

https://doi.org/10.1093/sleep/zsad063 Advance access publication 10 March 2023 Research Letter

Research Letter

Novel CLOCK and NR1D2 variants in 64 sighted Japanese individuals with non-24-hour sleep–wake rhythm disorder

Akiko Hida^{1,*}, Aritoshi Iida^{2,}, Motoki Ukai¹, Hiroshi Kadotani^{3,}, Makoto Uchiyama⁴, Takashi Ebisawa⁵, Yuichi Inoue^{6,}, Shingo Kitamura^{1,} and Kazuo Mishima^{1,7,*},

¹Department of Sleep-Wake Disorders, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan,

²Department of Clinical Genome Analysis, Medical Genome Center, National Center of Neurology and Psychiatry, Tokyo, Japan,

³Department of Psychiatry, Shiga University of Medical Science, Shiga, Japan,

⁴Department of Psychiatry, Nihon University School of Medicine, Tokyo, Japan,

⁵Department of Psychiatry, Tokyo Metropolitan Police Hospital, Tokyo, Japan,

⁶Department of Somnology, Tokyo Medical University, Tokyo, Japan and

⁷Department of Neuropsychiatry, Akita University Graduate School of Medicine, Akita, Japan

*Corresponding author. Akiko Hida, Department of Sleep-Wake Disorders, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8553, Japan. Email: hida@ncnp.go.jp, Kazuo Mishima, Department of Neuropsychiatry, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita, Akita 010-8543, Japan. Email: mishima@med.akita-u.ac.jp.

Circadian rhythm sleep-wake disorders (CRSWDs) are characterized by an inability to fall asleep and awaken at desired times. A subtype of CRSWDs, non-24-hour sleep-wake rhythm disorder (N24SWD), exhibits a free-running pattern of sleep-wake cycles that are not synchronized with the external 24-hour day. N24SWD occurs commonly in visually impaired individuals and rarely in sighted individuals. We have shown that the intrinsic circadian period (τ) determined under a forced desynchrony protocol is longer in sighted individuals with N24SWD than intermediate-type controls [1]. Therefore, it appears that prolonged τ and/ or impaired entrainment mechanisms contribute to the pathogenesis of N24SWD. Some clock gene variants are associated with CRSWDs and transgenic animals carrying human clock variants exhibit altered τ [2]. These findings suggest that clock gene variants might disrupt the circadian clock system and lead to the onset of CRSWDs.

The study population consisted of 64 participants with N24SWD (45 males and 19 females; mean \pm SD age: 27.7 \pm 9.61 years). Most of the participants were examined in our previous studies [1, 3]. They were all unrelated and sighted Japanese. They were diagnosed by trained psychiatrists according to the International Classification of Sleep Disorders' second edition. This study was approved by the Ethics Committee of National Center of Neurology and Psychiatry and was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from each participant. DNA samples were extracted from the participants' blood samples using the QIAamp DNA Blood Mini Kit (QIAGEN). Targeted sequencing of 76 genes was performed in 17 individuals with N24SWD (11 males and six females; mean \pm SD age: 32.82 \pm 10.05 years) using next-generation

sequencing by RIKEN GENESIS (RIKEN GENESIS CO., LTD.). Briefly, DNA samples were captured using the SureSelect DNA Capture Custom Kit (Agilent Technologies) and sequenced on the MiSeq system (Illumina) with 151 bp paired-end reads. The reads were aligned to a human reference sequence (University of California Santa Cruz assembly GRCh37/hg19). The 76 genes examined in this study are listed in Supplementary Table 1. Sanger sequencing was performed using BigDye™ Terminator v1.1 Ready Reaction Mix (ThermoFisher Scientific) and an ABI Prism 3130 DNA Analyzer (Applied Biosystems). All primers were designed by Primer3Plus. The possible impact of amino acid substitutions on protein function was tested by Polyphen-2 and PROVEAN (Protein Variation Effect Analyzer).

In this study, we performed targeted sequencing of 76 genes by next-generation sequencing in 17 N24SWD individuals and found a total of 94 variants (Supplementary Table 2). A novel missense variant was initially found in each of the APOE (apolipoprotein E), CLOCK (CLOCK), NR1D2 (nuclear receptor subfamily 1 group D member 2), and PER1 genes The NR1D2 (PERIOD1) and PER1 missense variants were found in an individual with N24SWD. These four variants were further evaluated by public databases, the Genome Aggregation Database, 1000 Genomes and Human Genetic Variation Database, and the Japanese Whole Genome Reference Panel 8.3KJPN. The APOE and CLOCK variants (designated as rs1969838696 and rs1723064872, respectively) were recently observed as rare variants in 8.3KJPN (alternative allele frequency = 0.00012), while the NR1D2 and PER1 variants were not found in any database. Previous studies using animal models have suggested that Clock and REV-ERBβ (NR1D2) are involved in some mechanisms that regulate circadian rhythms and

© Sleep Research Society 2023. Published by Oxford University Press on behalf of the Sleep Research Society.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons. org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com sleep–wakefulness [2, 4, 5]. In contrast, APOE-deficient and Per1null mice show a robust behavioral rhythm comparable to that of WT mice [6, 7]. Therefore, our initial focus was on the CLOCK and NR1D2 genes, which have been implicated as core components of negative transcriptional feedback loops regulating multiple clock genes in the circadian clock system [2, 4, 5]. We subsequently performed Sanger sequencing on the coding regions of CLOCK and NR1D2 in a total of 64 N24SWD individuals, including 17 N24SWD individuals.

One novel and four known CLOCK variants were identified in our study population of 64 N24SWD individuals (Supplementary Table 3). A novel variant in exon 18 was identified in one of the additional 47 N24SWD individuals (NM_004898.3: c.1488C>G: p.Q[Gln]496H[His]) (Figure 1A). The amino acids Q and H differ in isoelectric point and the Q496H substitution is predicted to be possibly damaging (0.887) by Polyphen-2 and deleterious (-2.854) by PROVEAN. The Q496H substitution occurs in the domain that potentially associates with SIRT1, a NAD+-dependent histone deacetylase. SIRT1 is recruited to the CLOCK:BMAL1 chromatin complex and regulates target gene transcription by modulating the histone acetyltransferase function of CLOCK [8]. The Q496H substitution could alter the binding interaction between CLOCK and SIRT1 thereby disrupting chromatin remodeling. The known variant in exon 22 (rs1723064872) causes the amino acid substitution of glutamine to glutamate (NM_004898.3: c.2278C>G: p.Q[Gln]760E[Glu]). The amino acids Q and E differ in isoelectric point, although the Q760E substitution is predicted to be benign (0.033) by Polyphen-2 and neutral (-1.289) by PROVEAN. The Q760E substitution is located in the poly-Q region of the C-terminal domain. The Q-rich motif is known to characterize the activation domain of transcription factors. Furthermore, Clock mutant mice show a longer period of behavioral rhythms than wild-type mice. The genetic variant carried by Clock mutants results in exon skipping and a deletion of 51 amino acids within the CLOCK transactivation domain [4]. Notably, the missense variants in the potentially functional domains of CLOCK were identified in two N24SWD individuals. These CLOCK missense variants might contribute to the N24SWD phenotype.

One novel and eight known NR1D variants were identified in our study population of 64 N24SWD individuals (Supplementary Table 3). The novel variant in exon 2 causes an amino acid substitution of glycine to serine (NM_005126.4: c.274G>A: p.G[Gly]92S[Ser]) (Figure 1B). The amino acids G and S differ in polarity, although the G92S substitution is predicted to be benign (0.011) by Polyphen-2

and neutral (-1.094) by PROVEAN. A known variant in exon 5 (rs139583758) causes the amino acid substitution of glutamine to histidine (NM_005126.4: c.696A>C: p.Q[Gln]232H[His]). The amino acids Q and H differ in isoelectric point and the Q232H substitution is predicted to be possibly damaging (0.925) by Polyphen-2 and be deleterious (-2.518) by PROVEAN. Another known variant in exon 7 (rs78292562) causes the amino acid substitution of alanine to threonine (NM_005126.4: c.1351G>A: p.A[Ala]451T[Thr]). Amino acids A and T differ in polarity. Furthermore, the A451T substitution is predicted to be probably damaging (0.995) by Polyphen-2 and deleterious (-3.157) by PROVEAN. The A451T substitution occurs in the potential ligand-binding domain of NR1D2. Heme binds to the ligand-binding domain and modulates the ability of NR1D2 to recruit the corepressor and repress target gene transcription [9]. NR1D1 (REV-ERBa) and NR1D2 (REV- $ERB\beta$) regulate sleep architecture and emotional behavior in mice [5]. REV-ERB agonists induce wakefulness and reduce rapid eye movement and slow-wave sleep. Intriguingly, a pharmacological study in REV-ERBB-deficient mice suggests that REV-ERBB modulates the maintenance of wakefulness during the activity period [10]. These NR1D2 missense variants could alter the function of NR1D2, resulting in impaired sleep regulation. Also, the novel PER1 variant was found in the N24SWD individual carrying the novel NR1D2 variant in exon 2. The PER1 variant in exon 10 (NM_002616.2: c.1198G>A: p.E[Glu]400K[Lys]) was confirmed by Sanger sequencing in the N24SWD individual (Figure 1C).

Further analysis is required to demonstrate that these variants contribute to the N24SWD phenotype. However, our findings will provide potential genetic factors associated with the N24SWD phenotype and expand the current understanding of circadian and sleep regulation in humans.

Supplementary Material

Supplementary material is available at SLEEP online.

Funding

This study was supported by the Japan Society for the Promotion of Science (JSPS) under grant numbers 18K07580 and 16H05381, the Japan Agency for Medical Research and Development (AMED) under grant number JP21dk0307103, Joint Usage and Joint Research Programs, the Institute of Advanced Medical Sciences,



Figure 1. Novel missense variants of the CLOCK, NR1D2, and PER1 genes in N24SWD individuals. Sanger sequencing confirms a novel missense variant in each of CLOCK (A), NR1D2 (B) and PER1 (C) as indicated by an arrow.

Tokushima University (2019, A9 to A.I.), Intramural Research Grant for Neurological and Psychiatric Disorders of National Center of Neurology and Psychiatry (NCNP) under grant numbers 26-2 and 30-9, and a grant from the Takeda Research Foundation. Part of this study is the result of "Understanding of Molecular and Environmental Bases for Brain Health" carried out under the Strategic Research Program for Brain Sciences from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Acknowledgments

The authors would like to thank all the participants and all the staff who helped with sampling and data collection.

Disclosure Statement

Financial disclosure: None. Non-financial disclosurve: None.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

References

 Kitamura S, et al. Intrinsic circadian period of sighted patients with circadian rhythm sleep disorder, free-running type. Biol Psychiatry. 2013;73(1):63–69. doi: 10.1016/j.biopsych.2012.06.027

- Takahashi JS, et al. The genetics of mammalian circadian order and disorder: implications for physiology and disease. Nat Rev Gene. 2008;9(10):764–775. doi: 10.1038/nrg2430
- Hida A, et al. Screening of clock gene polymorphisms demonstrates association of a PER3 polymorphism with morningness-eveningness preference and circadian rhythm sleep disorder. Sci Rep. 2014;4:6309. doi: 10.1038/srep06309
- King DP, et al. Positional cloning of the mouse circadian clock gene. Cell. 1997;89(4):641–653. doi: 10.1016/s0092-8674(00)80245-7
- Banerjee S, et al. Pharmacological targeting of the mammalian clock regulates sleep architecture and emotional behaviour. Nat Commun. 2014;5:5759. doi: 10.1038/ncomms6759
- Chalfant JM, et al. Circadian disruption with constant light exposure exacerbates atherosclerosis in male ApolipoproteinEdeficient mice. Sci Rep. 2020;10(1):9920. doi: 10.1038/ s41598-020-66834-9
- Takasu NN, et al. In vivo monitoring of multi-unit neural activity in the suprachiasmatic nucleus reveals robust circadian rhythms in *Period1-/-* mice. *PLoS One.* 2013;8(5):e64333. doi: 10.1371/journal.pone.0064333
- Nakahata Y, et al. The NAD+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. Cell. 2008;134(2):329–340. doi: 10.1016/j.cell.2008.07.002
- Burris TP. Nuclear hormone receptors for heme: REV-ERBalpha and REV-ERBbeta are ligand-regulated components of the mammalian clock. Mol Endocrinol. 2008;22(7):1509–1520. doi: 10.1210/me.2007-0519
- Amador A, et al. REV-ERBβ is required to maintain normal wakefulness and the wake-inducing effect of dual REV-ERB agonist SR9009. Biochem Pharmacol. 2018;150:1–8. doi: 10.1016/j. bcp.2018.01.009

Supplementary Table 1: 76 circadian- and sleep-related genes examined in 17 subjects with N24SWD

Chromosome	Gene
chr17	AANAT
chr19	APOE
chr11	ARNTL
chr12	ARNTL2
chrX	ASMT
chr20	AVP
chr12	AVPR1A
chr1	AVPR1B
cnrx	AVPR2
chr11	
chr12	BHLHE40 BHLHE41
chr4	CLOCK
chr12	CRY1
chr11	CRY2
chr17	CSNK1D
chr22	CSNK1E
chr3	GSK3B
chr17	HCRT
chr6	HCRTR2
chr6	HLA-A
chro	HLA-B
chr6	HLA-C HLA DMA
chr6	HLA-DMR
chr6	HLA-DOA
chr6	HLA-DOB
chr6	HLA-DPA1
chr6	HLA-DPB1
chr6	HLA-DPB2
chr6	HLA-DQA1
chr6	HLA-DQA2
chr6	HLA-DQB1
chr6	HLA-DQB2
chr6	HLA-DRA
chr6	HLA-DRB1
chr6	HLA-DRB5
chr6	HLA-DRB6
chr6	HLA-E
chro	
chr6	HI A-G
chr6	HLA-H
chr6	HLA-L
chr5	HTR1A
chr13	HTR2A
chrX	HTR2C
chr11	HTR3A
chr11	HTR3B
chr3	HTR3C
chr3	HTR3D
chr3	HTR3E
chr5	HIK4
CDT/	
chr2	HTR6
chr10	HTR7
chr7	// 6
chr4	MTNR1A
chr11	MTNR1B
chr2	NPAS2
chr17	NR1D1
chr3	NR1D2
chr10	OPN4
chr17	PER1
chr2	PER2
chr1	PER3
chr22	PPARA
chr15	RORA
CNIY	
cnr12	I IMELESS THE
chr6	\/IP
chr3	VIPR1
chr7	VIPR2

Supplementary Table 2: 94	variants of circadian	 and sleep-related genes in 	17 individuals with N24SWD
---------------------------	-----------------------	--	----------------------------

	Chromosome	Start Position	End Position	Reference Allele	Alternative Allele	Type	Known	Gene	Function	dbSNP	Reference Sequence		Genotype Count		Average
	chr17	74465813	74465813	(U) G	(1) A	SNV	Known	AANAT	Missense	rs28936679	NM 001166579.1	0 0 16	0 1	0	190.00
	chr19	45409167	45409167	c	G	SNV	Known	APOE	Missense	rs440446	NM 001302688.1	4	11	2	88.59
	chr19	45411139	45411139	С	т	SNV	Novel*	APOE	Missense	rs1969838696	NM_001302688.1	16	1	0	232.59
	chr19	45411941	45411941	т	с	SNV	Known	APOE	Missense	rs429358	NM_001302688.1	16	1	0	199.24
	chr19 chr11	45412079	45412079	C	T	SNV	Known	APOE	Missense	rs7412 re10741617	NM_001302688.1	16	1	0	315.24
and in 2 20000 C I Biol	chr12	63541279	63541279	Å	Ť	SNV	Known	AVPR1A	Missense	rs183401493	NM 000706.4	15	2	0	429.76
mnn porta p	chr11	27679916	27679916	С	т	SNV	Known	BDNF	Missense	rs6265	NM_001143810.1	10	5	2	406.76
and State bit c C C Bit Core Number NUMBER <td>chr12</td> <td>26277654</td> <td>26277654</td> <td>A</td> <td>G</td> <td>SNV</td> <td>Known</td> <td>BHLHE41</td> <td>Missense</td> <td>rs201545489</td> <td>NM_030762.2</td> <td>16</td> <td>1</td> <td>0</td> <td>360.82</td>	chr12	26277654	26277654	A	G	SNV	Known	BHLHE41	Missense	rs201545489	NM_030762.2	16	1	0	360.82
OND Delation L 0 Bits Prove Part Part Part Part Part Part Part Part	chr4	56304532	56304532	G	c	SNV	Novel*	CLOCK	Missense	rs1723064872	NM_004898.3	16	1	0	233.59
min partial pa	chr11 chr6	45869013	45869013	C	A	SNV	Known	UCRY2	Missense	rs3/4/548	NM_021117.3	15	2	14	308.06
diff 201214 20141 0 - Corr No. AL-LA Bisseering mitHee MALE	chr6	29912395	29912396	~	66	INS	Known	HI A-A	Frameshift	rs545184037	NM_002116.7	11	6	0	409.59
dist 3 3 1 C No Parts MACS Materials at 132800 MLC (S102) S 0	chr6	29912414	29912414	G	-	DEL	Known	HLA-A	Splice donor site	rs9278466	NM_002116.7	5	6	6	350.76
def 210546 210546 C C C Participant Partitipant Partitipant Partitpant </td <td>chr6</td> <td>31237124</td> <td>31237124</td> <td>т</td> <td>С</td> <td>SNV</td> <td>Known</td> <td>HLA-C</td> <td>Missense</td> <td>rs1130838</td> <td>NM_002117.5</td> <td>0</td> <td>5</td> <td>12</td> <td>321.18</td>	chr6	31237124	31237124	т	С	SNV	Known	HLA-C	Missense	rs1130838	NM_002117.5	0	5	12	321.18
mode Statistic G 1 BOX Process	chr6	31239449	31239449	С	G	SNV	Known	HLA-C	Missense	rs28626310	NM_002117.5	16	1	0	512.59
Bit of the second sec	chr6	32917544	32917544	c	Ť	SNV	Known	HLA-DMA	Missense	rs1063478	NM_006120.3	13	4	0	392.29
met State S	chr6	32904981	32904981	G	Т	SNV	Known	HLA-DMB	Missense	rs1042337	NM_002118.4 NM_002118.4	9	8	9	326.00
def 221530 221531 D A B/N Mean AA-CO Number PR01011 D 2 2 0 D <thd< th=""> <thd< th=""> D <t< td=""><td>chr6</td><td>32974551</td><td>32974551</td><td>G</td><td>Ť</td><td>SNV</td><td>Known</td><td>HLA-DOA</td><td>Missense</td><td>rs2582</td><td>NM 002119.3</td><td>7</td><td>9</td><td>1</td><td>259.18</td></t<></thd<></thd<>	chr6	32974551	32974551	G	Ť	SNV	Known	HLA-DOA	Missense	rs2582	NM 002119.3	7	9	1	259.18
def 202401 CD 20401 CD 20401 CD 20401 AU (2012) F	chr6	32781554	32781554	G	А	SNV	Known	HLA-DOB	Missense	rs2070121	NM_002120.3	15	2	0	326.94
mdd XXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	chr6	32784676	32784676	с	Т	SNV	Known	HLA-DOB	Missense	rs2071554	NM_002120.3	12	5	0	338.53
mid 202009 <td>chr6</td> <td>33036435</td> <td>33036435</td> <td>T</td> <td>G</td> <td>SNV</td> <td>Known</td> <td>HLA-DPA1</td> <td>Missense</td> <td>rs1126769</td> <td>NM_001242524.1</td> <td>5</td> <td>7</td> <td>5</td> <td>290.18</td>	chr6	33036435	33036435	T	G	SNV	Known	HLA-DPA1	Missense	rs1126769	NM_001242524.1	5	7	5	290.18
add 2020/08 2020/08 Col 700 A NV None Add-SMA Spire structure in T272071 NV <	chro	33036600	33036666	T	C C	SNV	Known	HLA-DPA1	Missense	rs1042308	NM_001242524.1	5	7	5	324.18
and b SD2142 SD2142 </td <td>chr6</td> <td>33037080</td> <td>33037080</td> <td>G</td> <td>A</td> <td>SNV</td> <td>Known</td> <td>HLA-DPA1</td> <td>Splice acceptor site</td> <td>rs73739671</td> <td>NM_001242524.1</td> <td>5</td> <td>7</td> <td>5</td> <td>257 76</td>	chr6	33037080	33037080	G	A	SNV	Known	HLA-DPA1	Splice acceptor site	rs73739671	NM_001242524.1	5	7	5	257 76
def 202113 S202113 C A BV Notes M-L-DP1 Built deturs in a "1100020 N.N. (D120224.1 5 7 5 1173 def 2202720 320720 T C BW Notes M-L-DP1 Materia N.N. (D120224.1 5 7 5 9174 def 2202720 320720 T C BW Notes M-L-DP1 Materia N.N. (D120224.1 5 7 5 9174 def 220270 320720 T C BW Notes M-L-DP1 Materia N.N. (D12024.1 5 7 5 9174 def 220270 320720 T C C BW Notes M-L-DP1 Materia N.N. (D12024.1 B 6 7 5 3 32180 def 3207107 C C BW Notes M-L-DP1 Materia<	chr6	33037412	33037412	G	С	SNV	Known	HLA-DPA1	Splice donor site	rs114707319	NM_001242524.1	5	7	5	165.59
def 332114 Solitation C A Dev Notes H.4.2024 Splitation of the second seco	chr6	33037413	33037413	С	Α	SNV	Known	HLA-DPA1	Splice donor site	rs116509985	NM_001242524.1	5	7	5	167.53
check 32071/2	chr6	33037419	33037419	G	A	SNV	Known	HLA-DPA1	Splice donor site	rs1126543	NM_001242524.1	5	7	5	182.18
mini 322/279 3	chr6	33037424	33037424	T	c	SNV	Known	HLA-DPA1	Missense	rs1126542	NM_001242524.1	5	7	5	191.82
ability 3327280 3227280 T G BVV Nume Hz.26797 Massense Hz.25791 Nume Hz.25791 H	chr6	33037579	33037522	A	т	SNV	Known	HLA-DPA1	Missense	rs2308912	NM_001242524.1	5	7	5	314 76
check 3325369 Socket A SV Norm PL-4-DB1 Magenie n1154211 Magenies Na State cde 3255369 S 255369 A G A SV Norm PL-4-DB1 Magenies Na State A G State cde State Magenies State State State State State State State State State State <t< td=""><td>chr6</td><td>33037580</td><td>33037580</td><td>т</td><td>G</td><td>SNV</td><td>Known</td><td>HLA-DPA1</td><td>Missense</td><td>rs2308911</td><td>NM 001242524.1</td><td>5</td><td>7</td><td>5</td><td>313.65</td></t<>	chr6	33037580	33037580	т	G	SNV	Known	HLA-DPA1	Missense	rs2308911	NM 001242524.1	5	7	5	313.65
dref 3534881 A G BW Form HL-D-DPI Massess Int 707191 BL 4 0 0 1 1 1 0 0 1 1 1 1 0 1 1 1 1 1 1 1 1	chr6	33053609	33053609	G	А	SNV	Known	HLA-DPB1	Missense	rs11551421	NM_002121.5	8	6	3	273.59
ched 3364808 S364808 C A B S364808 S364808 C A S	chr6	33048661	33048661	A	G	SNV	Known	HLA-DPB1	Missense	rs1042151	NM_002121.5	13	4	0	435.12
cred 3201442 220107 C G SV	chr6	33048663	33048663	G	A	SNV	Known	HLA-DPB1	Missense	rs1042153	NM_002121.5	13	4	0	433.53
$ \begin{array}{c} \mbox{const} \begin{tabular}{l l l l l l l l l l l l l l l l l l l $	chro	32634447	32634447	C A	6	SNV	Known	HLA-DQA1 HLA-DOR1	Splice acceptor site Splice acceptor site	rs3210146	NM_002122.3 NM_001243961.1	12	5	0	355.24
end 3222860 T C SNV Koon HL+COR Statustication Incl2001277 ALL Distance Incl2001277	chr6	32628633	32628633	т	c	SNV	Known	HLA-DQB1	Splice donor site	rs9273528	NM 001243961.1	6	9	2	313.18
def 3207773 G C SNV Keener <i>H.A.DPR</i> Missense r:19822289 NK.01911-14 1 0 338.0 def 3201324 2302509 CCCCL/C - DEL Koener <i>H.A.DPR</i> Missense r:19822289 NK.021123.3 7 10 0 315.31 def 3205094 CCCCL/C - DEL Koener <i>H.A.DPR</i> Missense r:1502479 NK.021123.3 7 10 0 315.31 def 3205094 CCCCL/C A DEL Keener <i>H.A.DPR</i> Missense r:1709243 MK.001984791 0 0 7 41.12 def 20068301 20088301 A C A DNV Keener <i>H.A.P.A</i> Missense r:1709241 MK.001984791 0 0 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 <t< td=""><td>chr6</td><td>32628660</td><td>32628660</td><td>т</td><td>c</td><td>SNV</td><td>Known</td><td>HLA-DQB1</td><td>Splice acceptor site</td><td>rs28688207</td><td>NM_001243961.1</td><td>11</td><td>6</td><td>0</td><td>317.76</td></t<>	chr6	32628660	32628660	т	c	SNV	Known	HLA-DQB1	Splice acceptor site	rs28688207	NM_001243961.1	11	6	0	317.76
cdrd 3341103 A C SNV Koron <i>HLADBM</i> Splot acceptor and the ADDM medbed medbed MALBMA A 6 7 33723 cdrd 3525084 3252508 22525508 2252508 2252	chr6	32407773	32407773	G	С	SNV	Known	HLA-DRA	Missense	rs16822586	NM_019111.4	16	1	0	338.00
chem 201188 201188 CCLOAC 0 STEL Norm PLACEM Device NULL	chr6	32411035	32411035	A	С	SNV	Known	HLA-DRA	Splice acceptor site	rs8084	NM_019111.4	4	6	7	337.53
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	chr6	32411646	32411646	CCGCAC	G	SNV	Known	HLA-DRA	Deletion	rs/192	NM_019111.4 NM_002124.3	4	6 10	6	348.41
eds 3045837 C A SNV Kown HLA-F Milescrate m14810280 Milescrate m14810280 Milescrate Milescrate <th< td=""><td>chr6</td><td>30458064</td><td>30458064</td><td>G</td><td>Ā</td><td>SNV</td><td>Known</td><td>HLA-E</td><td>Missense</td><td>rs1264457</td><td>NM 005516.5</td><td>9</td><td>7</td><td>1</td><td>259.88</td></th<>	chr6	30458064	30458064	G	Ā	SNV	Known	HLA-E	Missense	rs1264457	NM 005516.5	9	7	1	259.88
chr 2280301 2280301 C T SNV Koom M.A.F.F Materias nr173024 M.M.(D108477)1 0 0 17 441.8 chr 2280301 2280481 28000 280000 280000 280000 280000 280000 280000 280000 280000 280000 280000 2800000 2800000 2800000 2800000 2800000 2800000 2800000 28000000 28000000 28000000 28000000000000000000000000000000000000	chr6	30459317	30459317	c	А	SNV	Known	HLA-E	Missense	rs148162840	NM_005516.5	16	1	0	355.82
chtd 2562523 2662523 C T SNV Koom H.A.F.N Massare ch7231419 ML_001694791 10 1 0 4112 chds 2596451 2014637 2014637 2014637 5 3 327718 chds 2597657 20174878 C A SNV Koom H.A.F.A Massare rs1723477 NL_0012773 5 7 5 316.88 chds 559726 6325726 6325726 5 7 5 346.80 333.00 chds 559726 6325726 6325726 6325716 347.40 343.30 345.71 343.30 345.71 345.30	chr6	29693011	29693011	С	т	SNV	Known	HLA-F	Missense	rs1736924	NM_001098479.1	0	0	17	461.76
chr 2.88 2.88 2.88 2.87 3 3.27 3 3.27 3 3.27 3 3.27 3 3.27 3 3.27 3 3.27 3 3.27 3 3.27 3 4.37 3 4.37 3 4.37 3 4.37 3 4.37 3 4.37 3 4.37 3 4.37 3 4.38 3 3.28 3 3 3.28 3 3 3 3 3 3 3 3 3 3 3 3 <td>chr6</td> <td>29693233</td> <td>29693233</td> <td>c</td> <td>T</td> <td>SNV</td> <td>Known</td> <td>HLA-F</td> <td>Missense</td> <td>rs57237143</td> <td>NM_001098479.1</td> <td>16</td> <td>1</td> <td>0</td> <td>431.82</td>	chr6	29693233	29693233	c	T	SNV	Known	HLA-F	Missense	rs57237143	NM_001098479.1	16	1	0	431.82
cbds 22978079 22978079 C A SNV Koom /fill.4-G Maarsee rst 272477 NML 0005217.5 5 7 5 319.8 chrds 5255729 5255729 5255729 525729	chro	29694680	29694680	A A	L T	SNV	Known	HLA-F-AST	Missense	rs3/34814	NM_001098479.1	9	5	3	320.03
cb:35 62:352:29 cb:3257:29 cb:3255:29 cb:3255:29 cb:3255:29 cb:3255:29 cb:3255:29 cb:3255:29 cb:3255:29 cb:3255:29 cb:3255:29 cb:3255:29 <td>chr6</td> <td>29796376</td> <td>29796376</td> <td>ĉ</td> <td>Å</td> <td>SNV</td> <td>Known</td> <td>HLA-G</td> <td>Missense</td> <td>rs12722477</td> <td>NM 002127.5</td> <td>5</td> <td>7</td> <td>5</td> <td>319.88</td>	chr6	29796376	29796376	ĉ	Å	SNV	Known	HLA-G	Missense	rs12722477	NM 002127.5	5	7	5	319.88
dr13 dr47024 4747024 C T SNV Kown H7R2A Miserse m5012 NM_001165472 0 0 17 38.3 dr11 11380000 11380000 T C SNV Kown H7R2B Spice cappor she m11114773 NM_000234 10 1 0 325.51 dr14 11380000 11380000 T C SNV Kown H7R2B Spice cappor she m11114773 NM_000234 10 1 0 325.51 dr14 11380000 113877610 G C SNV Kown H7R2C Miserse m6676410 NM_100770.2 0 8 9 24.12 dr13 113776710 11377672 1357777 SNS Kown H7R2C Miserse m657362 NM_01156411 1 0 25.59 dr13 1137772 11332422 NSS1547 Kown H7R2C Miserse m7305411 10 1 </td <td>chr5</td> <td>63256729</td> <td>63256729</td> <td>c</td> <td>т</td> <td>SNV</td> <td>Known</td> <td>HTR1A</td> <td>Missense</td> <td>rs1800042</td> <td>NM_000524.3</td> <td>13</td> <td>4</td> <td>0</td> <td>343.00</td>	chr5	63256729	63256729	c	т	SNV	Known	HTR1A	Missense	rs1800042	NM_000524.3	13	4	0	343.00
drift 113846041 13846041 G T SN/ Known H7784 Massene ms1004073 MM_21827.3 16 1 0 235.41 drift 11397472 11377472 11377472 13 7 335.71 335.71 3	chr13	47470824	47470824	С	т	SNV	Known	HTR2A	Missense	rs6312	NM_001165947.2	0	0	17	349.35
$ \begin{array}{c} \mathrm{ch} \mathrm{ch} 1 & 11380308 & 11380308 & \mathrm{T} & \mathrm{C} & \mathrm{SNV} & \mathrm{Kroum} & \mathrm{H}^{2}\mathrm{H}^{2}\mathrm{SD} & \mathrm{Shele accorder site} & \mathrm{ch}^{1}\mathrm{L}^{2}\mathrm{H}^{2}\mathrm{H}^{2} & \mathrm{NM} & \mathrm{SO}^{2}\mathrm{SD} & S$	chr11	113846041	113846041	G	Т	SNV	Known	HTR3A	Missense	rs190646973	NM_213621.3	16	1	0	235.41
Lui 113774722 13774710 G C C N SNV Koom HTR2C Masenes 112756410 NML337752 3 7 7 836.88 chr3 113774721 13775770 G C G SNV Koom HTR2C Masenes 112756410 NML337752 0 8 9 7 7 326.88 chr3 1137574771 13775771 G A SNV Koom HTR2C Masenes 11275621 NML337752 0 6 8 0 224.12 chr3 113754278 1375527 G G SNV Koom HTR2D Masenes 11200521 NML0115846.1 1 4 2 100.47 chr3 113752251 13755227 G A SNV Koom HTR2D Masenes 11200521 NML0115846.1 1 4 2 255.59 chr3 113822701 13322591 G A SNV Koom HTR2E Masenes 11200522 NML00115846.1 1 0 1 0 225.59 chr3 113822701 13322591 - A SNV Koom HTR2E Masenes 11200521 NML0011584.6 1 0 2 255.59 chr3 113822701 13322701 0 2 A SNV Koom HTR2E Masenes 11200521 NML001173.2 1 4 2 247.53 chr10 12200319 0250348 C G G SNV Koom HTR2 Masenes 113970544 NL00173.2 1 4 2 247.53 chr10 12200319 0250348 C G G SNV Koom HTR2 Masenes 113970544 NML019593 1 6 1 0 256.59 chr3 113826270 1332271 1 A A SNV Koom HTR2 Masenes 113970544 NML09593 1 6 1 0 256.54 chr10 12200319 0250348 C G G SNV Koom HTR2 Masenes 113970544 NML09593 1 6 1 0 256.54 chr10 12200319 0250348 C G A SNV Koom HTR2 Masenes 113970544 NML09593 1 6 1 0 256.11 chr10 12200319 0250348 C G A SNV Koom HTR2 Masenes 113970544 NML09593 1 6 1 0 256.12 chr10 12476420 21715620 G A SNV Koom HTR2 Masenes 11397054 NML00593 1 6 1 0 256.11 chr10 12476420 21715620 G A SNV Koom HTR2 Masenes 11397054 NML00593 1 6 1 0 256.12 chr10 12476420 21715620 G A SNV Koom HTR2 Masenes 11397054 NML00593 1 6 1 0 256.12 chr10 1147781 1147781 C G G SNV Koom MTR2 Masenes 11397054 NML00593 1 6 1 0 256.12 chr2 101437810 C G A SNV Koom MTR2 Masenes 11397054 NML00593 1 6 1 0 256.12 chr2 2171568 SN ML00598 NML00598 NML00598 1 6 1 0 256.12 chr2 2171648 NML00598 NML00598 NML00598 1 6 1 0 256.12 chr2 2171648 NML00598 NML00598 NML00598 NML00598 NML00598 NML00598 NML00598 1 6 1 0 256.12 chr2 21916168 C A SNV Koom PR2 Masenes 11200508 NML00598 1 6 1 0 256.52 chr10 8841602 6 A SNV Koom PR2 Masenes 11200702 NML005921 4 0 0 17 2 20.65 chr1 788777 77 7 A SNV Koom PR2 Masenes 11200717 NML003001	chr11	113803008	113803008		C	SNV	Known	HIR3B	Splice acceptor site	rs11214//3	NM_006028.4	16	1	0	305.71
ch/3 193778010 83778010 G C SNV Known HTR2D Missense rs600737 NU_01163461 12 6 0 327.88 ch/3 19375377 G A SNV Known HTR2D Missense rs73183412 NU_001163461 12 5 0 327.88 ch/3 19375622 IS375622 G A SNV Known HTR2D Missense rs73183412 NU_001163461 0 1 1 117.00 ch/3 193316418 IS3816416 IS3816416 G A SNV Known HTR2D Missense rs7278173 NU_00100173.2 1 4 2 2.26.85 ch/10 9250348 9250348 9250348 9250348 9250348 147.00255341 NU_00100173.2 1 4 2 1 34.08 ch/10 9250348 9250348 9250348 9250348 9250348 1 0 0 35.09 ch/10 9250348 9250348 9250348 94 4.00147 30.00 <td< td=""><td>chr3</td><td>183774762</td><td>183774762</td><td>ĉ</td><td>A</td><td>SNV</td><td>Known</td><td>HTR3C</td><td>Missense</td><td>rs6766410</td><td>NM 130770.2</td><td>3</td><td>7</td><td>7</td><td>358.88</td></td<>	chr3	183774762	183774762	ĉ	A	SNV	Known	HTR3C	Missense	rs6766410	NM 130770.2	3	7	7	358.88
ch3 1875777 187574277 G A SNV Known HTR3D Masense ns3002077 NML_00116346.1 1 4 2 1047 ch3 183754278 183754278 183754278 183754278 Num_00115346.1 0 1 16 173.00 ch3 183754278 183754278 183754278 Num_00115346.1 0 1 6 11 10 225.05 ch3 18325209 18322209 16322209 16322209 16322209 16 4 2 225.55 ch470 12520816 G A NV Known HTR3E Masense ns14805164 NML_011980712 1 4 2 225.55 ch471 2520816 92503469 17 C SNV Known HTR3E Masense ns13870544 NML_01198073 16 1 0 323.09 1 4 2 1 340.85 ch471 197745630 18747380 G A SNV Known HTR14 Masense ns13870543 NML_005583.3	chr3	183778010	183778010	G	С	SNV	Known	HTR3C	Missense	rs6807362	NM_130770.2	0	8	9	264.12
ch3 18374272 18374272 63745272 G G SNV Known HTR3D Masense n*37153412 NML_00116346.1 12 5 0 322.88 ch3 183755522 G A SNV Known HTR3D Masense n*37153712 NML_00116346.1 0 1 16 171.50 ch4 18381640 18381240 G A SNV Known HTR3D Masense n*1027107 NML_0012661.1 0 6 1 331.17 ch4 18381240 G A SNV Known HTR3E Frameshift m506073114 MML_0012661.1 6 0 226.86 ch41 19250368 S253048 C G SNV Known HTR7 Masense rs3740048 MML_0018953.3 16 1 0 326.86 ch41 192503619 S2503468 C A SNV Known HTR7 Masense rs3740048 MML_0018953.3 16 0 0 326.95 33.1 0 2 38.05 1	chr3	183753777	183753777	G	A	SNV	Known	HTR3D	Missense	rs36092077	NM_001163646.1	11	4	2	169.47
ch3 183/558/2 183/58/2 G A SNV Known r/17.30 Massense rs10005/2 NM_00126641 0 1 16 17.30 ch3 183516416 G A SNV Known r/17.30 Massense rs1027151 NM_001256411 16 1 0 2355 ch4 183252730 18332231 C T NN Known r/17.30 NM_0012656141 16 1 0 2355 ch4 14726225 C G SNV Known HTR4 Splice door site rs2753051 NM_0010553 16 1 0 336.00 ch4 167455428 D37455420 G A SNV Known HTR7 Massense rs3740648 NM_000503 16 1 0 322.00 232.00 232.00 232.00 232.00 232.00 232.00 232.00 236.71 24.00 232.00 236.71 24.00 232.00 236.71 24.00 232.00 236.71 24.00 232.00 24.00 23.00 24.00 <td>chr3</td> <td>183754278</td> <td>183754278</td> <td>С</td> <td>G</td> <td>SNV</td> <td>Known</td> <td>HTR3D</td> <td>Missense</td> <td>rs73183412</td> <td>NM_001163646.1</td> <td>12</td> <td>5</td> <td>0</td> <td>327.88</td>	chr3	183754278	183754278	С	G	SNV	Known	HTR3D	Missense	rs73183412	NM_001163646.1	12	5	0	327.88
abile 13322709 13322709 c A SNV Norm HTTE Name 114681010 Nucleice 0 0 0 2315.09 ch5 41332270 147028225 C C T SNV Known HTTR2 Finameshift 1155007111 11 4 0 2316.09 ch7 41702225 147028225 147028225 C G SNV Known HTTR7 Missense ri3370364 NM, 010659.3 16 1 0 325.06 ch71 22771039 T A SNV Known HTTR7 Missense ri3306353 NM, 000593.3 15 2 0 386.71 ch41 187476360 G A SNV Known MTT14 Missense ris100684 NM, 000593.3 16 1 0 323.09 ch41 187476360 1914498 G A SNV Known MTT14 Missense ris100684 NM, 000593.3 16 1 0 323.29 ch22 10134895 C	chr3	183755822	183755822	G	A	SNV	Known	HIR3D	Missense	rs1000952	NM_001056614.1	0	1	16	1/3.00
ch3 1838/2270 1838/270 180/227183 180/270 190/227183 180/270 190/227183 190/227183 190/227183 190/227183 190/227182 190/227182 190/227182 190/227182 190/227182 190/227182 190/227182 <td>chr3</td> <td>183818410</td> <td>183822699</td> <td>G</td> <td>A A</td> <td>SNV</td> <td>Known</td> <td>HTR3E</td> <td>Missense</td> <td>rs146851567</td> <td>NM_001256614.1</td> <td>16</td> <td>1</td> <td>0</td> <td>295.59</td>	chr3	183818410	183822699	G	A A	SNV	Known	HTR3E	Missense	rs146851567	NM_001256614.1	16	1	0	295.59
chris 1478225 1478225 C T SNV Known HTR7 Missense ns272832 NL 0.0104173.2 11 4 2 2475.00 chr10 9250348 9250349 7 C SNV Known HTR7 Missense ns3740048 NM_019583.3 14 2 1 340.80 chr1 9250348 18747350 G A SNV Known HTR7 Missense ns3740048 NM_005093.3 15 2 0 366.71 chr4 18747580 G A SNV Known MTNR7A Missense ns100084 NM_005083.3 15 2 0 366.71 chr4 10154965 C T SNV Known MTNR7B Missense ns72328752 NM_002518.3 1 0 1 230.72 chr3 23990245 G A SNV Known MR7D2 Missense ns2021710 NM_002518.4 0	chr3	183822730	183822731	-	ATTCCTCT	INS	Known	HTR3E	Frameshift	rs560673114	NM 001256614.1	16	1	ō	263.65
ch10 9250369 9250369 9250369 C G SNV Known HTR7 Missense rs13270544 NML_019895.3 16 1 0 338.00 chr4 1274571039 22771039 T A SNV Known HTR7 Missense rs13306435 NML_019895.3 16 1 0 338.00 chr4 112745422 G A SNV Known MTNR7H Missense rs1300643 NML_0059563.3 15 2 0 386.01 chr4 112745620 G A SNV Known MTNR7H Missense rs1800885 NML_0059563.3 15 2 0 286.12 chr11 192714906 G A SNV Known MTNR7H Missense rs1800885 NML_0059563.3 16 1 0 236.21 chr2 101437601 C G SNV Known MTNR7 Missense rs2298160 NML_0025163.3 1 0 237.22 1 1 0 235.21 1 0 237.22 </td <td>chr5</td> <td>147928225</td> <td>147928225</td> <td>С</td> <td>т</td> <td>SNV</td> <td>Known</td> <td>HTR4</td> <td>Splice donor site</td> <td>rs2278392</td> <td>NM_001040173.2</td> <td>11</td> <td>4</td> <td>2</td> <td>247.53</td>	chr5	147928225	147928225	С	т	SNV	Known	HTR4	Splice donor site	rs2278392	NM_001040173.2	11	4	2	247.53
chr01 92503619 92503619 T C SNV Known ILG Missense rs3740048 NML_019850.3 14 2 1 342.88 chr4 18747584 1874758420 G A SNV Known ILG Missense rs1800844 NML_005686.3 15 2 0 386.71 chr4 1874758400 G A SNV Known MTNRTA Missense rs1800844 NML_005686.3 15 2 0 286.71 chr1 197475800 G A SNV Known MTNRTB Missense rs1800844 NML_0055863.3 16 1 0 233.29 chr12 101543695 C T SNV Known MPAS2 Missense rs229850 NML_005126.4 16 1 0 233.29 0 0 17 260.00 0 0 17 260.00 0 0 17 260.00 0 0 17 260.00 0 0 17 260.00 0 0 275.20 0	chr10	92503408	92503408	С	G	SNV	Known	HTR7	Missense	rs138700544	NM_019859.3	16	1	0	336.00
chr/l 22/1039 1 A SW Known Mitselfnee fs1304943 NM_000003 10 1 0 328.06 chr41 10714582 G A SWV Known Mitselfnee rs130084.30 NM_000803.3 15 2 0 328.06 chr41 10714586 10745958 G A SWV Known Mitselfnee rs130087.30 NM_000803.3 15 2 0 328.06 chr41 101474601 1014347601 G A SWV Known Mitselfnee rs1230872 NM_002518.3 1 9 7 280.00 chr32 20068265 23096285 G A SWV Known NPA22 Missense rs2305160 NM_005164 16 1 0 2256.25 chr32 23006265 23096277 T A SWV Known NRTD2 Missense rs20015105 1 0 235.22 chr10 88419663 G A SWV Known PER1 Missense rs2001706	chr10	92503619	92503619	т	c	SNV	Known	HTR7	Missense	rs3740048	NM_019859.3	14	2	1	340.88
chrl 18747330 18747330 G A SNV Noum MT04714 Missense 11500855 NIL_0055813 15 2 0 28212 chrl 101544055 10154095 C T SNV Known MT22 Splice door sile rr22229250 NIL_005583 16 1 0 22312 chrl 101437601 C G SNV Known MT42 NIL_005583 1 6 10 227782 chrl 101437601 A G SNV Known MPA22 Missense rds542900 NIL_002518.3 1 6 10 22552 chrl 23060285 G A SNV Known MPA22 Missense rds542900 NIL_002518.4 10 0 17 28567 chrl 28060477 2400477 T A SV//r <known< td=""> PM4 Missense rds58007 NIL_005126.4 10 0 275682 chrl</known<>	chr/	197455426	197455426	G	A A	SNV	Known	MTNR14	Missense	rs13300433	NM_000000.3	10	1	0	328.00
chrl1 927 44966 G A SNV Known MT/RT/B Missense ns/2228752 NNL_005593. 16 1 0 32340 chrl2 101544965 C G SNV Known MPA32 Missense rs/2289060 NNL_002518.3 1 9 7 2800 chrl2 101591340 101591340 A G SNV Known MPA32 Missense rs/2305160 NNL_002518.3 1 9 7 2800 chrl3 23096285 2996285 G A SNV Known MRD2 Missense rs/2305160 NNL_005124.4 16 1 0 2258.2 chrl3 2400477 T A SVT Known OPH4 Missense rs/2901468 NNL_001030015.2 16 1 0 2258.2 chrl3 8841963 8841663 G A SNV Known OPH4 Missense rs/2901468 NNL_001030015.2 16 1 0 2266.32 chrl3 8942716 C T S	chr4	187476360	187476360	G	A	SNV	Known	MTNR1A	Missense	rs1800885	NM 005958.3	15	2	õ	266.12
chr.2 10158/4895 101437601 C T SNV Known NPA22 Splice dono site rs25429990 NM_002518.3 1 9 4 24070 chr.2 101437601 C G SNV Known NPA22 Missense rs25429090 NM_002518.3 1 9 7 24000 chr.3 23962285 G A SNV Known NPA22 Missense rs2542900 NM_005128.4 10 0 273.52 chr.3 24006477 24000477 T A S/UTR Known NR102 Missense rs7501458 NM_00130015.2 16 1 0 2396724 chr.10 88419062 88419062 G A SNV Known PPN4 Missense rs7501458 NM_00130015.2 16 1 0 2256.82 chr.10 88429062 B84219062 G A SNV Known PER1 Missense rs255405 NM_0012015.2 16 1 0 2367.63 chr.17 8051531 C	chr11	92714996	92714996	G	Α	SNV	Known	MTNR1B	Missense	rs772328752	NM_005959.3	16	1	0	323.29
chrl2 101437601 101437601 C G SNV Known MPAS2 Missense rs626542690 NM_002518.3 1 9 7 2000 chrl3 23096265 23996265 G A SNV Nown NR1D2 Missense rs2305160 NM_005126.4 16 1 0 2259.72 chrl3 24006477 T A SV UK NN NN <td>chr2</td> <td>101584895</td> <td>101584895</td> <td>С</td> <td>т</td> <td>SNV</td> <td>Known</td> <td>NPAS2</td> <td>Splice donor site</td> <td>rs2289950</td> <td>NM_002518.3</td> <td>4</td> <td>9</td> <td>4</td> <td>240.76</td>	chr2	101584895	101584895	С	т	SNV	Known	NPAS2	Splice donor site	rs2289950	NM_002518.3	4	9	4	240.76
chr3 2396/282 G A S S/V Nixe Missense rs2001b0 Nixe Missense Nixe	chr2	101437601	101437601	c	G	SNV	Known	NPAS2	Missense	rs6542990	NM_002518.3	1	9	7	280.00
chr3 24009477 T A S'UTR Known MR/D2 Missense re485807 NL_05124. 0 0 17 28076 chr10 88419062 88419062 G A SNV Known OPH4 Missense rr2001458 NM_001030015.2 16 1 0 225070 chr10 884219062 6 A SNV Known OPH4 Missense rr2001458 NM_001030015.2 16 1 0 225070 chr10 8842116 C T SNV Known PER1 Missense rs2055405 NM_00103015.2 16 1 0 225076 chr17 805151 20148581 T C SNV Known PER1 Missense rs255405 NM_022817.2 16 1 0 25512 chr1 789073 239161890 G A SNV Known PER2 Missense rs25734027 NM_022817.2 15 2	chr2	23996285	23996285	G	۵ ۵	SNV	Novel	NPAS2 NR1D2	Missense	152305160	NM_002518.3	16	1	0	235.82
chr10 88419963 88419963 G A SNV Known OPM4 Missense rs701458 NM_D01030015.2 16 1 0 30.94 chr10 88419963 88419963 6 A SNV Known OPM4 Missense rs20217106 NM_D01030015.2 16 1 0 329.54 chr17 8046772 C G SNV Known PER1 Missense rs20217106 NM_D01030015.2 0 5 12 256.82 chr17 8061751 2815168651 C T SNV Novel PER1 Missense rs205405 NM_D02816.2 16 1 0 256.53 chr12 2316168651 2316168651 T C SNV Known PER2 Missense rs763749027 NM_D02816.2 16 1 0 258.12 chr12 231616867 Z331616867 T C SNV Known PER2 Missense rs1597472.0	chr3	24006477	24006477	T	A	5' UTR	Known	NR1D2	Missense	rs4858097	NM 005126.4	0	o.	17	269.76
chr10 88419062 88419062 G A SNV Known OPN4 Missense ns20171086 NM_00133015.2 16 1 0 275.08 chr10 8842216 B842216 C G SNV Known PPR4 Missense rs107610 NM_00133015.2 0 5 12 250.62 chr17 8064772 8046772 C G SNV Known PER1 Missense rs107610 NM_002616.2 1 0 250.63 chr12 23916186651 239161869 G A SNV Known PER2 Missense rs16974027 NM_022817.2 16 1 0 258.12 chr2 239161869 G A SNV Known PER2 Missense rs16974027 NM_022817.2 16 1 0 258.12 chr3 789073 C GCCCTCTACTGCA FER2 Missense rs16776347228 NM_00128962.1 0 1 3 307.06 chr1 7887493 T C SNV Known	chr10	88416963	88416963	G	А	SNV	Known	OPN4	Missense	rs7901458	NM_001030015.2	16	1	0	309.94
chr10 88422116 8046772 C G SNV Known PER1 Missense rs2585405 NM_00130015.2 0 5 1.2 206.82 chr17 8046772 C G SNV Now PER1 Missense rs2585405 NM_002616.2 1 0 286.55 chr2 239166651 T C SNV Now PER2 Missense rs25854020 NM_02216.2 16 1 0 286.55 chr2 23916651 T C SNV Known PER2 Missense rs75874020 NM_022817.2 16 1 0 286.51 chr2 239166212 2391662312 Z391662312 T C SNV Known PER2 Missense rs763347228 NM_022817.2 16 1 0 286.12 chr1 7889973 789026 GCCCTCTGTCC - DEL Known PER3 Missense rs57575989 NM_01228962.1 0 0 17 431.76 chr1 7887493 7887579 C	chr10	88419062	88419062	G	A	SNV	Known	OPN4	Missense	rs202171086	NM_001030015.2	16	1	0	275.00
dm17 abid172 bb/b172 C G S/V Nixed PER1 Missense NNL_002616.2 2 7 8 2076 dm17 239168651 239168651 T C T S/V Nixed PER1 Missense rs758749027 NNL_002616.2 16 1 0 335.12 chr2 239168651 239161869 G A S/V Known PER2 Missense rs758749027 NNL_002817.2 15 2 0 335.12 chr12 2391618651 Z39161869 G A S/V Known PER2 Missense rs189746320 NNL_002817.2 15 2 0 335.12 chr1 7889737 Z8907662A T C S/V Known PER3 Deletion rs57875989 NML_001289862.1 0 4 13 307.06 chr1 7887473 7887493 T C S/V Known PER3 Missense rs226667 NM_001289862.1 0 0 17 431.76 chr1 <td< td=""><td>chr10</td><td>88422116</td><td>88422116</td><td>c</td><td>T</td><td>SNV</td><td>Known</td><td>OPN4</td><td>Missense</td><td>rs1079610</td><td>NM_001030015.2</td><td>0</td><td>5</td><td>12</td><td>206.82</td></td<>	chr10	88422116	88422116	c	T	SNV	Known	OPN4	Missense	rs1079610	NM_001030015.2	0	5	12	206.82
chr.2 239168651 259168651 T C SNV Known PER2 Milesense rs75374027 NNL_022817.2 16 1 0 2551.2 chr.2 239168651 239168650 G A SNV Known PER2 Milesense rs753347027 NNL_022817.2 15 2 0 330.00 chr.2 23916851 2391682312 239162312 T C SNV Known PER2 Missense rs783347228 NNL_022817.2 15 2 0 330.00 chr1 7889973 789026 CoCCTGTACTGCCA DEL Known PER3 Missense rs27875989 NML_001289862.1 0 4 13 307.06 chr1 7867403 T C SNV Known PER3 Missense rs278696 NM_001289862.1 0 0 17 431.76 chr1 7867403 T C SNV Known PPR3 Missense rs228696 <t< td=""><td>chr17</td><td>8040772</td><td>8040772</td><td>c</td><td>G T</td><td>SNV</td><td>Noval</td><td>PER1</td><td>Missense</td><td>152080400</td><td>NM_002616.2</td><td>16</td><td>1</td><td>8</td><td>250.76</td></t<>	chr17	8040772	8040772	c	G T	SNV	Noval	PER1	Missense	152080400	NM_002616.2	16	1	8	250.76
chr2 239161889 239161889 G A SNV Known PER2 Missense rs193748230 NNL_022817.2 15 2 0 330.00 chr2 239161899 23916312 23916312 T C SNV Known PER2 Missense rs763347228 NNL_022817.2 16 1 0 288.12 chr1 7889973 7890026 GCCTCTGTCC CA A Nov PER3 Deletion rs57875989 NML_001289862.1 0 4 13 307.06 chr1 788773 788779 C G SNV Known PER3 Missense rs228007 NML_001289862.1 0 0 17 431.76 chr1 7887579 7887579 C G SNV Known PER3 Missense rs228007 NML_001289862.1 11 6 0 457.59 chr1 7887579 7887579 C G SNV Known TMLELSS Missense rs228007 NML_00320.3 3 11 3 340.24 ch	chr2	239168651	239168651	т	ċ	SNV	Known	PER2	Missense	rs758749027	NM 022817.2	16	1	0	355 12
chrl2 239162312 239162312 T C SNV Known PER2 Missense rs78337228 NM_022817.2 16 1 0 288.12 chrl 7889973 7780026 - DEL Known PER3 Detelon rs5787589 NM_001289862.1 0 4 13 307.06 chrl1 7887493 780026 CGCCTGTCC - DEL Known PER3 Missense rs228606 NM_001289862.1 0 0 1 431.76 chrl1 7887493 7807493 T C SNV Known PER3 Missense rs228606 NM_001289862.1 0 0 1 431.76 chrl1 7887493 78073 C SNV Known PER3 Missense rs228606 NM_001289862.1 0 0 1 431.76 chrl1 7887797 C G SNV Known PER3 Missense rs228606 NM_001289862.1 0 0 1 3 340.24 chrl2 56818610 G A SNV Known TMELESS Missense rs224779 NM_003203.3 1 1 0 286.72 <	chr2	239161869	239161869	G	Ā	SNV	Known	PER2	Missense	rs199746230	NM_022817.2	15	2	0	330.00
AGAATCCATCCC ATCCTATCGCA - DEL Known PER3 Deletion rs57875989 NM_001289862.1 0 4 13 307.06 chr1 7889973 7887579 7887579 C SNV Known PER3 Missense rs228696 NM_001289862.1 0 0 17 431.76 chr1 7887579 7887579 C G SNV Known PER3 Missense rs228696 NM_001289862.1 10 0 17 431.76 chr1 7887579 7887579 C G SNV Known PER3 Missense rs228697 NM_001289862.1 11 6 0 457.59 chr12 5681693 56814653 G A SNV Known TMELESS Missense rs724017 NM_00320.3 1 12 4 297.65 chr12 56815922 C T SNV Known TMELES	chr2	239162312	239162312	т	С	SNV	Known	PER2	Missense	rs763347228	NM_022817.2	16	1	0	288.12
chrl 7889973 789026 All Clark IGCAR chrl 7889973 789026 CGCCTCTGC CCC - DEL Known PER3 Deletion ns57875989 NM_001289862.1 0 4 13 307.06 chrl 7887433 7887493 T C SNV Known PER3 Missense ns228696 NM_001289862.1 0 0 17 431.76 chrl 7887433 7887493 T C SNV Known PER3 Missense ns2286967 NM_001289862.1 0 0 17 431.76 chrl1 7887493 T887579 C G SNV Known PER3 Missense ns228697 NM_001289862.1 1 0 313.02 chrl2 6681580 G614658 G A SNV Known TMELES Missense ns229779 NM_00320.3 1 1 3 340.24 chrl2 5681962 568149610 G A				AGAATCCATCCC											
ACAGGATOCCC TCCATA International of the second sec	chr1	7889973	7890026	GCGCTCTGTCC		DEL	Known	PER3	Deletion	rs57875989	NM 001289862.1	0	4	13	307.06
chr1 788749 7887579 7887579 C G SNV Known PER3 Missense rs228696 NM_001289862.1 0 0 17 431.76 chr1 7887579 7887579 C G SNV Known PER3 Missense rs228696 NM_001289862.1 11 6 0 457.55 chr2 5681562 2661580 T C SNV Known PER3 Missense rs2291739 NM_005363.4 16 1 0 316.35 chr12 56815922 S6815922 C T SNV Known TIMELESS Missense rs274047 NM_00320.3 1 12 4 278.57 chr12 56815922 S6815922 C T SNV Known TIMELESS Missense rs274047 NM_00320.3 1 1 0 288.47 chr12 56815922 56815922 T A SNV Known TIMELESS				ACAGGATCGCC								-		-	
chrl r887433 r87433 T C SNV Known PER3 Missense rs228696 NM_001289862.1 0 0 17 43.759 chrl 7887579 C G SNV Known PER3 Missense rs228696 NM_001289862.1 0 0 11 6 0 43.759 chrl2 46615880 46615880 T C SNV Known PER3 Missense rs1800234 NM_005035.4 16 1 0 340.24 chrl2 56814653 56914653 G A SNV Known TMMELSS Missense rs221799 NM_003920.3 3 11 3 340.24 chrl2 56818610 G A SNV Known TMMELSS Missense rs15123555 NM_003920.3 16 1 0 276.57 chrl3 56818610 G A SNV Known TMMELSS Missense rs151235555 NM_0003920.3				TCCCATGA		er				ar		-			
Unit root or stra root of stra <throot of="" stra<="" th=""> root of stra</throot>	chr1	7887493	7887493	Т	c	SNV	Known	PER3	Missense	rs228696	NM_001289862.1	0	0	17	431.76
chr12 56814653 C A SNV Known TIMELESS Missense rs2291739 NL_003920.3 3 11 3 340.24 chr12 56814653 C T SNV Known TIMELESS Missense rs2291739 NL_003920.3 3 11 3 340.24 chr12 56815922 56815922 C T SNV Known TIMELESS Missense rs15720655 NL_003920.3 1 1 0 288.47 chr12 56812610 G A SNV Known TIMELESS Missense rs15720655 NL_003920.3 1 1 0 288.47 chr3 42567463 A G SNV Known TIMELESS Missense rs14470463 NL_003920.3 1 12 4 278.00 chr3 42567463 A G SNV Known VIPR1 Missense rs14467043 NL_003920.3 15 2 0 30.	chr22	46615880	46615880	т	c	SNV	Known	PPARA	Missense	rs228097 rs1800234	NM 0050364	16	1	0	407.09
chr12 56815922 56815922 C T SNV Known TIMELESS Missense rs774047 NM_003920.3 1 12 4 297.85 chr12 56815922 5681592 C T SNV Known TIMELESS Missense rs774047 NM_003920.3 1 12 4 297.85 chr12 56819810 66818610 G A SNV Known TIMELESS Missense rs17123855 NM_003920.3 1 12 4 297.85 chr3 42667463 6682278 T A SNV Known TIMELESS Missense rs174077 NM_003920.3 1 12 4 297.85 chr3 42667463 42657463 A G SNV Known VIPR1 Missense rs14470843 NM_004624.3 15 2 0 305.12 chr3 158835860 G A SNV Known VIPR2 Missense rs34492909	chr12	56814653	56814653	G	Ă	SNV	Known	TIMELESS	Missense	rs2291739	NM_003920.3	3	11	3	340.24
chr12 56818610 56818610 G A SNV Known TMMELESS Missense rs15123855 NML_00320.3 16 1 0 28847 chr3 5682278 T A SNV Known TMMELESS Missense rs174070 NML_00320.3 16 1 0 28847 chr3 42567463 42567463 A G SNV Known VIPR1 Missense rs144670843 NML_004624.3 15 2 0 305.12 chr3 42567463 42567463 A G SNV Known VIPR2 Missense rs144670843 NML_003262.4 16 1 0 154.82 uhma procome sequence vas effecting LUSCS G A SNV Known VIPR2 Missense rs144670843 NML_00382.4 16 1 0 154.82	chr12	56815922	56815922	c	т	SNV	Known	TIMELESS	Missense	rs774047	NM_003920.3	1	12	4	297.65
cmrini2 bitsectoria <	chr12	56818610	56818610	G	A	SNV	Known	TIMELESS	Missense	rs151238555	NM_003920.3	16	1	0	288.47
UIII 3 42/20/49/3 4/20/49/3 A G 3/W KNOWN V/P*K1 MISSINSIP IS1440/10/43 NM_UV4924.3 15 2 0 305.12 chr7 158835860 IS8835860 G A SNV Known V/PR2 Missense rs534492909 NM_003382.4 16 1 0 154.82 Liman percence was referred to LICSC assembly CRCh37/In19 *These variants were recently besrved in the Jacquese Whole Genome Reference Daniel R 3K (IP)	chr12	56822378	56822378	T	A	SNV	Known	TIMELESS	Missense	rs774027	NM_003920.3	1	12	4	278.00
Imman genomes sequences assembly GRCh27/h19 ⁻¹ These viriality war recently cherrowing in the Japanese Whole Genome Basence Basel 24/EDN	chr3	4200/403 158835860	4200/403	A	G	SNV	Known	VIPR1	Missense	rs144670843 rs534492909	NM_003382.4	15 16	2	0	305.12 154.82
	Human genome ce	nuence was referre	to UCSC assemb	ly GRCh37/ha19 · *T	nese variants were r	cently obee	rved in the Jac	anese Whole Ceno	me Reference Panel 9 34 II	PN	000002.4	10		~	104.02

Gene	Reference Sequence	Chromosome Position	Exon	Reference Allele	Alternative Allele	Known /Novel	dhSND	Function	Alternative Allele Frequency (AAF)	AAF in public databases (population)			
							doola			gnomAD-Exomes (Global)	1000Genomes (Global)	HGVD (Japanese)	8.3KJPN (Japanese)
СГОСК	NM 004898.3	56314997	18	C	G	Novel		missense	0 0078125				
CLOCK	NM 004898.3	56309992	21	A	G	Known	rs3736544	synonymous	0.8359375	0.695777	0.723	0.7728	0.79075
CLOCK	NM 004898.3	56304532	22	G	c	Known	rs1723064872	missense	0.0078125				0.00012
CLOCK	NM 004898.3	56301663	23	Т	C	Known	rs192938463	synonymous	0.0078125	0.00002	0.0002	0.0045	0.004
CLOCK	NM_004898.3	56301369	23	А	G	Known	rs1801260	3' ÚTR	0.1640625	0.242754*	0.2296	0.16	0.17208
NR1D2	NM 005126.4	23986895	1	С	т	Known	rs536068754	5' UTR	0.0078125	0.000424*	0.0002		0.02011
NR1D2	NM 005126.4	23986930	1	A	С	Known	rs4858565	5' UTR	0.953125	0.794666*	0.7704		0.58014
NR1D2	NM 005126.4	23986947	1	С	Т	Known	rs575779558	5' UTR	0.015625	0.011979*	0.0254		0.03103
NR1D2	NM_005126.4	23986983	1	С	G	Known	rs7644275	5' UTR	0.0078125		0.244		0.05372
NR1D2	NM_005126.4	23996056	2	С	Т	Known	rs72627100	synonymous	0.046875	0.009695	0.0184	0.0276	0.03126
NR1D2	NM_005126.4	23996285	2	G	А	Novel		missense	0.0078125				
NR1D2	NM_005126.4	24003646	5	А	С	Known	rs139583758	missense	0.015625		0.0026	0.0033	
NR1D2	NM_005126.4	24006497	6	G	А	Known	rs72628104	synonymous	0.046875	0.009537	0.018	0.0306	0.03138
NR1D2	NM_005126.4	24009322	7	G	А	Known	rs78292562	missense	0.0078125	0.000853	0.0024	0.0142	0.01426
	-												

Supplementary Table 3: Allele frequency of the CLOCK and NR1D2 variants in 64 individuals with N24SWD

Human genome sequence was referred to UCSC assembly GRCh37/hg19.; gnomAD: Genome Aggregation Database; HGDV: Human Genetic Variation Database; *AAF in gnomAD-Genomes