacttttaattgcacatccctttattctgtttcagAATGTAAGACCTTTA
CTTCCTTCCACCAAACACTGAAAAACAATAGTGTGTACACTGAGCCCTGTGAGGATTTGAGGAACGATGAGCACAGCC
CATCCTATCAACAGATCAACTGTATCGACAGTGTCATCAGgtatgagaccgcaagtttggataccatgtaagtctgttccggaag**catacactgccactgtag
ag**

Exon14:**agcaaagaggtgggaaatgg**cacaattagggaacaggtaagaatgtgtggcctaattatgttgttacagATACCTGAAGAGCTACAACATTCCAGCTTT
GAAAAGAAAGTGTATCTCCTGTACAAATACAACTTCTTCCTCCTCAGAAGAAGACAAACAGAACCACAAGGCAGATGA
TGTCCAAGCCTTACAAGGtaacaagaatgcccctcagagttaaattcaaagaactgtaaatacatccttcttgtttctctttaatgtcttatattgttataagcataaaattctggttt**catatt
acctctttatgacagta**

Exon15:**aatttctcagttacaaacttctg**taaactgggtcttttatgtaaatttctcgttgggaatttttcttttcactgtcagtttctcttacaccaccagCTGGTTTGCAAATCCCAGC
CATACCTAAATCAGAAATGCCAACAAATGGACGGTCCATAGACACAGGAGGAGGAGCTCCACAGATCCTGTCCACGGC
GATGCTGAGCTTGGGGTCGGGCATAAGCCAATGCGGTTACAGCAGCACCATTGTCCATGTCCCACCCCCAGAGACAGgt
accacactcgcctcttactttgaaaatatactcaactttaactacattgtgatgagaaaacaaaagt**catgaataccattcgctcgg**

Exon16:**aagatttttcgtattccagcag**ttataataatgtttgtaaaaatgtatcaaaaggcagttaacaaagtaaaataaatacaaataattgataggaattaaaattaaatatgtcttcttccacctca
gCCAGGGATGCTACCCTCTTCTGTGAGCCCTGGACCCTGAACATGCAGCCAGCCCCTTTGACCTCGGAAGAATTTAAAC
ACGTGGGGCTCACAGCGGCTGTTCTGTCAGCGCACACCCAGAAGGAAGAGCAGAATTATGTTGATAAATTCCGAGAAA
AGATCCTGTCATCACCCTACAGCTCCTATCTTCAGCAAGAAAGCAGGAGCAAAGCTAAATATTCATATTTTCAAGgtacgta
atttttttaaaaataaatgccattaatctatgtaaatgttacaaa**ctgtatctaaggactaggaga**

Exon17a:**gtcattctggtagtattggca**aatgctcattcgtcagctacttataactacctgtaagtggcatccttctcttctttttgggtttaattttccataatttgcctctacctttatccttccagGAG
ATTCTACTTCCAAGCAGACGCGGTCGGCCGGCTGCAGGAAAGGGAAGCACAAGCGGAAGAAGCTGCCGGAGCCGCCA
GACAGCAGCAGCTCGAACACCGGCTCTGGTCCCCGCAGGGGAGCGCATCAGAACGCACAGCCCTGCTGCCCCTCCGCG
GCCTCCTCTCCGCACACCTCGAGCCCGACCTTCCCACCTGCCGCCATGGTGCCCAGCCAGGCCCCTTACCTCGTCCCAG
CTTTTCCCCTCCCAGCCGCGACCTCACCCGGAAGAGAATACGCAGCCCCCGGAACTGCACCGGAAGGCCTGCATGGGC
TGCCCTTGTCCGAGGGC**TTGCAGCCTTACCCAGCTTT**

Exon17b:**ttgcagccttacccagcttt**CCCTTTTCCTTACTTGGATACTTTTATGACCGTTTTCCTGCCTGACCCCCCTGTCTGTCCTCT
GTTGTCGCCATCGTTTTTGCCATGTCCATTCCTGGGGGCGACAGCCTCTTCTGCGATATCACCCTCAATGTCGTCAGCAA
TGAGTCCAACTCTGGACCCACCCCCTTCAGTCACCAGCCAAAGGAGAGAGGAGGAAAAGTGGGAGGCACAAAGCGAG
GGGCACCCGTTCATTACTTCGAGAAGCAGCTCACCCTTGCAGTTAAACTTACTTCAGGAAGAGATGCCCAGACCCTCTG
AATCTCCAGATCAGATGAGAAGGAACACGTGCCCACAAACTGAGTATgtaagtgatgctcattttcaacactcaagtgagaaagtgaatatcttactaa**a
gttaaggtggttgcgttgg**

Exon18:**aaaaccatgaataaaggcggac**tactgtattttgtgataagaagattaaagtgtcttttcatgtgcccttactttctagcagTGTGTTACAGGCAACAATGGCAGT
GAGAGCAGTCCTGCTACTACCGGTGCACTGTCCACGGGGTCACCTCCCAGGGAGAATCCATCCCATCCTACTGCCAGCG
CTCTGTCCACAGGATCGCCTCCCATGAAGAATCCATCCCATCCTACTGCCAGCGCTCTGTCCACAGGATCGCCTCCCAT
GAAGAATCCATCCCATCCTACTGCCAGCACACTGTCCATGGGATTGCCTCCCAGCAGGACTCCATCCCATCCTACTGCC
ACTGTTCTGTCCACGGGGTCACCTCCCAGCGAATCCCCATCCAGAACTGGTTCAGCAGCATCAGgtagtggatcaggacaactaatgtt
tcaaactccaatgccagacattcac**tatgtgctgagctctcactg**

Exon19:**ctgaagaatgagagccagttt**ggcaaatcagtcggacaggtcttttctaattatgtgttgttgatttttgacagGAAGCAGCGACAGCAGTATATACCTTACT
AGTAGTGTTTATTCTTCTAAAATCTCCCAAAATGGGCAGCAATCTCAGGACGTACAGAAAAAAGAAACATTTCCTAATG
TCGCCGAAGAGCCCATCTGGAGAATGATACGGCAGACACCTGAGCGCATTCTCATGACATACCAGGTACCTGAGAGgtaa
gaaagcactttagaaaacccacttttatatttttgtggtttctttttttctttttttctttttt**gagacggagtctcgccct**

Exon20:**gaagtgctattcctagatgac**gggaaaagaaccctgtgtcttattcaggactattaagattctgtttgtttgttttcagGGTTAAAGAAGTTGTACTAAAAGAAG
ACCTGGAAAAGCTAGAAAGTATGAGGCAGCAGCAGCCCCAGTTTTCTCATGGGCAAAAGGAGGAGCTGGCTAAGGTGT
ATAATTGGATTCAAAGCCAGACTGTCACTCAAGAAATCGACATTCAAgtaagcacagtaataatggctgtcatatactcatgtattttggccaggtagtg
cttttaatata**ggtcgtgttcttgcatgatc**

Exon21:**ttagaaacatgtgaccagcctt**ttactgttttaaaactctttaggtgacattgacatcaagtaactcgcctgctttgttctttttggagGCCTGTGTCACTTGTGAAAATG
AAGATTCAGCTGATGGTGCGGCCACATCCTGTGGTCAGGTTCTGGTAGAAGACAGCTGTTGAgtgactgtgaggatgaaccttcataccc
tttccaag**acgtgttacacagacagacc**