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# (54) METHOD FOR ASSESSMENT OF POTENTIAL FOR DEVELOPMENT OF DRAVET SYNDROME AND USE THEREOF

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G01N 33/53 (2006.01)

G01N 33/50 (2006.01)

C12Q 1/68 (2006.01)

C12Q 1/02 (2006.01)

C12N 15/01 (2006.01)

# (57) ABSTRACT

Provided is a method of assessing a potential for development of Dravet syndrome with high accuracy, and use thereof. The method according to the present invention of assessing a potential for development of Dravet syndrome includes, with use of a sample taken from a subject, detecting whether or not a mutation is on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na  $_{\nu}1.1$ , and detecting whether or not a mutation is on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca  $_{\nu}2.$ 

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1' MEQIVLVPPGEDSENFFIRESLAAIERRIAEEKAKNPKPDKKODDENGPKDNSDLEAGKN ************************************	1021' 1	KGYATVKKIYEFIQOSFIFKQKILDBIKPLDDIANIKKDSCASNHTFEIGKDLDYLKDVN ************************************
LPFIYGDIPPEMVSEPLEDLDPYYINKTFIVLNKGKAIFERSATSALYILTPFNPLRKI ************************************	1081,	GTTSGIGTGSSVEKYIIDESDYMSFINNPSLTVTVPIAVGESDFENLNTEDFSSESDLEE ***********************************
AIKILVHSLFSMLIMCTILTNCVFWTMSNDPDWTKNVFYTFTGIYTFESLIKIIARGFCL ************************************	1141' 3	SKEKLNESSSSEGGSTVDIGAEVEEOPVVEPEETLEPEACFTEGCVQREKCCQINVEEGR ***********************************
EDFTFLRDFWNWLDFTVITFRYVTEFVDLGNVSALRTFRVLRALKTISVIEGLKTIVGAL ************************************	1201' ç 1201" (	GKOMWILRRTCERIVEHNWEETEIVEMILLSSGALAFEDIYIDORKTIKTMLEVADKVET ************************************
IQSVKKLSDVALLTYPCLSVFALLCLQLFMGNLRNKCIQWPPTNASLEEHSIEKNITVNY ************************************	1261 1	YIFILEMLLKWVAYGYQTYFTNAWCWLDFLIVDVSLVSLFANALGYSELGAIKSLRTLFA ************************************
NGTLINETVEBEDWKSYIQDSRYHYFLEGFLDALLCGNSSDAGQCPEGYMCYKAGRNENY ****	1321' 1	LRPIRALSRFEGARVVVNALLGAIPSIMNVLIVCLIFWIIFSIMGVNLFAGKFYHCINTT ***********************************
Gynsedteswaelslerlatodewenlzoltraagktymitevlvielgseylinlila ***********************************	1381' 7	TEDREDIEDVNNHTDCLKLIERNETARWKNYKYNEDNYGFCYLSLLOVAFFKGMDIMTA *** * * **** *********************
VVANAYEBONOATLEBEAEOKBAEFOONTEOLKKOOBAAOOAATATASEHSEEPSAAGRLS ************************************	1441" 2	AVDSRNVELQPRVEESLYMYLYPVIFIIFGSPFTLALFIGVIIDNFNQQRKKFGGQDIFM ************************************
SEGGEEKDEDEFOKSESEDSTRRKGFRFSIEG ******* *** *************************	1501' 3	TEEOKKYYNAMKKIGSKKPOKPIPRPCNKROGAVFDFVTROVFDISIMILICINMYTAMV ************************************
nrlyyekryssphosilsirgslesprrnsryslesprgakovgsendfaddehstfed ************************************	1561' 1 1561" 1	ETDDQSEYVTTILSRINLVETVLETGECVLKLISLRHYYFTIGMNIFDFVVVILSIVGMF ****** *** *** **********************
NESRRDSLFVPRRHGERRNSNLSQTSRSSRMLAVFPANGKMHSTVDCNGVVSLVGGPSVP ***********************************	1621' ] 1621" ]	laeliekypvsptiprvirlarigriirlikgakgirtilealamsipalenigilelu ***********************************
TSEVGQLLPEVIIDKEATDDNGTTTETEMEKRRSSSFHVSMDFLEDFSGRQRAMSIASIL ************************************	1681' h	METYALFGKSNFAYVKREVGIDDMENFETFGNSMICLFQITTSAGMDGLLAPIINSKPPD ***********************************
DCSEYWLKVKHVVNLVVMDPEVDLAITICIVL ************************************	1741' (	CDPNKVNPCSSVKGDCGNPSVGIFFFVSYIIISFLVVVNMYIAVILENFSVATEBSAEPI ************************************
NTLENAMEHYPMTDHENNYLTVGNLVFTGTFTAEMETKITAMDPYYYFQEGRNIFDGFTV ************************************	1801' 3	SEDDFEMFYEVWEKFDPDATQFWEFEKLSQFAALEPPINIPQPNKLQIIAMDIPWYSGD ************************************
TISIVELGLANVEGLSVIRSFRILRVFKLAKSWPTINMIIKIIGNSVGALGNITLVIAII **********************************	1861' j 1861" j	RIHCLD LLBAFTKRVLGBSGENDALKLQMEBRFMASNPSKVSYQP ITTTLKRKQBEVSAV ***********************************
VEIBAVVŒMOLDGKSYKDCVCKIASDCOLPRWHMDFFHSFLIVFRVLCGBWIETMMDCM **********************************	1921	IIQRAYRRHILKRTVKQASFTYNKNKIKGGANLIKEDMIIDRINENSITEKTDLTMSTA ************************************
EVAGGAMCLIVEMMYMVIGNLVVINLETALLLSSESADNLAATDDDNEMNNLGIAVDEMH ************************************	1981' 7	ACPPSYDRVTKPIVEKHEQEGKDEKAKGK ************************ ACPPSYDRVTKPIVEKHEQEGKDEKAKGK

F I G. 2

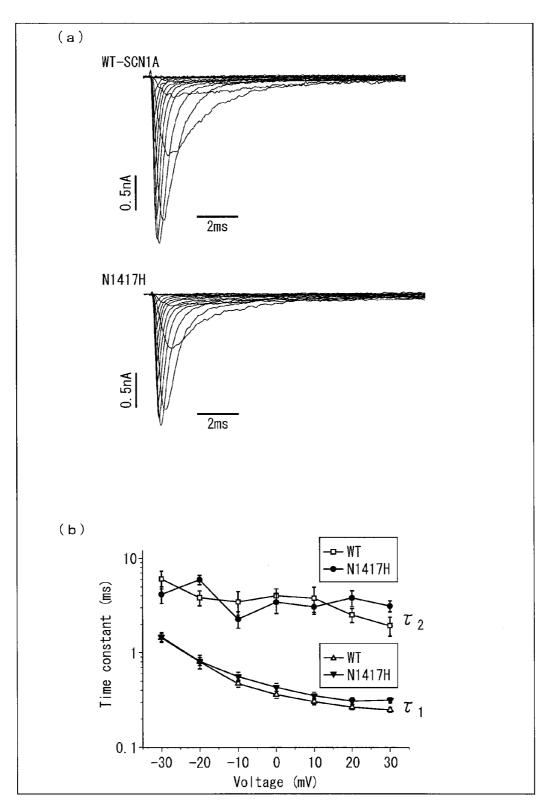
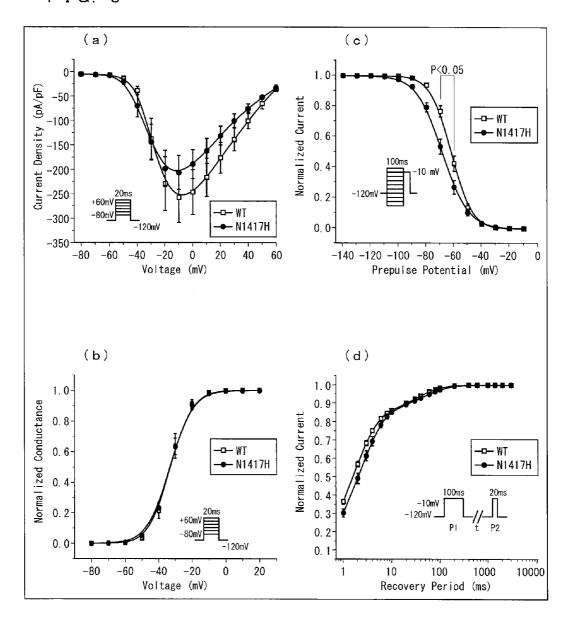
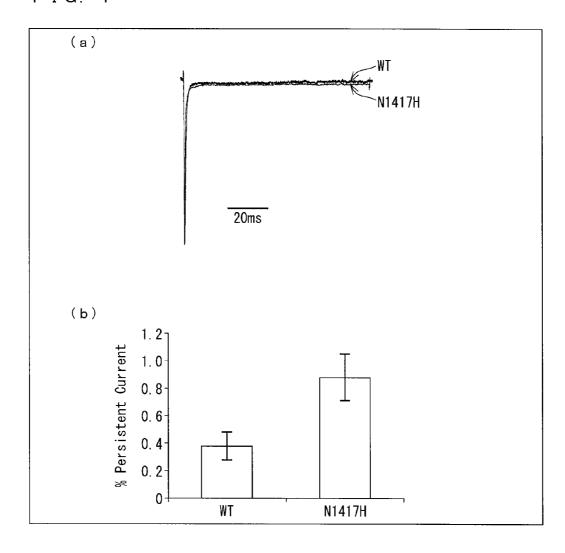


FIG. 3



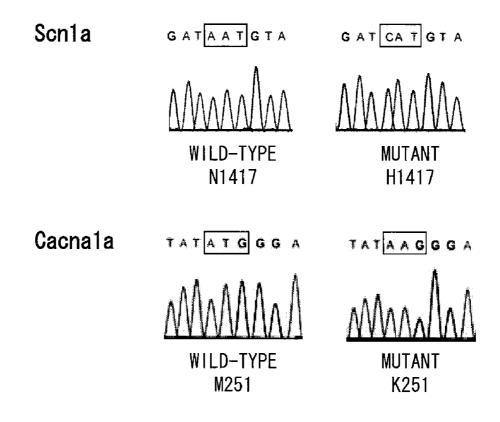
F I G. 4



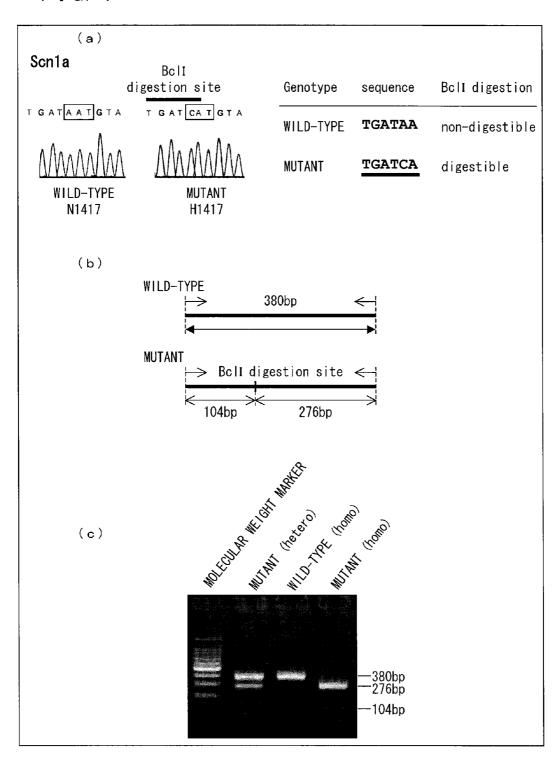
# F I G. 5

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(a)
P ; Scn1aMut/MutCacna1aWT/WT × Scn1aWT/WTCacna1aMut/Mut
    (Scn1A-mutated rat)
                               (Cacnala-mutated rat)
F1; Scn1aMut/WTCacna1aMut/WT
  (b)
F1; Scn1aMut/WTCacna1aMut/WT × Scn1aMut/WTCacna1aMut/WT
F2; Scn1aWT/WTCacna1aWT/WT
                             Scn1a wild-type (homo) + Cacna1a wild-type (homo) Control (1)
    Scn1aMut/WTCacna1aWT/WT
    Scn1aMut/MutCacna1aWT/WT
                             Scn1a mutant (homo) + Cacna1a wild-type (homo)
                                                                                                (2)
    Scn1aWT/WTCacna1aMut/WT
                             Scn1a wild-type (homo) + Cacna1a mutant (hetero) Control (4)
    Scn1aMut/WTCacna1aMut/WT
    Scn1a^{Mut/Mut}Cacna1a^{Mut/WT} Scn1a mutant (homo) + Cacna1a mutant (hetero)
                                                                                               (3)
    Scn1aWT/WTCacna1aMut/Mut
    Scn1a<sup>Mut/W⊤</sup>Cacna1a<sup>Mut/Mut</sup>
    Scn1aMut/MutCacna1aMut/Mut
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FIG. 6



F I G. 7



F I G. 8

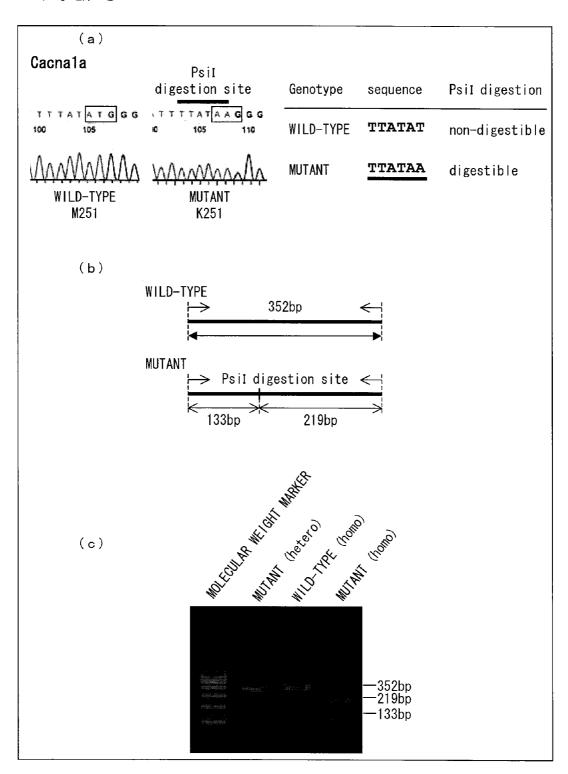


FIG. 9

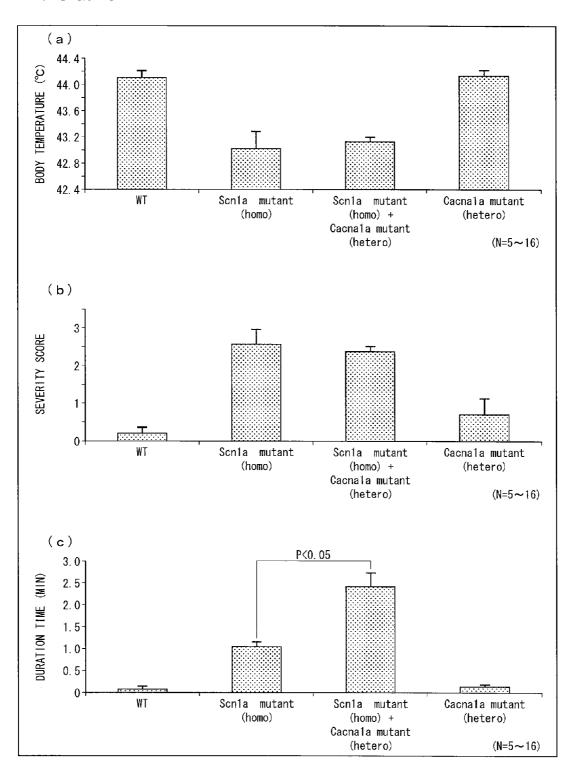
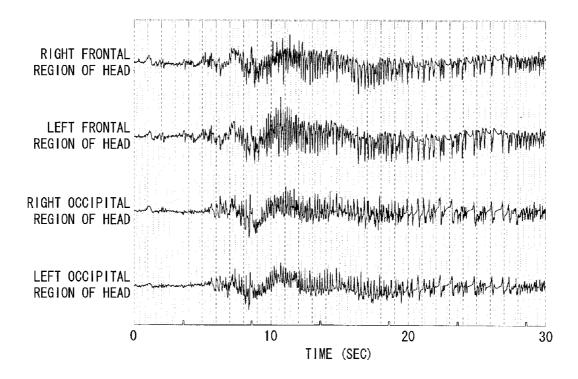


FIG. 10



QGAYFRDLWN ******** QGAYFRDLWN	AVEDCVVNSL ******** AVEDCVVNSL	EKNEVKARDR ******** EKNEVKARDR	MEMSIFYVVY ******** MEMSIFYVVY	TRHMPONKOS ******** TRHMPONKOS	FTSLFSLECV ******** FTSLFSLECV	FRAARLIKLL ******** FRAARLIKLL	DEDSDEDERQ ********* DEDSDEDERQ	GNEFAYFY ******* GNEFAYFYFV	ACGRIHYKOM * * * * ** AWGRMPYLDM	TALDIKIAKG ********* TALDIKIAKG	MEYYROSKAK ********* MEYYROSKAK	SSMKESPSWV * ****** SGLKESPSWV	LPMEGOTRAA ****** LPMEGOGRAA	RVPPEENORY ******* RVPPEENORH	PKDRKHRPHH ******** PKDRKHRQHH	SSSVSGSPAP ******** SSSVSGSPAP	APRRP- * ** QQQQAVARPG	RWP ACRHGGARWP	RS ** HASSGATGRS	EDDWC ****
KMIDIGIVLH ******** KMIDIGIVLH	KTIKRLPKLK ******* KTIKRLPKLK	RDCRGKYLLY ******** KDCRGKYLLY	ENOGPSPGYR ******* ENOGPSPGYR	IDFAISAKPL ******** IDFAISAKPL	ENALRVENIV ******** ENALRVENIV	NFINESFLRE ******** NFINESFLRE	VFGNIGIDGE ****** VFGNIGIDVE	KNSGIQKPEC **** KNSGILTREC	VRVWAEYDPA ****** VRVWAEYDPA	FNSTIMALIR ********* FNSTIMALIR	VGKIYAAMI ******* VGKIYAAMI	DPGGGLMAQE ****** DPGGALMAHE	TDGYSDSEHY ******* RDGYSDSEHY	ARRIDDYSLE ******* ARRIDDYSLE	SKDRDQDRGR ** *** *** SKERDQERGR	GREHATHROG **** **** GREHMAHROG	P0000000000	P * PGPARSESPR	GA-HEPAP ** GAYDAPPPVR	RGAHDAYSES
TGVFTFEMVI ******* TGVFTFEMVI	LRVLRVLRPL ******* LRVLRVLRPL	HCTDESKEFE ******** HCTDESKEFE	VLKHSVDATF ******** VLKHSVDATF	YSLEKNERAC ******* YSLEKNERAC	MKFYGASVAY ******** MKFYGASVAY	ILVTEFGN ****** ILVTEFGNPN	FFIYAIIGMQ ******** FFIYAIIGMQ	LSCLSGKPCD ******** LSCLSGKPCD	ILGPHHLDEY ******* ILGPHHLDEY	LPVADDNTVH	VTPHKSTDLT ******** VTPHKSTDLT	SQNALPSTQL ******* GONALPSTQL	SOSVEMREMG ******* SOSVEMREMG	KRSASVLGPK ******* KRSASVLGPK	SMTTQSGDLP	EORWSRSPSE ******* DORWSRSPSE	VIRKAGGSGP	GGSPRGCRRA * * * * * * * * * * * * * * * * * * *	REPPG SGGGEEAMA	APRPRTAR
NVLRYEDYVE ****** NVLRYEDYVE	KGKDINTIKS ******** KGKDINTIKS	AVQLEKGKEF ********* AVQLEKGKEF	TVSTGEGWPQ ******* TVSTGEGWPQ	QEQGDKWMEE \$ * * * * * * * * * * * * * * * * * * *	MIALNTIVLM ********* MIALNTIVLM	FVTVLGSITD ****** FVTVLGSITD	PYVCLLIAML ************************************	ATGEAWHNIM ******* ATGEAWHNIM	NFEYLTRDSS ********* NFEYLTRDSS	VACKRLLRMD ** ****** VAYKRLLRMD	NLSQKTLDLL ******** NLSQKTLDLL	PPSPTQEGGP ******** PPSPTQEGGP	PIDMPNSOPN ******* PTDMPNSOPN	LSTISDESPA ************************************	DVDTGLGTDL ******** DVDTGLGTDL	RPDTGRARAR *** **** RPDHGRARAR	TPRPLVSYSP **** TPRPHVSYSP	PP ** DRPPTGGHSS	GADYTEPDSP * * * * * GSDYDEADGP	LPNGYYAGHG A
DPVQPNAPRN ******* DPVQPNAPRN	LVAFAFTGNS ******** LVAFAFTGNS	MLEMFIFAVY ************************************	NVLWALLTLE ******** NVLWALLTLE	IFVALIITE IFVALIIITE	SPPFEYTIMA ************************************	YFRDAWNIFD ******* YFRDAWNIFD	WTFVQSFKAL ******** WTFVQSFKAL	FOALMLLFRS ******** FOALMLLFRS	LNLFVAVIMD ******** LNLFVAVIMD	LGLGKKCPHR ******* LGLGKKCPAR	LRKEMMAIWP ******* LRKEMMAIWP	RTPLMEORME ******* RTPLMEORME	TGTWSPERGP ****** TGTWSPEQGP	RREGRPRGNN ******* RRGRPRGNN	TSERSIGRYT ******* ASERSIGRYT	APDRERYAÇE * * * * * * PPDKDRYAÇE	GRROLPOTPC ******* GRROLPOTPS	AGPPA *** PGPTAEPLAG	RPR PGPRHHGYYR	CASP-RHGRR
AMSSIALAAE ******** AMSSIALAAE	ILDFIVVSGA ******** ILDFIVVSGA	KNVENILIVY * * * * * * * * * * * * * * * * * * *	EWKKYDFHYD **** EWKKYEFHYD	FVVEPEFFVN * * * * * * * * * * TVVEPEFFVN	FQYRMWQEVV ******* FQYRMWQEVV	LKVMAFGILN ******* LKVMAFGILN	ROGYTIRILL ************** ROGYTIRILL	ITEHNNFRTF ******* ITEHNNFRTF	SFIFICSFIM ******** SFIFICSFIM	YSLLRVISPP * ** ** YOMLRHMSPP	GADKQQNDAE ******** GADKQQNDAE	KLQAMREEQN ******** KLQAMREEQD	TORAQEMEOK ******* TORAQEMFOK	SMPRLPAENO ******** SMPRLPAENO	HORREDRGHR ****** ** HORREDRSHR	НННИНННЬЬ ******** ****	STSGTSTPRR ******** STSGTSTPRR	-AARRM ** RAATSGPRRY	AHAPEGP * *** ASGPHVSEGP	PRTPRAAG *****
1206 : 1258 :	1266 : 1318 :	1326 :	1386:	1446 :	1506 :	1566 : 1618 :	1624 :	1684 :	1744 :	1804 :	1864 :	1924 :	1984 : 2038 :	2044 :	2104 :	2164 : 2218 :	2224 :	2259 :	2285 :	2319 :
KOSMAORART * † * * * † * * * * KOSMAORART	IANCIVLALE IANCIVLALE	WNVMDEVVVL ******* WNVMDEVVVL	IGLLIFFAIL ******** IGLLIFFAIL	PYWEGPNNGI * * * * * * * * * * PYWEGPNNGI	FFELNLVLGV ******** FFELNLVLGV	TDVEQRHPED ** ***** TDGEQRHPED	FHKKERRMRF ******* FHKKERRMRF	LEMSEMFIKM ******** LEMSEMFIKM	RIFKVTKYWA ******* RIFKVTKYWA	TNEDTEPAAI ***********************************	FLAIAVDNLA ******* FLAIAVDNLA	KNOKPAKSVW ******* KNOKPAKSVW	VD POENRININ ******* VD POENRININ	SSPERAPGRE ** GSQEAELSRE	RPVAEG SGSPRIGADG	RHRHGPPA ***** RHRHGAPATY	DIDNMKNNKI * ****** DIDNMKNNKI	TPNNPGNPSN ******** TPNNPGNPSN	OVNKNANPDP ******* OVNKNANPDP	YFEMCILMVI *********
GGQPGAQRMY ** * * * * * * * * GGQPGAQRMY	PFEYMILATI ****** PFEYMILATI	FHKGSYLRNG ******** FHKGSYLRNG	IMKAMIPLLQ ******* IMKAMIPLLQ	RECPNGERCO ******** RECPNGERCO	YFIPLIIIGS ********* YFIPLIIIGS	AEEVILAEDE ******** AEEVILAEDE	KSAKLENSTF ******** KSAKLENSTF	LYYAEFIFLG ******** LYYAEFIFLG	ISVLRALRLL ********* ISVLRALRLL	Ofnedegypp ******** Ofnedegypp	LEGNYTLLNV ******** LEGNYTLLNV	NMSIAVKEQQ ********** NMSIAVKEQQ	VKTHLDRPLV ******** MKTHLDRPLV	DARRAWP **** AGLDARRPWA	H * HRQGGSRESR	DDGERKR * *** EGPDGGERRR	LGRODLPLAE ***** LGRODPPLAE	TNPONAASRR ******** TNPONASRR	CPPPLNHTVV * **********************************	RICHYILNIR *********
GGRGAGGSRQ ******** GGRGAGGSRQ	KYAKKITEWP ******* KYAKKITEWP	GIKIVALGFA **** **** GIKIIALGFA	IPSLQVVLKS ******** IPSLQVVLKS	PAPCGTEEPA ******** PAPCGTEEPA	DASGNIWNWL ******** DASGNIWNWL	INGYMEWISK ******* INGYMEWISK	VGSPFARASI ******** VGSPFARASI	YNQPEWLSDF ******* YNQPEWLSDF	AVIKEGISEG ******** AVIKEGISEG	ALLGMOLFGG ******* ALLGMOLFGG	VESIYEIVLT ******** VESIYEIVLT	VAEVSPLSAA ******** VAEVSPLSAA	TTYARPLRPD * * * * * * * * * * * * * * * * * * *	RESARDP *** HDRARDPSGS	KAGDAPRRHT **** KAGDPHRRHV	RPARAADGEG **** RPARGGEGEG	LSTTRPIQOD ********** LSTTRPIQOD	GPALA * * * GPMLAIPAMA	EHMAVEIPPA * * * * * * * * * * * * * * * * * * *	PKPMPPISSM FILSTINPLR ******* ******** DYDMDDVSCM bilenmini
PAAGVVVGAA ****** AAAGVVVGSG	FLESEDNVA ******* FLESEDNVA	YFIGIFCFEA	VLRPLKLVSG ******** VLRPLKLVSG	EGTDDIQGES ******* EGTDDIQGES	GWTDLLYNSN ******** GWTDLLYNSN	LRROCOIERE ******** LRROCOIERE	AEDQLADIAS ******** AEDQLADIAS	LNTLWLALVH **** LNTLCVALVH	IIGSIFEVIW ******** IIGSIFEVIW	FLLFLFIVVF **********************************	KSQGGVQGGW ******** KSQGVQGGM	ÇKLALÇKAKE ÇKLALÇKAKE	GDAAERWP * * * NEMDPDERWK	alrotard ** Edflekoary	VPWDADPERA * GFWEGEAERG	ERRPRPRDAT *** * ERRARHREGS	GSGVPMSGPN **** **** GSGVPVSGPN	PAKIGNSTNP *** *** * PAKMGNSTDP	PNSAKTARKP ******* TNSAKTARKP	PKPMPPYSSM *********
** ****** ** ***** . RYGGGGSG	QNCLTVNRSL *********	QHLPDDOKTP MSERLDDTEP ************************************	FDIRTLRAVR ******** FDIRTLRAVR	MGKFHTTCFE ******** MGKFHTTCFE	TOFDNILFAV LIVEQCITME ************************************	RVENERAFLK ******** RVENERAFLK	SKTDLLNPEE	FYWTVLSLVA ************************************	SSENCEDCGV ************************************	NSMKSIISLL *********************************	DWNEVMYDEI	DEQEEEEAAN ********************************	NLLASREALY ******** NLLASREALY	TNKSRAPE ****** INKSRAEPT VDQRLGQQRA	OREHAPPREH ** ARE-GSLEOP	PGDE-PDDRP ** * * PGEEGPEDKA	RRHRRRKESQ ******* RRHRRRKENQ	SLGHSGLPPS **** *** SLGHAGLPQS	LIVINESSTO	EEEADPGEDG *** * ***
: MARFGDEMPG RYGAGGGGSG ******* : MARFGDEMPA RYGGGGSG	: MALYNPIPVR : MALYNPIPVR	QHLPDDDDKTF	: TGILATVGTE ******** : TGILATVGTE	: IFAIIGLEFY : IFAIIGLEFY	TOFDNILFAV	LSGEFAKERE ******** LSGEFAKERE	GALRRATLKK GALRRTTIKK GALRRTTIKK	YIRRMVKTQA ******** YIRRMVKTQA	: YGLGTRPYFH ******** : YGLGTRPYFH	SLRNLVVSLL ********* SLRNLVVSLL	: MTVFQILTGE ******** : MTVFQILTGE	: NAQELTK ****** : NAQELTKVEA	: EORTSEMBKO ********* : EORTSEMBKO	: INKSRAPE ***** : INKSRAAEPT	GPYGRESEPQ ******* GPYGRESDHH	EPRRHRARR * **** ** EHRRHRAHRR	HDDRE * * EGDARREDKE	ATGEPASPHD ** * * ** ATAESAAPHG	: PGPPKTPENS ******** : PGPPKTPENS	LPKKEEEKKE ******************************
		121	181 :	241	301 :	361 :	421 :	481 :	541 : 539 :	601 : 599 :	661 : 659 :									• •

# FIG. 12

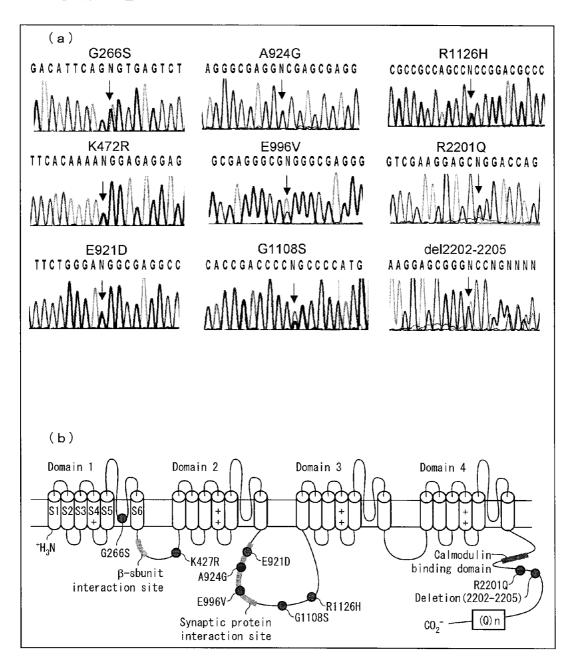


FIG. 13

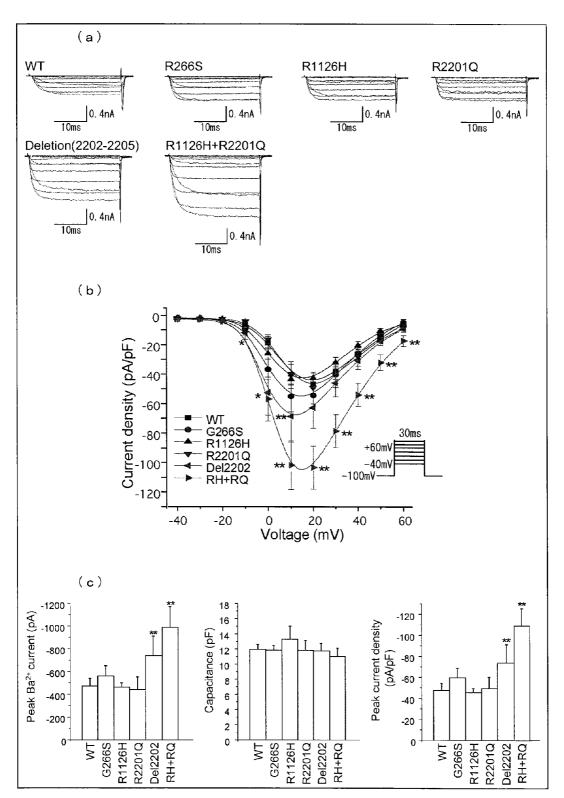
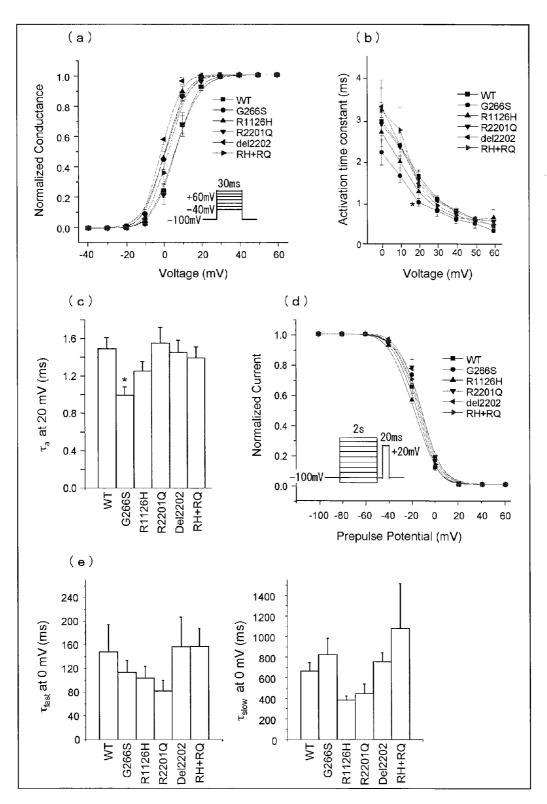


FIG. 14



# METHOD FOR ASSESSMENT OF POTENTIAL FOR DEVELOPMENT OF DRAVET SYNDROME AND USE THEREOF

#### TECHNICAL FIELD

[0001] The present invention relates to a method for assessing a potential for development of Dravet syndrome, and use thereof.

#### **BACKGROUND ART**

[0002] Febrile seizure is a disease that has a high incidence rate of approximately 8% in infants. A main symptom of febrile seizure is known as a continuation of generalized convulsions for 1 to 5 minutes while suffering a fever at or over 38° C. caused by a viral or bacterial infection such as a cold, or microbism. Most cases of febrile seizure that have an onset of between 6 months after birth and around 5 years old cure by the time when the patient turns 6 years old. In many cases, febrile seizure does not require active treatment. Therefore, febrile seizure is considered, in principle, as a benign disease.

[0003] However, among patients whose onset of febrile seizure was under the age of one, other than the patients of the benign disease which cease as a regular febrile seizure, there are some patients who suffer from convulsions continuously even after turning 6 years old, and there are some patients who are patients of Dravet syndrome (previously called "Severe Myoclonic Epilepsy in Infancy; SMEI"), which are patients of an intractable epilepsy disease.

[0004] The patients of Dravet syndrome are triggered in the onset of convulsions under the age of one. An average age of the onset of convulsions for patients of Dravet syndrome is 4 months to 6 months after birth. An incipient seizure of convulsion for a patient of Dravet syndrome is generally a systemic or a unilateral tonic-clonic or clonic convulsion, and during infancy, may lead to status epilepticus. Moreover, this convulsion seizure is easily induced by fever or bathing.

[0005] Conventionally, febrile seizure was diagnosed and treated by a general pediatrician or a family doctor, and Dravet syndrome is also diagnosed based on clinical symptoms characteristic of Dravet syndrome such as convulsion seizure or the like. However, by the time the patients of Dravet syndrome turn two to three years old, that is around when the clinical symptoms of Dravet syndrome have all appeared, these patients would have suffered repetitive convulsions many times and would often have had experienced critical conditions such as status epilepticus or the like. Hence, it is necessary to develop a diagnosis method that enables detection of Dravet syndrome in its possible earliest stage by a general pediatrician or family doctor, who is engaged in primary medical care. Detection of Dravet syndrome at an earlier stage would allow for the patent to see an epilepsy specialist in advance, which would allow for preventing the patient from reaching a critical condition.

[0006] Recently, it has been reported that 30% to 80% of Dravet syndrome patients find missense mutation (mutation causing a substitution of an amino acid) and nonsense mutation (mutation causing protein synthesis to stop in an incomplete state) on a SCN1A gene that encodes a voltage-gated sodium ion channel Na $_{\nu}$ 1.1  $\alpha$ -subunit type 1 (see Non Patent Literature 1 and 2). From such a point in view, attempts have been made to examine abnormalities in the SCN1A gene to diagnose Dravet syndrome on the basis of genes.

[0007] For example, Patent Literatures 1 to 4 disclose that mutation of the SCN1A gene is related to SMEI. Moreover, Patent Literatures 1 to 4 disclose that SMEI can be diagnosed by use of the mutation of the SCN1A gene as an indicator.

[0008] More specifically, Patent Literature 1 discloses the diagnosis of SMEI by assessing a plurality of mutations on the SCN1A gene that relate to SMEI, as a whole.

[0009] Patent Literature 2 discloses the diagnosis of SMEI performed by detecting a presence of a mutation that frequently occurs on the SCN1A gene of a nerve that is affected by SMEI.

[0010] Patent Literatures 3 and 4 disclose a method of diagnosing epilepsy syndromes including SMEI and syndromes associated with SMEI, by detecting a change in the SCN1A gene and confirming whether that change is known as being related to SMEI or a syndrome associated with SMEI or is known as not being related to SMEI or a syndrome associated with SMEI.

#### CITATION LIST

#### Patent Literature

Patent Literature 1

[0011] Japanese Patent Application Publication, Tokukai, No. 2004-329153 A (Publication Date: Nov. 25, 2004)

Patent Literature 2

[0012] Japanese Patent Application Publication, Tokukai, No. 2004-73058 A (Publication Date: Mar. 11, 2004)

Patent Literature 3

[0013] Published Japanese Translations of PCT International Publication, Tokuhyo, No. 2008-546376 A (Publication Date: Dec. 25, 2008)

Patent Literature 4

[0014] Published Japanese Translations of PCT International Publication, Tokuhyo, No. 2006-524490 A (Publication Date: Nov. 2, 2006)

# Non Patent Literature

Non Patent Literature 1

[0015] Sugawara T, Mazaki-Miyazaki E, Fukushima K, Shimomura J, Fujiwara T, Hamano S, Inoue Y, Yamakawa K. 2002. Frequent mutations of SCN1A in severe myoclonic epilepsy in infancy. Neurology 58: 1122-1124.

Non Patent Literature 2

[0016] Ohmori I, Ouchida M, Ohtsuka Y, Oka E, Shimizu K. 2002. Significant correlation of the SCN1A mutations and severe myoclonic epilepsy in infancy. Biochem Biophys Res Commun 295: 17-23.

Non Patent Literature 3

[0017] Escayg A, Heils A, MacDonald B T, Haug K, Sander T, and Meisler M H. 2001. A novel SCN1A mutation associated with generalized epilepsy with febrile seizures plus—and prevalence of variants in patients with epilepsy. Am J Hum Genet. 68: 866-873.

#### SUMMARY OF INVENTION

#### Technical Problem

[0018] As described above, the mutation on the SCN1A gene is found in an extremely large number of Dravet syndrome patients (30% to 80%). However, it is becoming revealed that the presence of a mutation on the SCN1A gene does not necessarily mean that the symptoms of Dravet syndrome would appear.

[0019] For example, Non Patent Literature 3 reports that not just the patients of the intractable Dravet syndrome, but also patients of febrile seizure and patients with a certain kind of benign epilepsy (e.g. GEFS+ (Generalized epilepsy with febrile seizure plus)) have a mutation on the SCN1A gene.

[0020] As such, the mutation on the SCN1A gene is not a phenomenon specific to Dravet syndrome. Hence, the conventional methods of examining just the abnormalities on the SCN1A gene as described in Patent Literatures 1 to 4 can be said as insufficient for specifically diagnosing Dravet syndrome

**[0021]** Therefore, in order to distinguish between the patients with benign febrile seizure and the patients with Dravet syndrome and to allow for the patients with Dravet syndrome to receive appropriate treatment by a specialist, further development is required in techniques for more accurately diagnosing Dravet syndrome.

**[0022]** The present invention is accomplished in view of the foregoing problems, and an object thereof is to provide a method of (specifically) assessing with high accuracy a potential for development of Dravet syndrome.

# Solution to Problem

[0023] Patients of GEFS+ and the patients of Dravet syndrome are common in a point that the SCN1A gene has a mutation. Meanwhile, the inventors performed diligent study based on their unique point of view of focusing on the difference in malignancy between the diseases; they considered that the development of Dravet syndrome is related to not just the mutation on the SCN1A gene but also another factor, and that another cause is related to the worsening and intractableness of Dravet syndrome. As a result, the inventors uniquely found out that many Dravet syndrome patients have a mutation on the SCN1A gene and further a mutation on the CACNA1A gene that encodes a P/Q type voltage-gated calcium ion channel Ca $_{\rm p}2.1~\alpha1$  subunit.

[0024] Furthermore, based on this finding, the inventors produced a rat having both the mutations on the SCN1A gene and the CACNA1A gene, and demonstrated that the rat having both the mutations on the SCN1A gene and the CACNA1A gene experienced more serious convulsion seizures as compared to rats having just the mutation on the SCN1A gene.

[0025] Based on these results of analyzing genes and animal testing results, it was found that the potential for development of Dravet syndrome can be assessed with high accuracy by detecting mutations for both  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>V</sub>1.1 and  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub>V</sub>2.1, and accomplished the present invention.

[0026] Namely, the present invention includes the following inventions.

[0027] An assessment method according to the present invention is a method of assessing a potential for development of Dravet syndrome, the method including:

[0028] with use of a sample taken from a subject,

[0029] detecting whether or not a mutation is on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>v</sub>1.1; and

[0030] detecting whether or not a mutation is on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel  $Ca_{\nu}2.1$ . It is preferable that the assessment method according to the present invention is a method of obtaining data for assessing potential for development of Dravet syndrome.

[0031] A kit according to the present invention is a kit for assessing a potential for development of Dravet syndrome, the kit comprising:

[0032] a polynucleotide being used for determining a mutation on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>7</sub>1.1: and

[0033] a polynucleotide being used for determining a mutation on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca  $_{\nu}2.1$ . The kit according to the present invention may be a kit for obtaining data for assessing a potential for development of Dravet syndrome.

[0034] A model animal of Dravet syndrome according to the present invention has a mutation on both  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub> $\nu$ </sub>1.1 and  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub> $\nu$ </sub>2.1.

[0035] A production method according to the present invention of a model animal of Dravet syndrome is a method of producing the model animal of Dravet syndrome described above, which method includes:

[0036] introducing a mutation on a  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel Na $_{\nu}1.1$ ; and

[0037] introducing a mutation on a  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$ .

[0038] A cell according to the present invention has a mutation on both  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na  $_{\nu}1.1$  and  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca  $_{\nu}2.1$ .

[0039] A method of producing a cell according to the present invention is a method of producing the cell described above, which method includes:

[0040] introducing a mutation on a  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel Na $_{\nu}1.1$ ; and

[0041] introducing a mutation on a  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel Ca<sub>p</sub>2.1.

[0042] A screening method according to the present invention of a drug for treating Dravet syndrome includes:

[0043] administering a candidate agent to the model animal of Dravet syndrome according to the present invention; and

[0044] assessing whether or not the administering of the candidate agent has made Dravet syndrome improve or cure in the model animal of Dravet syndrome.

[0045] A screening method according to the present invention of a drug for treating Dravet syndrome includes:

[0046] administering a candidate agent to the cell according to the present invention; and

[0047] assessing whether or not the administering of the candidate agent has made activity of the voltage-gated sodium ion channel Na $_{\nu}1.1$  and/or activity of the voltage-gated calcium ion channel Ca $_{\nu}2.1$  change in the cell.

[0048] For a fuller understanding of the nature and advantages of the invention, reference should be made to the ensuing detailed description taken in conjunction with the accompanying drawings.

Advantageous Effects of Invention

[0049] The method according to the present invention of assessing a potential for development of Dravet syndrome allows for obtaining data for assessing the potential for development of Dravet syndrome, by detecting mutations for both  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel

[0050] Na<sub>v</sub>1.1 and  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub>v</sub>2.1.

[0051] Patients of GEFS+, being a benign epilepsy, inherit the mutation of the SCN1A gene within the family. In comparison, in patients of Dravet syndrome, approximately 90% of the mutations on SCN1A gene are de novo mutation, i.e. are anew mutations in which a mutation arises even though their parents have no mutation. As such, although the GEFS+ patients and the Dravet syndrome patients are common in that a mutation is on the SCN1A gene, the cause for the difference in malignancy of the disease was unknown. However, it was clarified by the present inventors for the first time, that the presence of mutations on both the SCN1A gene and the CACNA1A gene is related to the worsening and intractableness of Dravet syndrome.

[0052] As described above, reports have already been made that a mutation on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>V</sub>1.1 (hereinafter, referred to as "sodium ion channel  $\alpha$ 1 subunit") is related to the development of Dravet syndrome. However, no reports have been made whatsoever that Dravet syndrome is related to a mutation on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub>V</sub>2.1 (hereinafter, referred to as "calcium ion channel  $\alpha$ 1 subunit").

[0053] Reports have been made that a mutation on a subunit other than the  $\alpha$ 1 subunit of voltage-gated calcium ion channel Ca $_{\nu}$ 2.1 is associated with Dravet syndrome (see Iori Ohmori et. Al., Neurobiology of Disease 32 (2008) 349-354). More specifically, this literature (Iori Ohmori et. Al.) discloses that a mutation on  $\beta$ 4 subunit of voltage-gated calcium ion channel Ca $_{\nu}$ 2.1 (hereinafter, simply referred to as "calcium ion channel (34 subunit") is associated with Dravet syndrome.

[0054] However, the foregoing literature strongly teaches regarding Dravet syndrome that a mutation on the "calcium ion channel  $\beta 4$  subunit" is important together with the mutation on the " $\alpha$ -subunit of sodium ion channel Na $_{\nu}1.1$ ". This description in the literature hinders a motivation to arrive at a point that a mutation suitable for detecting Dravet syndrome is present in the calcium ion channel  $\alpha$  1 subunit.

[0055] In the first place, a skilled person would not arrive at considering, just because a relationship of a mutation on a specific subunit with a disease is known for a specific channel, that other subunits would also have a mutation related to that disease. At least, the finding that the voltage-gated sodium ion channel  $Na_{\nu}1.1$  is related to Dravet syndrome is only known regarding the mutation on the " $\alpha$ 1 subunit"; this does not give motivation for analyzing mutations on other subunits.

[0056] As to a mutation on the calcium ion channel  $\alpha$  1 subunit, reports have been made stating a relationship with (1) epixodic ataxia type 2 (characterized in paroxysmal cerebellar ataxia), (2) familial hemiplegic migraine type 1 (e.g. hemiplegia, hemianopsia, dysphagia, throbbing headache), and (3) spinocerebellar ataxia type 6 (e.g. ataxic gait, limb ataxia, cerebellar dysarthria, nystagmus) (see Keiji IMOTO et al., "Igaku no Ayumi" (Development in Medical Science), Vol. 201, No. 13 (Issued Jun. 29, 2002); Taiji TSUNEMI et al., "Igaku no Ayumi" (Development in Medical Science), Vol. 201, No. 13 (Issued Jun. 29, 2002)). However, the dis-

eases of (1) to (3) all show no symptoms of epilepsy, and neither are diseases related to Dravet syndrome. At least, although the finding regarding the mutation on the calcium ion channel  $\alpha$  1 subunit is known as related to the diseases of (1) to (3), it is not one that gives motivation for analyzing a mutation on the calcium ion channel  $\alpha$  1 subunit in Dravet syndrome, which disease is completely unrelated to the diseases of (1) to (3).

[0057] The assessment method according to the present invention detects a mutation on  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel Na<sub>v</sub>1.1 and on  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel Ca<sub>1</sub>2.1. Hence, it is possible to detect Dravet syndrome with high accuracy. Consequently, the assessment method of the present invention brings about an effect that it is possible to improve reliability of a potential for detecting Dravet syndrome as compared to the conventional method by detecting a mutation on the SCN1A gene. Furthermore, detection of a mutation on α-subunit type 1 of the voltage-gated sodium ion channel  $Na_{\nu}1.1$  and a mutation on  $\alpha$ -subunit type 1 of the voltagegated calcium ion channel Ca<sub>v</sub>2.1 is possible even with an infant under the age of one. Hence, according to the assessment method of the present invention, an effect is brought about that data for assessing the potential for development in Dravet syndrome can be obtained from a patient in an early stage of development or in a stage prior to the onset of the intractable disease, in particular of an infant under the age of one.

[0058] Moreover, as shown in Examples later described, an effect is brought about that by detecting a mutation on both  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel Na $_{\nu}$ 1.1 and  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel Ca $_{\nu}$ 2.1, the detection sensitivity of Dravet syndrome patients dramatically improve.

[0059] Furthermore, with use of the kit according to the present invention, it is possible to easily detect the mutation on both  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel Na<sub> $\nu$ </sub>1.1 and  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel Ca<sub> $\nu$ </sub>2.1. Hence, the kit according to the present invention is useful for a general pediatrician to screen, at an early stage of disease of under the age of one, a patient of Dravet syndrome that requires treatment by a specialist, among benign febrile epilepsy.

[0060] By using the assessment method and kit according to the present invention, it is possible to detect the patients of Dravet syndrome with high accuracy at the point in time of an age under one, which is an age difficult to detect until now. Moreover, by sending a blood sample to an examination center and examining its abnormal genes, it is possible to detect a Dravet syndrome patient with high accuracy even in a private hospital at a remote location or the like.

[0061] Moreover, the Dravet syndrome model animal and cell according to the present invention can be usefully used for resolving a development mechanism of the intractable Dravet syndrome, and for development and the like of medicament for Dravet syndrome.

# BRIEF DESCRIPTION OF DRAWINGS

[0062] FIG. 1 is a view illustrating an amino acid sequence of a protein encoded by a human SCN1A gene and an amino acid sequence of a protein encoded by a rat Scn1a gene.

[0063] FIG. 2 is a view illustrating a result of performing function analysis of sodium ion channel, by use of patch clamping. Illustrated in (a) is a typical example of a sodium

current effected by a change in potential of a normal sodium ion channel and a mutant sodium ion channel. Illustrated in (b) is a result of examining a time constant ( $\tau$ ) at inactivation. [0064] FIG. 3 is a view illustrating a result of performing function analysis of a sodium ion channel, by use of patch clamping. Illustrated in (a) is a current-voltage relationship, illustrated in (b) is an activation curve of the sodium ion channel, illustrated in (c) is an inactivation curve of the sodium ion channel, and illustrated in (d) is a recovery curve from the inactivation of the sodium ion channel.

[0065] FIG. 4 is a view illustrating a result of performing function analysis of a sodium ion channel, by use of patch clamping. Illustrated in (a) is a sodium current flowing in the sodium ion channel, and illustrated in (b) is a relative value (%) of a persistent sodium current amount flowing into the sodium ion channel.

[0066] FIG. 5 is a view illustrating genotypes of parent rats (P), first filial generation (F1) rats, and second filial generation (F2) rats. Illustrated in (a) is a view showing genotypes of the parent rats (P) and the F1 rats. Illustrated in (b) are genotypes of the F1 rats and the F2 rats.

[0067] FIG. 6 is a view illustrating a method of identifying genotypes of the Scn1a gene and the Cacna1a gene of the F2 rat, by sequencing.

[0068] FIG. 7 is a view illustrating a method of identifying a genotype of the Scn1a gene of the F2 rat, by restriction enzyme digestion. Illustrated in (a) is a nucleotide sequence of where mutation is on a mutant Scn1a gene (N1417H), and a nucleotide sequence of a wild-type Scn1a gene corresponding to that nucleotide sequence of the mutant Scn1a gene. Illustrated in (b) is a size of a DNA fragment expected by the restriction enzyme digestion. Illustrated in (c) is a result of electrophoresis.

[0069] FIG. 8 is a view illustrating a method of identifying a genotype of the Cacna1a gene in a F2 rat, by restriction enzyme digestion. Illustrated in (a) is a nucleotide sequence of where a mutation is on a mutant Cacna1a gene (M251K), and a nucleotide sequence of a wild-type Cacna1a gene corresponding to that nucleotide sequence of the mutant Cacna1a gene. Illustrated in (b) is a size of a DNA fragment expected by the restriction enzyme digestion. Illustrated in (c) is a result of electrophoresis.

[0070] FIG. 9 is a view illustrating a result of examining an effect of a mutation on the Cacnala gene, in a rat having a mutation on Scnla gene. Illustrated in (a) is a body temperature at a time of convulsion onset (convulsion threshold), illustrated in (b) is a severity score, and illustrated in (c) is duration of the convulsion.

[0071] FIG. 10 is a view illustrating a part of an electroencephalogram at a time of seizure of a rat in group (3) (Scn1a mutant (homo)+Cacna1a mutant (hetero)).

[0072] FIG. 11 is a view illustrating an amino acid sequence of a protein encoded by a human CACNA1A gene and an amino acid sequence of a protein encoded by a rat Cacna1a gene.

[0073] FIG. 12 is a view illustrating a result of detecting a mutation on voltage-gated calcium ion channel  $Ca_{\nu}2.1$  a 1 subunit. Illustrated in (a) is a result of a mutation analysis of the CACNA1A gene, and schematically illustrated in (b) is a part where a mutation was detected in the calcium ion channel  $\alpha1$  subunit.

[0074] FIG. 13 is a view illustrating a result of performing function analysis of the calcium ion channel, by use of patch clamping. Illustrated in (a) is a barium current record effected by a change in potential of a normal calcium ion channel and a mutant calcium ion channel. Illustrated in (b) is a current-

voltage relationship, and illustrated in (c) is peak current value (pA), a total charge (pF) and a peak current density (pA/pF).

[0075] FIG. 14 is a view illustrating a result of performing function analysis of a calcium ion channel, by use of patch clamping. Illustrated in (a) is an activation curve of the calcium ion channel. Illustrated in (b) is a time constant of voltage-gated activation of the calcium ion channel. Illustrated in (c) is a time constant of voltage-gated activation at 20 mV. Illustrated in (d) is a voltage-gated inactivation curve of the calcium ion channel. Illustrated in (e) is a result of examining fast and slow inactivation time constants  $(\tau)$ .

#### DESCRIPTION OF EMBODIMENTS

[0076] Described below is an embodiment of the present invention in detail. The present invention is not limited to this embodiment however, and may be carried out in modes of various modifications that are made within the described scope. Moreover, all academic literature and patent literature disclosed in the present specification are incorporated as reference. Unless mentioned otherwise, numerical ranges expressed as "A to B" denote "not less than A but not more than B"

[0077] 1. Assessment method according to the present invention

[0078] A method of assessing a potential for development of Dravet syndrome according to the present invention (also referred to as "assessment method according to the present invention") is a method of assessing a potential for development of Dravet syndrome in a subject, by use of a sample taken from the subject. In the present specification, the "potential for development of Dravet syndrome" includes a potential that the Dravet syndrome is already developed and a potential that the Dravet syndrome may develop in the future. [0079] The subject is not particularly limited, and may be

an individual in which Dravet syndrome has developed (individual having potential for development) or may be an individual in which the Dravet syndrome is not developed (individual having no potential for development). Out of such individuals, it is preferable that the subject is of either infants or children.

[0080] The assessment method according to the present invention, more specifically, may be of any method as long as it includes, with use of a sample taken from the subject: detecting whether or not a mutation is on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na $_{\nu}1.1$ ; and detecting whether or not a mutation is on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca $_{\nu}2.1$ . Any other specific configurations are not limited in particular.

[0081] In the embodiment, the voltage-gated sodium ion channel Na $_{\nu}1.1$  is made up of  $\alpha$ -subunit type 1,  $\beta_1$  subunit, and  $\beta_2$  subunit. The  $\beta_1$  subunit and the  $\beta_2$  subunit are auxiliary subunits.

[0082] The  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na $_{\nu}1.1$  (hereinafter, referred to as "sodium ion channel  $\alpha1$  subunit") is for example a polypeptide that is registered as GenBank accession No. AB093548 (i.e. amino acid sequence represented by SEQ ID NO. 1). Moreover, an example of a gene that encodes the  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na $_{\nu}1.1$  (hereinafter, called "sodium ion channel  $\alpha1$  subunit gene") is, as a SCN1A gene, a polynucleotide made up of a nucleotide sequence registered as GenBank accession No. AB093548 (i.e. nucleotide sequence represented by SEQ ID NO. 2).

[0083] The voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$  is made up of  $\alpha$ -subunit type 1,  $\beta$  subunit,  $\gamma$  subunit, and  $\alpha2\delta$  subunit.

[0084] The voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$   $\alpha$ -subunit type 1 (hereinafter, referred to as "calcium ion channel al subunit") is for example a polypeptide registered as GenBank accession No. NM 023035 (i.e. amino acid sequence represented by SEQ ID NO. 3). Moreover, an example of a gene that codes the  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$  (hereinafter, referred to as "calcium ion channel  $\alpha$ 1 subunit gene") is, as a CACNA1A gene, a polynucleotide made up of a nucleotide sequence registered as GenBank accession No. NM 023035 (i.e. nucleotide sequence represented by SEQ ID NO. 4).

[0085] In the present specification, for example, the term " $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>v</sub>1.1" denotes " $\alpha$ -subunit type 1 protein of voltage-gated sodium ion channel Na<sub>v</sub>1.1". Namely, in the present specification, unless it is clearly described as indicating a gene as like "gene encoding  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>v</sub>1.1" or " $\alpha$ -subunit type 1 gene of voltage-gated sodium ion channel Na<sub>v</sub>1.1", a protein is denoted. This way of description is not limited to the " $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>v</sub>1.1", and " $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>v</sub>1.1", is denoted similarly thereto.

[0086] It is preferable that the assessment method according to the present invention further includes, in addition to the detecting the presence of a mutation: detecting a change in activity of the voltage-gated sodium ion channel  $Na_{\nu}1.1$ ; and detecting a change in activity of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$ .

[0087] The assessment method according to the present invention may include, for detecting the mutation, a step such as preprocessing of a sample that is taken from the living organism. The "preprocessing" indicates, for example, a process of extracting DNA from the sample taken from the living organism, a process of extracting RNA from the sample taken from the living organism, a process of extracting protein from the sample taken from the living organism, or like process. These preprocessing can be carried out by use of conventionally known methods.

[0088] The assessment method according to the present invention may be a method of obtaining data for assessing a potential for development of Dravet syndrome. In this case, the present invention does not include the step of determining by a doctor.

[0089] (1-1. Detecting Presence of Mutation)

[0090] In the present specification, the "detecting presence of a mutation" denotes detecting a presence of a mutation on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>V</sub>1.1 and detecting a presence of a mutation on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub>V</sub>2.1.

[0091] In the assessment method according to the present invention, the detecting of the presence of a mutation on the  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>V</sub>1.1 may be performed prior to the detecting of the presence of a mutation on the  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub>V</sub>2.1 or vice versa, or may be performed simultaneously.

[0092] By detecting the presence of a mutation in both the sodium ion channel  $\alpha 1$  subunit and the calcium ion channel  $\alpha 1$  subunit, it is possible to obtain the data that enables accurate assessment of the potential for development of Dravet syndrome.

[0093] The mutation detected by the assessment method according to the present invention may be a mutation on a nucleotide sequence of a gene, or may be a mutation on an amino acid of a protein. The "mutation on a nucleotide sequence of a gene" is not limited in particular by a specific kind of mutation as long as it is a mutation that causes a change in an amino acid sequence of a protein encoded by a gene having a mutation on its nucleotide sequence as compared to an amino acid sequence of a protein encoded by a wild-type gene. Mutations on the nucleotide sequence as described above are, for example, missense mutation (substitution of an amino acid), nonsense mutation (synthesis of an amino acid stops in an incomplete state), frameshift (a frame of an amino acid codon shifts caused by insertion or deletion of a nucleotide, which causes an amino acid sequence downstream of the mutation position to change, thereby losing its original function), splicing defect (e.g. deletion of its exon region), minority nucleotide insertion or deletion (a part of amino acids is newly added or lost however its downstream is synthesized as normal amino acid), and minor deletion of an exon region (loss of one or a plurality of exon). Variations on the nucleotide sequence as such are not limited to mutations, and may also include gene polymorphism.

[0094] Moreover, in the assessment method according to the present invention, the detection of mutation may be performed to mRNA, cDNA, and proteins obtained from these genes.

[0095] In the present specification, "gene" can be replaced by "polynucleotide", "nucleic acid" or "nucleic acid molecule".

[0096] The "polynucleotide" means a polymer of a nucleotide. Hence, the term "gene" in the present specification includes not only the double stranded DNA but also a single stranded DNA and RNA (mRNA, etc.) such as a sense strand and an antisense strand that construct the double stranded DNA.

[0097] The term "DNA" encompasses cDNA, genomic DNA and the like that can be obtained by cloning, a chemically synthesized technique or a combination of these. Namely, DNA may be a "genome" type DNA, which includes a noncoding sequence such as intron or the like that is a form included in an animal genome, or may be a cDNA obtained from mRNA with use of reverse transcriptase or polymerase, i.e. "transcription" type DNA that does not include a noncoding sequence such as intron.

[0098] Examples of the mutation on sodium ion channel a 1 subunit is, more specifically, a mutation of asparagine (N) at position 1417 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, and is preferably a mutation of asparagine (N) at position 1417 to histidine (H) ("N1417H" in Table 1). This mutation is caused by, for example, a mutation of adenine (A) at position 4249 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of adenine (A) at position 4249 with cytosine (C) (A4249C). [0099] Moreover, another embodiment is a mutation of lysine (K) at position 1027 of the amino acid sequence of the sodium ion channel a 1 subunit represented by SEQ ID NO. 1, preferably a mutation of lysine (K) at position 1027 to a stop codon ("K1027X" in Table 1). This mutation is caused by, for example, a mutation of adenine (A) at position 3079 of the nucleotide sequence of sodium ion channel α1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of adenine (A) at position 3079 with thymine (T) (A3079T).

[0100] Yet another embodiment is a mutation of glutamine (Q) at position 1450 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a mutation of glutamine (Q) at position 1450 to arginine (R) ("Q1450R" in Table 1). This mutation is caused by, for example, a mutation of adenine (A) at position 4349 of a nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of adenine (A) at position 4349 with guanine (G) (A4349G).

[0101] Yet another embodiment is a mutation of threonine (T) at position 1082 of the amino acid sequence of sodium ion channel α1 subunit represented by SEQ ID NO. 1, preferably a mutation causing generation of a stop codon at position 1086 by frameshift ("T1082fsX1086" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 3245 of a nucleotide sequence of sodium ion channel a 1 subunit gene represented by SEQ ID NO. 2, preferably a deletion of cytosine (C) at position 3245 (C3245de1).

[0102] Yet another embodiment is a mutation of lysine (K) at position 547 of the amino acid sequence of the sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a mutation causing generation of a stop codon at position 570 by frameshift ("K547fsX570" in Table 1). This mutation is caused by, for example, a mutation at position 1641 of the nucleotide sequence of the sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably an insertion of adenine (A) into position 1641 (1641insA).

[0103] Yet another embodiment is a mutation of proline (P) at position 707 of the amino acid sequence of sodium ion channel α1 subunit represented by SEQ ID NO. 1, preferably a mutation causing generation of a stop codon at position 714 by frameshift ("P707fsX714" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 2120 in the nucleotide sequence of sodium ion channel al subunit gene represented by SEQ ID NO. 2, preferably a deletion of cytosine (C) at position 2120 (C2120de1).

[0104] Yet another embodiment is a mutation of arginine

(R) at position 712 of the amino acid sequence of sodium ion channel a subunit represented by SEQ ID NO. 1, preferably a mutation of arginine (R) at position 712 to a stop codon ("R712X" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 2134 of the nucleotide sequence of the sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of cytosine (C) at position 2134 with thymine (T) (C2134T). [0105] Yet another embodiment is a mutation of leucine (L) at position 1265 of the amino acid sequence of the sodium ion channel α 1 subunit represented by SEQ ID NO. 1, preferably a mutation of leucine (L) at position 1265 to proline (P) ("L1265P" in Table 1). This mutation is caused by, for example, a mutation of thymine (T) at position 3794 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of thymine (T) at position 3794 with cytosine (C) (T3794C).

**[0106]** Yet another embodiment is a deletion of amino acid of positions 460 to 554 of the amino acid sequence of the sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1 ("Exon10" in Table 1). This mutation is caused by, for example, a deletion of nucleotide at positions 1378 to 1662 (exon 10) of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2.

[0107] Yet another embodiment is a mutation of arginine (R) at position 865 of the amino acid sequence of the sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, pref-

erably a mutation of arginine (R) at position 865 to a stop codon ("R865X" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 2593 of the nucleotide sequence of the sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of cytosine (C) at position 2593 with thymine (T) (C2593T). [0108] Yet another embodiment is a mutation of arginine (R) at position 1648 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a substitution of arginine (R) at position 1648 with cysteine (C) ("R1648C" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 4942 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of cytosine (C) at position 4942 with thymine (T) (C4942T).

[0109] Yet another embodiment is a mutation of arginine (R) at position 931 in the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a substitution of arginine (R) at position 931 with cysteine (C) ("R931C" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 2791 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of cytosine (C) at position 2791 with thymine (T) (C2791T).

[0110] Yet another embodiment is a mutation of arginine (R) at position 501 in the amino acid sequence of sodium ion channel α1 subunit represented by SEQ ID NO. 1, preferably a mutation causing generation of a stop codon at position 543 by frameshift ("R501fsX543" in Table 1). This mutation is caused by, for example, a mutation of guanine (G) at position 1502 of the nucleotide sequence of sodium ion channel al subunit gene represented by SEQ ID NO. 2, preferably a deletion of guanine (G) at position 1502 (G1502de1).

[0111] Yet another embodiment is a mutation of alanine (A) at position 1002 in the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a mutation causing generation of a stop codon at position 1009 by frameshift ("A1002fsX1009" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 3006 of the nucleotide sequence of sodium ion channel al subunit gene represented by SEQ ID NO. 2, preferably a deletion of cytosine (C) at position 3006.

[0112] Yet another embodiment is a mutation of phenylalanine (F) at position 902 of the amino acid sequence of sodium ion channel  $\alpha 1$  subunit represented by SEQ ID NO. 1, preferably a mutation of phenylalanine (F) at position 902 to cysteine (C) ("F902C" in Table 1). This mutation is caused by, for example, a mutation of thymine (T) at position 2705 of the nucleotide sequence of sodium ion channel  $\alpha 1$  subunit gene represented by SEQ ID NO. 2, preferably by a substitution of thymine (T) at position 2705 with guanine (G) (T2705G).

[0113] Yet another embodiment is a mutation of glycine (G) at position 1674 of the amino acid sequence of aodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a substitution of glycine (G) at position 1674 with arginine (R) ("G1674R" in Table 1). This mutation is caused by, for example, a mutation of guanine (G) at position 5020 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of guanine (G) at position 5020 with cytosine (C) (G5020C).

[0114] Yet another embodiment is a mutation of valine (V) at position 1390 of the amino acid sequence of sodium ion channel  $\alpha 1$  subunit represented by SEQ ID NO. 1, preferably a mutation of valine (V) at position 1390 to methionine (M)

("V1390M" in Table 1). This mutation is caused by, for example, a mutation of guanine (G) at position 4168 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of guanine (G) at position 4168 with adenine (A) (G4168A).

[0115] Yet another embodiment is a mutation of serine (S) at position 607 in the amino acid sequence of sodium ion channel α1 subunit represented by SEQ ID NO. 1, preferably a mutation causing generation of a stop codon at position 622 by frameshift ("S607fsX622" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 1820 of the nucleotide sequence of sodium ion channel al subunit gene represented by SEQ ID NO. 2, preferably a deletion of cytosine (C) at position 1820 (C1820de1).

[0116] Yet another embodiment is a mutation of tryptophan (W) at position 1434 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a substitution of tryptophan (W) at position 1434 with arginine (R) ("W1434R" in Table 1). This mutation is caused by a mutation of thymine (T) at position 4300 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of thymine (T) at position 4300 with cytosine (C) (T4300C).

[0117] Yet another embodiment is a mutation of threonine (T) at position 1909 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a substitution of threonine (T) at position 1909 with isoleucine (I) ("T1909I" in Table 1). This mutation is caused by, for example, the mutation of cytosine (C) at position 5726 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably by a substitution of cytosine (C) at position 5726 with thymine (T) (C5726T).

[0118] Yet another embodiment is a mutation of phenylalanine (F) at position 1289 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a deletion of phenylalanine (F) at position 1289 ("F1289de1" in Table 1). This mutation is caused by, for example, mutations of cytosine (C) at position 3867, thymine (T) at position 3868, and thymine (T) at position 3869, each in the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a deletion of cytosine (C) at position 3867, thymine (T) at position 3868, and thymine (T) at position 3868, and thymine (T) at position 3869.

[0119] Yet another embodiment is a mutation of tryptophan (W) at position 1271 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a mutation of tryptophan (W) at position 1271 to a stop codon ("W1271X" in Table 1). This mutation is caused by, for example, a mutation of guanine (G) at position 3812 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably by a substitution of guanine (G) at position 3812 with adenine (A) (G3812A).

[0120] Yet another embodiment is a mutation of alanine (A) at position 1429 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a mutation causing generation of a stop codon at position 1443 by frameshift ("A1429fsX1443" in Table 1). This mutation is caused by, for example, a mutation of five-nucleotide CCACA between positions 4286 to 4290 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of CCACA at positions 4286 to 4290, with ATGTCC.

[0121] Moreover, another embodiment is a mutation of glycine (G) at position 1880 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a mutation causing generation of a stop codon at position 1881 by frameshift ("G1880fsX1881" in Table 1). This mutation is caused by mutation of six-nucleotide AGAGAT between positions 5640 to 5645 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of six-nucleotide AGAGAT between positions 5640 to 5645 with CTAGAGTA.

[0122] Yet another embodiment is a mutation of alanine (A) at position 1685 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a substitution of alanine (A) at position 1685 with aspartic acid (D) ("A1685D" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 5054 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably by a substitution of cytosine (C) at position 5054 with adenine (A) (C5054A).

[0123] Yet another embodiment is a mutation of arginine (R) at position 377 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a substitution of arginine (R) at position 377 with leucine (L) ("R377L" in Table 1). This mutation is caused by, for example, a mutation of guanine (G) at position 1130 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably by substitution of guanine (G) at position 1130 with thymine (T) (G1130T).

[0124] Yet another embodiment is a mutation of serine (S) at position 1574 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a mutation of serine (S) at position 1574 to a stop codon ("51574X" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 4721 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of cytosine (C) at position 4721 with guanine (G) (C4721G).

[0125] Yet another embodiment is a mutation of glutamine (Q) at position 1277 in the amino acid sequence of the sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a mutation of glutamine (Q) at position 1277 to a stop codon ("Q1277X" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 3829 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably by a substitution of cytosine (C) at position 3829 with thymine (T) (C3829T).

[0126] Yet another embodiment is a mutation of glycine (G) at position 177 of the amino acid sequence of sodium ion channel  $\alpha 1$  subunit represented by SEQ ID NO. 1, preferably a mutation of glycine (G) at position 177 to arginine (R) ("G 177R" in Table 1). This mutation is caused by, for example, a mutation of guanine (G) at position 529 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably by a substitution of guanine (G) at position 529 with adenine (A) (G529A).

[0127] Yet another embodiment is a mutation of glutamic acid (E) at position 788 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a substitution of glutamic acid (E) at position 788 with lysine (K) ("E788K" in Table 1). This mutation is caused by, for example, a mutation of guanine (G) at position 2362 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably by a substitution of guanine (G) at position 2362 with adenine (A) (G2362A).

[0128] Yet another embodiment is splicing defects at positions 1429 and subsequent positions of the amino acid sequence of sodium ion channel α1 subunit represented by SEQ ID NO. 1, preferably a deletion of positions at and subsequent to 1429 ("intron 21" in Table 1). This mutation is caused by, for example, a mutation of adenine (A) at a second last position (position -2), preferably a mutation in which adenine (A) at a second last position (position -2) of the intron 21 is substituted with guanine (G) (intron 21 ag(-2) gg), out of the intron 21 present in a genomic DNA between positions 4284 and 4285 of the nucleotide sequence of sodium ion channel a 1 subunit gene represented by SEQ ID NO. 2. Namely, the second last nucleotide sequence of the intron 21 present in the genomic DNA between positions 4284 (exon 21) and 4285 (exon 22) of the nucleotide sequence of sodium ion channel a 1 subunit gene represented by SEQ ID NO. 2 is ag, and is connected to the beginning of the exon 22. Generally, since the ag of the intron 21 is a recognition sequence that is spliced, in a case in which an abnormality exists at that position, the intron is determined as still continuing, which thus causes the exon immediately after (or in its downstream) to be abnormally spliced. This makes it impossible to generate a full-length protein.

[0129] Yet another embodiment is a mutation of serine (S) at position 1574 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a mutation of serine (S) at position 1574 to a stop codon ("51574X" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 4721 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of cytosine (C) at position 4721 with guanine (G).

[0130] Yet another embodiment is a mutation of valine (V) at position 212 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a substitution of valine (V) at position 212 with alanine (A) ("V212A" in Table 1). This mutation is caused by, for example, a mutation of thymine (T) at position 635 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of thymine (T) at position 635 with cytosine (C) (T635C).

[0131] Yet another embodiment is a mutation of threonine (T) at position 1539 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a mutation of threonine (T) at position 1539 to proline (P) ("T1539P" in Table 1). This mutation is caused by, for example, a mutation of adenine (A) at position 4615 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of adenine (A) at position 4615 with cytosine (C) (A4615C).

[0132] Yet another embodiment is a mutation of tryptophan (W) at position 738 of the amino acid sequence of sodium ion channel α1 subunit represented by SEQ ID NO. 1, preferably by mutation causing generation of a stop codon at position 746 by frameshift ("W738fsX746" in Table 1). This mutation is caused by, for example, a mutation of guanine (G) at position 2213 in the nucleotide sequence of the sodium ion channel a 1 subunit gene represented by SEQ ID NO. 2, preferably a deletion of guanine (G) at position 2213 (G2213de1).

[0133] Yet another embodiment is a mutation of leucine (L) at position 990 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably by a mutation of leucine (L) at position 990 to phenylalanine (F) ("L990F" in Table 1). This mutation is caused by, for

example, a mutation of guanine (G) at position 2970 of the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of guanine (G) at position 2970 with thymine (T) (G2970T).

[0134] Yet another embodiment is a mutation of glycine (G) at position 163 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a mutation of glycine (G) at position 163 to glutamic acid (E) ("G163E" in Table 1). This mutation is caused by, for example, a mutation of guanine (G) at position 488 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of guanine (G) at position 488 with adenine (A) (G488A).

[0135] Yet another embodiment is a mutation of alanine (A) at position 1662 of the amino acid sequence of sodium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 1, preferably a mutation of alanine (A) at position 1662 to valine (V) ("A1662V" in Table 1). This mutation is caused by, for example, a mutation of cytosine (C) at position 4985 in the nucleotide sequence of sodium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 2, preferably by a substitution of cytosine (C) at position 4985 with thymine (T) (C4985T).

[0136] Yet another embodiment is a mutation of lysine (K) at position 1057 of the amino acid sequence of sodium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 1, preferably a mutation causing generation of a stop codon at position 1073 by frameshift ("K1057fsX1073" in Table 1). This mutation is caused by, for example, a mutation of 14 nucleotides (AGAAAGACAGTTGT) between positions 3170 to 3183 of the nucleotide sequence of sodium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 2, preferably a substitution of the 14 nucleotides between the positions 3170 to 3183 with TCATTCTGTATG.

[0137] It is needless to say that the mutation on the  $\alpha$ -sub-unit type 1 of the voltage-gated sodium ion channel Na  $_{\nu}1.1$  is not limited to the mutations exemplified above.

[0138] Examples of mutations on a calcium ion channel al subunit encompass, more specifically, a mutation on methionine (M) at position 249 of an amino acid sequence of calcium ion channel  $\alpha$ 1 subunit represented by SEQ ID NO. 3, preferably a mutation on methionine (M) at position 249 to lysine (K) ("M249K" in Table 2). This mutation is caused by, for example, a mutation on thymidine (T) at position 746 of the nucleotide sequence of calcium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 4, preferably a mutation on thymidine (T) at position 746 substituted with adenine (A) (T746A).

[0139] Moreover, another embodiment is a mutation on glutamic acid (E) at position 921 of the amino acid sequence of calcium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 3, preferably a mutation on glutamic acid (E) at position 921 to aspartic acid (D) ("E921D" in Table 2). This mutation is, for example, caused by a mutation on adenine (A) at position 2762 of the nucleotide sequence of calcium ion channel  $\alpha$ 1 subunit gene represented by SEQ ID NO. 4, preferably a substitution of adenine (A) at position 2762 with cytosine (C) (A2762C).

[0140] Yet another embodiment is a mutation on glutamic acid (E) at position 996 of the amino acid sequence of calcium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 3, preferably a mutation on glutamic acid (E) at position 996 to valine (V) ("E996V" in Table 2). This mutation is, for example, caused by a mutation on adenine (A) at position 2987 of the nucleotide sequence of the calcium ion channel  $\alpha$ 

1 subunit gene represented by SEQ ID NO. 4, preferably a substitution of adenine (A) at position 2987 with thymine (T) (A2987T).

[0141] Yet another embodiment is a mutation on arginine (R) at position 1126 of the amino acid sequence of calcium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 3, preferably a mutation on arginine (R) at position 1126 to histidine (H) ("R1126H" in Table 2). This mutation is, for example, caused by a mutation on guanine (G) at position 3377 of the nucleotide sequence of calcium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 4, preferably a substitution of guanine (G) at position 3377 with adenine (A) (G3377A).

[0142] Yet another embodiment is a mutation on arginine (R) at position 2201 of the amino acid sequence of calcium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 3, preferably a mutation on arginine (R) at position 2201 to glutamine (Q) ("R2201Q" in Table 2). This mutation is, for example, caused by mutation on guanine (G) at position 6602 of the nucleotide sequence of calcium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 4, preferably by a substitution of guanine (G) at position 6602 with adenine (A) (G6602A).

[0143] Yet another embodiment is a mutation on glycine (G) at position 1108 of the amino acid sequence of calcium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 3, preferably a mutation on glycine (G) at position 1108 to serine (S) ("G1108S" in Table 2). This mutation is, for example, caused by a mutation on guanine (G) at position 3322 of the nucleotide sequence of calcium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 4, preferably a substitution of guanine (G) at position 3322 with adenine (A) (G3322A).

[0144] Yet another embodiment is a mutation on alanine (A) at position 924 of the amino acid sequence of calcium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 3, preferably a mutation of alanine (A) at position 924 to glycine (G) ("A924G" in Table 2). This mutation is, for example, caused by a mutation on cytosine (C) at position 2771 of the nucleotide sequence of calcium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 4, preferably a substitution of cytosine (C) at position 2771 with guanine (G) (C2771G).

[0145] Yet another embodiment is a mutation on glycine (G) at position 266 of the amino acid sequence of calcium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 3, preferably a mutation on glycine (G) at position 266 to serine (S) ("G2665" in Table 2). This mutation is, for example, caused by a mutation on guanine (G) at position 796 of the nucleotide sequence of calcium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 4, preferably by a substitution of guanine (G) at position 796 with adenine (A) (G796A).

[0146] Yet another embodiment is a mutation on lysine (K) at position 472 of the amino acid sequence of calcium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 3, preferably a mutation on lysine (K) at position 472 to arginine (R) ("K472R" in Table 2). This mutation is, for example, caused by a mutation on adenine (A) at position 1415 of the nucleotide sequence of calcium ion channel  $\alpha$  1 subunit gene represented by SEQ ID NO. 4, preferably by a substitution of adenine (A) at position 1415 with guanine (G) (A1415G).

[0147] Yet another embodiment is a deletion of an amino acid at positions 2202 to 2205 of the amino acid sequence of calcium ion channel  $\alpha$  1 subunit represented by SEQ ID NO. 3 ("de12202-2205" in Table 2). This mutation is, for example, caused by a mutation on ACCAGGAGCGGG of positions 6605 to 6616 of the nucleotide sequence of calcium ion chan-

nel a 1 subunit gene represented by SEQ ID NO. 4, preferably a deletion of ACCAGGAGCGGG at positions 6605 to 6616 (de16605-6616).

[0148] It is needless to say that the mutations related to the function abnormality of voltage-gated calcium ion channel  $Ca_{\nu}2.1$  is not limited to the mutations exemplified above.

[0149] The mutations on the foregoing sodium ion channel a 1 subunit and the mutations on the foregoing calcium ion channel  $\alpha$  1 subunit are organized into Table 1 and Table 2.

TABLE 1

M	Mutations on sodium ion channel α1 subunit								
1289de1F,	G177R,	Q1450R,	T1539P,						
A1002fsX1009,	G1880fsX1881,	R1648C,	T1909I,						
A1429fsX1443,	intron 21,	R377L,	V1390M,						
A1662V,	K1027X,	R501fsX543,	V212A,						
A1685D,	K1057fsX1073,	R712X,	W1271X,						
E788K,	K547fsX570,	R865X,	W1434R,						
Exon10*,	L1265P,	R931C,	W738fsX746,						
F902C,	L990F,	S1574X,	N1417H,						
G163E,	P707fsX714,	S607fsX622,							
G1674R,	Q1277X,	T1082fsX1086,							

Exon10\* exon deletion detected by MLPA

TABLE 2

Mutations on calcium ion channel α1 subunit								
A924G, del 2202-2205, E921D, M249K	E996V, G1108S, G266S,	K472R, R1126H, R2201Q,						

[0150] In the assessment method according to the present invention, it is preferable that the mutation on sodium ion channel  $\alpha$  1 subunit is, more specifically, at least one mutation shown in Table 1, and the mutation on calcium ion channel al subunit is, more specifically, at least one mutation shown in Table 2.

[0151] The assessment method according to the present invention is not limited in particular of how the presence of a mutation is detected for both the sodium ion channel a 1 subunit and the calcium ion channel  $\alpha$  1 subunit, and any method conventionally known may be used.

[0152] Examples of methods for detecting the presence of the mutation for both the sodium ion channel  $\alpha$  1 subunit gene and the calcium ion channel  $\alpha$  1 subunit gene encompass mutation detecting methods such as DNA sequencing method using PCR, SSCP method (Single strand conformation polymorphism), DHPLC method (denaturing high performance liquid chromatography); polymorphism detecting methods using real-time PCR or DNA chip; method of detecting micro-deletion of exons of a gene; and Northern blotting, RT-PCR, Real-time PCR, and cDNA array, each of which detect an increase and decrease of mRNA. Moreover, when the presence of mutation is to be detected for both of sodium ion channel  $\alpha$  1 subunit protein and calcium ion channel  $\alpha$  1 subunit protein, a method such as Western blotting, immunostaining, protein array or the like may be used.

[0153] The following provides more specific descriptions, by separating into the following embodiments: (A) an embodiment detecting a gene mutation with use of a genomic DNA included in a sample taken from a subject, (B) an embodiment detecting a gene mutation with use of mRNA (cDNA) included in a sample taken from a subject, and (C) an embodiment detecting a protein mutation with use of a protein included in a sample taken from a subject.

[0154] (A) Embodiment Using Genomic DNA

[0155] In the embodiment detecting a gene mutation with use of a genomic DNA included in a sample taken from a subject, first, a genomic DNA is extracted from the sample taken from the subject, by a conventionally known method.

[0156] The "sample taken from the subject" is not limited in particular, and any sample from which a genomic DNA is extractable can be used. More specifically, a sample of blood, oral mucosa cells, bone marrow fluid, hair, various organs, peripheral lymphocytes, synovial cells or the like can be used. Moreover, cells taken from the subject may be cultured and a genomic DNA may be extracted from its proliferated cells.

[0157] Moreover, the extracted genomic DNA may be used upon amplification by a gene amplification method generally performed, for example, PCR (Polymerase Chain Reaction), NASBA (Nucleic acid sequence based amplification), TMA (Transcription-mediated amplification), SDA (Strand Displacement Amplification), LAMP (Loop-Mediated Isothermal Amplification), and ICAN (Isothermal and Chimeric primer-initiated Amplification of Nucleic acids).

[0158] The method of detecting the presence of mutation for both the sodium ion channel  $\alpha$  1 subunit gene and the calcium ion channel  $\alpha$  1 subunit gene with use of a sample including a genomic DNA prepared as such is not limited in particular, and examples encompass allele-specific oligonucleotide probe method, Oligonucleotide Ligation Assay, PCR-SSCP, PCR-CFLP, PCR-PHFA, invader method, RCA (Rolling Circle Amplification), Primer Oligo Base Extension, and like methods.

[0159] More specifically, a polynucleotide for detecting a mutation on  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel Na $_{\nu}1.1$  and a polynucleotide for detecting a mutation on  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel Ca $_{\nu}2.1$  are used to detect, from the genomic DNA, the presence of a mutation for both the sodium ion channel  $\alpha$  1 subunit gene and the calcium ion channel  $\alpha$ 1 subunit gene.

[0160] The "polynucleotide for detecting a mutation on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na $_{\nu}1$ . 1" is indicative of a polynucleotide having a nucleotide sequence complementary to a set region in a sodium ion channel al subunit gene (e.g. a region including an exon, or boundary region between an exon and an intron). The "polynucleotide for detecting a mutation on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca $_{\nu}2$ .1" is indicative of a polynucleotide having a nucleotide sequence complementary to a set region in the calcium ion channel  $\alpha$ 1 subunit gene (e.g. a region including an exon, or a boundary region between an exon and an intron).

[0161] The "polynucleotide for detecting a mutation on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na $_{\nu}1$ . 1" is, more specifically, a polynucleotide having a nucleotide sequence represented by any one of SEQ ID NOs.: 5, 6, and 9 to 62, for example. Moreover, the "polynucleotide for detecting a mutation on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca $_{\nu}2$ .1" is, more specifically, a polynucleotide having a nucleotide sequence represented by any one of SEQ ID NOs.: 7, 8, and 63 to 143.

**[0162]** Two kinds of the polynucleotides may be used in combination as a primer pair, or one kind may be used as a probe. When the two kinds are used in combination as a primer pair, the polynucleotides may be used in combinations as exemplified in Examples described later.

[0163] When two kinds of the polynucleotides are used in combination as a primer pair, it is possible, for example, to amplify a set region in the gene by PCR with use of a corre-

sponding primer pair, and thereafter, directly sequence the obtained PCR product, to detect the presence of the mutation in the gene.

[0164] Moreover, two kinds of fluorescence-labeled polynucleotides may be used as a primer pair, to amplify a set region of the gene by PCR, perform gel electrophoresis or capillary electrophoresis with the obtained PCR product, and study a strength of the signals, so as to detect the presence of a mutation in the gene.

[0165] Moreover, when one kind of the polynucleotides is to be solely used as a probe, the presence of the mutation on the gene can be detected by, for example, digesting the genomic DNA with an appropriate restriction enzyme and detecting a difference in size of the digested genomic DNA fragment by Southern blotting or the like.

[0166] As such, by detecting the presence of mutations for both the sodium ion channel  $\alpha$  1 subunit gene and calcium ion channel  $\alpha$  1 subunit gene with use of the genomic DNA included in the sample taken from the subject, it is possible to obtain data for assessing a potential for development of Dravet syndrome in the subject. More specifically, when a mutation is found on both the sodium ion channel  $\alpha$  1 subunit gene and the calcium ion channel  $\alpha$  1 subunit gene in the obtained data, it can be assessed that the subject has a high potential for development of Dravet syndrome.

[0167] The primer pair and probe used in the method of detecting the mutation may be prepared by a DNA synthesizer or the like, as in law of the art.

[0168] (B) Embodiment Using mRNA (cDNA)

[0169] In the embodiment of detecting a mutation with use of mRNA included in a sample taken from the subject, first, mRNA is extracted from a sample taken from the subject, with use of a conventionally known method.

[0170] The "sample taken from the subject" is not limited in particular, and any sample can be used as long as mRNA can be extracted therefrom and a gene that can be subjected to the detection of a mutation is expressed or is possibly expressed. The "sample taken from the subject" is preferably, for example, a peripheral blood leukemic cell, dermal fibroblast, oral mucosa cell, neuron, or muscle cell, each of a patient.

[0171] Subsequently, cDNA is prepared from the extracted mRNA by reverse transcription reaction. Furthermore, if necessary, the obtained cDNA may be amplified by a gene amplification method generally performed, for example PCR (Polymerase Chain Reaction), NASBA (Nucleic acid sequence based amplification), TMA (Transcription-mediated amplification), SDA (Strand Displacement Amplification), LAMP (Loop-Mediated Isothermal Amplification), and ICAN (Isothermal and Chimeric primer-initiated Amplification of Nucleic acids).

[0172] The method of detecting the presence of the mutation for both the sodium ion channel  $\alpha$  1 subunit gene and calcium ion channel  $\alpha$  1 subunit gene with use of a sample including cDNA prepared as such is not limited in particular; whether or not a gene mutation is present in a subject that is subjected to mutation detection may be detected with use of a similar method as with a case in which a gene mutation is detected with use of a genomic DNA, as described in the foregoing "(A) Embodiment using genomic DNA".

[0173] By detecting the presence of the mutation for both the sodium ion channel  $\alpha$  1 subunit gene and calcium ion channel  $\alpha$ 1 subunit gene with use of mRNA included in the sample that is taken from the subject, it is possible to obtain data for assessing a potential for development of Dravet syn-

drome in the subject. More specifically, when a mutation is found in both the sodium ion channel  $\alpha$  1 subunit gene and the calcium ion channel  $\alpha$  1 subunit gene in the obtained data, it can be assessed that the subject has a high potential for the development of Dravet syndrome.

[0174] (C) Embodiment Using Protein

[0175] In the embodiment of detecting a mutation using protein included in the sample taken from a subject, first, protein is extracted from the sample taken from the subject with use of a conventionally known method.

[0176] The sample taken from the subject is not limited in particular, and may be any sample from which protein is extractable and in which both of sodium ion channel a 1 subunit protein and calcium ion channel  $\alpha$  1 subunit protein are expressed or is possibly expressed.

[0177] The method of detecting the presence of mutation for both the sodium ion channel  $\alpha$  1 subunit protein and the calcium ion channel  $\alpha$  1 subunit protein with use of the sample including the protein prepared as described above is not limited in particular, and for example an antibody which specifically recognizes just a protein having a set mutation may be prepared, to detect the mutation by ELISA or Western blotting using that antibody. In the present specification, the term "protein" may be used replaceable with "polypeptide" or "peptide".

[0178] Moreover, mutation may be detected by isolating a protein to be subjected to the mutation detection from the sample including the foregoing protein, and digesting the isolated protein with an enzyme or the like directly or if necessary, with use of a protein sequencer or a mass spectrometer. Alternatively, the mutation may be detected on the basis of an isoelectric point of the isolated protein.

[0179] As such, by detecting the presence of a mutation for both of the sodium ion channel  $\alpha 1$  subunit protein and the calcium ion channel  $\alpha 1$  subunit protein with use of a protein included in the sample taken from the subject, it is possible to obtain data for assessing potential for development of Dravet syndrome in the subject. More specifically, when a mutation is found on both the sodium ion channel  $\alpha 1$  subunit protein and the calcium ion channel  $\alpha 1$  subunit protein in the obtained data, it is possible to assess that the subject has a high potential for development of Dravet syndrome.

[0180] (1-2. Step of Detecting Change in Activity)

[0181] In the present specification, the "step of detecting change in activity" is indicative of a step of detecting whether activity of the voltage-gated sodium ion channel  $\mathrm{Na}_{\nu}1.1$  has changed and a step of detecting whether activity of the voltage-gated calcium ion channel  $\mathrm{Ca}_{\nu}2.1$  has changed.

[0182] As described in Examples later described, it is considered that the change in activity in both the voltage-gated sodium ion channel  $Na_{\nu}1.1$  and the voltage-gated calcium ion channel  $Ca_{\nu}2.1$ , caused by the mutations on the sodium ion channel  $\alpha 1$  subunit, is related to the development of Dravet syndrome. Hence, although the mutation on the sodium ion channel  $\alpha 1$  subunit is not particularly limited in its position, it is preferable that the mutation is on a position that causes a change in the activity of the voltage-gated sodium ion channel  $Na_{\nu}1.1$ . Moreover, although the mutation on the calcium ion channel  $\alpha 1$  subunit is not particularly limited in its position, it is preferable that the mutation is on a position that causes a change in the activity of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$ .

[0183] Here, the activity of the voltage-gated sodium ion channel  $Na_{\nu}1.1$  is, more specifically, an activity to allow transmission of sodium ion (Na+) into the cell by depending on membrane potential. The change in activity of the voltage-gated sodium ion channel  $Na_{\nu}1.1$  is not limited in particular, and may be an increase of activity or may be a decrease in activity. Namely, the change is sufficiently one that shows an abnormality in the activity of the voltage-gated sodium ion channel  $Na_{\nu}1.1$ .

[0184] In the present specification, "the activity of the voltage-gated sodium ion channel  $\mathrm{Na}_{\nu}1.1$  is changed" indicates that an activity of a mutant voltage-gated sodium ion channel  $\mathrm{Na}_{\nu}1.1$  including the sodium ion channel  $\alpha1$  subunit on which the mutation is present is of a value having a statistically significant difference based on a significant test as compared to an activity of a wild-type voltage-gated sodium ion channel  $\mathrm{Na}_{\nu}1.1$ , and preferably indicates that p is equal to or smaller than 0.05 by Student's t-test.

[0185] Moreover, the activity of the voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$  is, more specifically, an activity that causes transmission of calcium ion  $(\text{Ca}^{2+})$  into the cell to be membrane voltage-gated. The change in function of the voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$  is not particularly limited, and may be the increase of activity or the decrease in activity. Namely, the change is sufficiently one that shows abnormality of the activity of the voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$ .

[0186] In the present specification, "the activity of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  is changed" indicates that the activity of a mutant voltage-gated calcium ion channel  $Ca_{\nu}2.1$  including the calcium ion channel al subunit on which a mutation is present is of a value having a statistically significant difference based on a significant test as compared to an activity of a wild-type voltage-gated calcium ion channel  $Ca_{\nu}2.1$ , and preferably indicates that p is equal to or smaller than 0.05 by Student's t-test.

[0187] An example of a method of detecting that the activity of the voltage-gated sodium ion channel Na<sub>v</sub>1.1 is changed by the mutation is, for example, (i) coexpressing, in a culture cell with use of a expression vector or the like, a sodium ion channel  $\alpha$ 1 subunit gene on which a mutation is present with a wild-type gene ( $\beta_1$  subunit gene and  $\beta_2$  subunit gene) that encodes a subunit ( $\beta_1$  subunit and  $\beta_2$  subunit) other than the  $\alpha 1$  subunit, which wild-type gene makes up the voltage-gated sodium ion channel Na<sub>v</sub>1.1, (ii) measuring an activity of the voltage-gated sodium ion channel Na<sub>v</sub>1.1 on which a mutation is present with use of the obtained cultured cell, and (iii) comparing the activity with an activity of the wild-type voltage-gated sodium ion channel Na<sub>v</sub>1.1, to confirm whether the activity of the voltage-gated sodium ion channel Na<sub>v</sub>1.1 is changed. The method of measuring the activity of the voltage-gated sodium ion channel Na<sub>v</sub>1.1 is not particularly limited, however it is possible to use the conventionally known patch clamping, imaging with use of a fluorescence probe, or like method.

[0188] An example of a method of detecting that the activity of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  is changed by mutation is by (i) coexpressing, in a culture cell with use of an expression vector or the like, a calcium ion channel al subunit gene on which a mutation is present with a wild-type gene ( $\beta$  subunit gene,  $\gamma$  subunit gene, and  $\alpha 2\delta$  subunit gene) that encodes a subunit ( $\beta$  subunit,  $\gamma$  subunit, and  $\alpha 2\delta$  subunit) other than the  $\alpha 1$  subunit, which wild-type gene makes up the voltage-gated calcium ion channel  $Ca_{\nu}2.1$ , (ii)

measuring, with the obtained cultured cell, an activity of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  on which the mutation is present, and (iii) comparing the activity with an activity of the wild-type voltage-gated calcium ion channel  $Ca_{\nu}2.1$ , to confirm whether the activity of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  is changed. The method of measuring the activity of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  is not limited in particular, however it is possible to use the conventionally known patch clamping, imaging using an optical probe, a calcium indicator, or a caged compound, for example.

[0189] The assessment method according to the present invention, since it includes the foregoing configuration, it is possible to obtain data for assessing a potential for development of Dravet syndrome in the subject. Hence, with the assessment method according to the present invention, it is possible to find out, with high accuracy and at an early stage, Dravet syndrome having the unfavorable prognosis, which thus allows for preparing a treatment management system by an epilepsy specialist from an earlier stage for a Dravet syndrome patient. As a result, it is possible to improve treatment intervention of the patient, reduce the mental burden on their families, and reduce the economical burden. Furthermore, it is possible to provide appropriate treatment for the patient of Dravet syndrome; this hence reduces medical fees.

[0190] 2. Kit According to the Present Invention

[0191] The present invention also encompasses a kit for assessing the potential for development of Dravet syndrome, with use of the assessment method according to the present invention (hereinafter, also referred simply as "kit according to the present invention").

[0192] The kit according to the present invention is not limited in its specific configuration in particular as long as it includes at least a reagent for detecting the presence of mutation on  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel Na<sub> $\nu$ </sub>1.1 and a reagent for detecting the presence of mutation on  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel Ca<sub> $\nu$ </sub>2.1.

[0193] As described in "1. Assessment method according to the present invention", ways considered to detect the presence of mutation for both of  $\alpha$ -subunit type 1 of the voltagegated sodium ion channel Na $_{\nu}$ 1.1 and  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel Ca $_{\nu}$ 2.1 are (A) detecting a gene mutation with use of a genomic DNA included in a sample taken from a subject, or (B) detecting a gene mutation with use of mRNA (cDNA) included in a sample taken from the subject.

[0194] Hence, in order to detect a mutation using a genomic DNA included in the sample taken from the subject or mRNA (cDNA) included in the sample taken from the subject, the kit according to the present invention includes a polynucleotide being used for determining a mutation on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub> $\nu$ </sub>1.1; and a polynucleotide being used for determining a mutation on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub> $\nu$ </sub>2.1. Such polynucleotides can be used as, for example, a primer pair or a probe. These polynucleotides may be included solely or may be included as a combination of a plurality thereof.

[0195] The kit according to the present invention encompasses (A) a kit for detecting a mutation with use of a genomic DNA included in a sample taken from a subject and (B) a kit for detecting a mutation with use of a mRNA (cDNA) included in a sample taken from a subject. The following specifically describes the reagents included in the embodiments of the kits in (A) or (B).

[0196] (A) Kit for detecting mutation with use of genomic DNA included in sample taken from subject

[0197] For example, a configuration of the sodium ion channel  $\alpha 1$  subunit and the calcium ion channel  $\alpha 1$  subunit may include a primer pair designed so as to allow amplification of the genomic DNA of each of the genes or a part of its region, or may include a probe designed so that one of genomic DNA of its mutant type or wild-type can be specifically detected. These polynucleotides are as described in the foregoing (A) Embodiment using genomic DNA in "1. Assessment method according to the present invention", so hence its description has been omitted here.

[0198] Furthermore, such a kit may be configured to include, in addition to the primer pair or probe, a combination of one or more reagent necessary for detecting the presence of the mutation on the gene, such as a reagent used in PCR, Southern blotting, and nucleic acid sequencing.

[0199] The reagent is selected and employed as appropriate in accordance with the detection method of the present invention, and examples thereof are dATP, dCTP, dTTP, dGTP, DNA polymerase and the like. Furthermore, the kit according to the present invention may include a suitable buffer solution and a washing solution that can be used in the PCR, Southern blotting, and nucleic acid sequencing.

[0200] (B) Kit detecting mutation with use of mRNA (cDNA) included in sample taken from subject For example, a configuration of the sodium ion channel  $\alpha 1$  subunit and the calcium ion channel  $\alpha 1$  subunit may include a primer pair designed so as to allow amplification of the cDNA of each of the genes or a part of its region, or include a probe designed so that one of mRNA of its mutant type or wild-type can be specifically detected. These polynucleotides are as described in (B) Embodiment using mRNA (cDNA) in "1. Assessment method according to the present invention", so hence its description has been omitted here.

[0201] Furthermore, such a kit may be configured to include, in addition to the primer pair or probe, a combination of one or more reagent necessary for detecting the presence of a mutation on the gene, such as a reagent used in RT-PCR, Northern blotting, nucleic acid sequencing or the like.

[0202] The reagent is selected and employed as appropriate in accordance with the detection method of the present invention, and examples thereof are dATP, dCTP, dTTP, dGTP, DNA polymerase and the like. Furthermore, the kit according to the present invention may include a suitable buffer solution and a washing solution that can be used in RT-PCR, Northern blotting, and nucleic acid sequencing.

[0203] The kit according to the present invention may include the exemplified configuration in any combination. Furthermore, the kit may include other reagents other than the reagents exemplified above.

[0204] As described in the item "1. Assessment method according to the present invention", in order to detect the presence of mutation for both the sodium ion channel a 1 subunit and the calcium ion channel  $\alpha$  1 subunit, it is further considerable to (C) detect the mutation with use of a protein included in the sample taken from a subject.

**[0205]** Therefore, the kit according to the present invention may include, for example, an antibody that specifically bonds to just the wild-type or mutant protein among the proteins of the sodium ion channel  $\alpha$  1 subunit and the calcium ion channel  $\alpha$  1 subunit. Furthermore, the configuration may be

one which, in addition to the antibody, includes one or more reagent in combination, which reagent is used for ELISA or Western blotting.

[0206] Furthermore, the kit according to the present invention may include a reagent used for measuring activity of the voltage-gated sodium ion channel  $Na_{\nu}1.1$ , a reagent used for measuring activity of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$ , or the like.

[0207] With use of the kit according to the present invention as described above, it is possible to easily obtain data for assessing the potential for development of Dravet syndrome in the subject. A subject to which the kit may be applied is not particularly limited, however is preferably applied to infants or children.

[0208] 3. Model Animal of Dravet Syndrome According to the Present Invention and its Production Method

**[0209]** The present invention encompasses a model animal of Dravet syndrome, and its production method.

[0210] (3-1. Model Animal of Dravet Syndrome According to the Present Invention)

[0211] The model animal of Dravet syndrome according to the present invention has a mutation on both the sodium ion channel  $\alpha$  1 subunit and the calcium ion channel  $\alpha$  1 subunit. The mutation on the sodium ion channel  $\alpha$  1 subunit and the mutation on the calcium ion channel  $\alpha$  1 subunit are as described in the item "1. Assessment method according to the present invention" described above, so therefore specific descriptions thereof are omitted here.

[0212] It is preferable in the model animal of the Dravet syndrome that both the activity of the voltage-gated sodium ion channel Na<sub>v</sub>1.1 and the activity of the voltage-gated calcium ion channel Ca<sub>v</sub>2.1 are changed as compared to a wildtype animal. This change in activity is not particularly limited, and may be an increase of activity or may be a decrease in activity. The method of confirming whether or not an activity of the voltage-gated sodium ion channel Na<sub>V</sub>1.1 of the model animal of Dravet syndrome according to the present invention is changed from that of a wild-type, and the method of confirming whether or not an activity of the voltage-gated calcium ion channel Ca<sub>v</sub>2.1 of the model animal of Dravet syndrome according to the present invention is changed from that of a wild-type, are both not particularly limited. For example, with an individual of a model animal of Dravet syndrome according to the present invention or cells collected from the model animal of Dravet syndrome according to the present invention, confirmation may be made by measuring the activity by use of the conventionally known patch clamping, slice patching, imaging with use of fluorescence probe and like method.

[0213] The model animal of Dravet syndrome according to the present invention has the mutation on both the sodium ion channel  $\alpha$  1 subunit and the calcium ion channel  $\alpha$  1 subunit, so therefore develops Dravet syndrome. Such a model animal of Dravet syndrome can be used advantageously for clarification of the development mechanism of the intractable Dravet syndrome, and for development of medicament for Dravet syndrome.

[0214] In the present specification, "model animal" denotes an experiment animal used for developing a prevention method or treatment against human diseases, and more specifically is a non-human mammal such as a mouse, rat, rabbit, monkey, goat, pig, sheep, cow, or dog, and other vertebrates.

[0215] (3-2. Production Method of Model Animal of Dravet Syndrome According to the Present Invention)

**[0216]** A method of producing a model animal of Dravet syndrome, according to the present invention, includes: introducing a mutation on sodium ion channel  $\alpha$  1 subunit and introducing a mutation on calcium ion channel  $\alpha$  1 subunit.

[0217] More specifically, a mutation can be introduced on each of the genes by manipulating the gene of the model animal. Here, the "manipulating the gene of the model animal" intends to mean manipulation of a gene of a model animal by use of a conventionally known gene manipulation technique. More specifically, this encompasses all of destruction of a gene of the model animal, an introduction of a mutation to that gene, a substitution of that gene with a mutant gene, and furthermore, introduction of a foreign gene into the model animal, and crossing of model animals.

[0218] The production method according to the present invention of the model animal of Dravet syndrome may include steps other than those described above. Specific steps, materials, conditions, used devices, used equipment and the like are not limited in particular.

[0219] With the production method according to the present invention of a model animal of Dravet syndrome, it is possible to produce a model animal developed in Dravet syndrome by manipulating genes of a model animal so that a mutation is introduced into the genes of the sodium ion channel a 1 subunit and the calcium ion channel  $\alpha$  1 subunit.

[0220] 4. Cells According to the Present Invention and its Production Method

[0221] The present invention also encompasses cells having a mutation on both the sodium ion channel  $\alpha$  1 subunit and the calcium ion channel  $\alpha$  1 subunit, and its production method.

[0222] (4-1. Cell According to the Present Invention)

[0223] The cell according to the present invention is a cell having a mutation on both the sodium ion channel  $\alpha$  1 subunit and the calcium ion channel  $\alpha$  1 subunit. The mutation on the sodium ion channel  $\alpha$  1 subunit and the mutation on the calcium ion channel  $\alpha$  1 subunit are as described in the item "1. Assessment method according to the present invention" described above, so therefore specific description thereof have been omitted here.

[0224] The cell according to the present invention intends to mean experimental culture cells having a mutation on both the sodium ion channel  $\alpha$ 1 subunit and the calcium ion channel  $\alpha$ 1 subunit. More specifically, the cell is an experimental culture cell derived from a mammal such as a human, mouse, rat, hamster, rabbit, monkey and the like, and other vertebrates.

[0225] It is preferable that with such a cell, both of activity of the voltage-gated sodium ion channel  $\mathrm{Na}_{\nu}1.1$  and activity of the voltage-gated calcium ion channel  $\mathrm{Ca}_{\nu}2.1$  are changed. This change in activity is not particularly limited, and may be an increase of activity or a decrease in activity. The method of confirming whether or not the activity of the voltage-gated sodium ion channel  $\mathrm{Na}_{\nu}1.1$  of the cell according to the present invention is changed from that of a wild-type, and a method of confirming whether or not the activity of both of the voltage-gated calcium ion channel  $\mathrm{Ca}_{\nu}2.1$  of the cell according to the present invention is changed from that of the wild-type are as described in "1. Assessment method according to the present invention" described above, so hence specific description thereof have been omitted here.

[0226] Such a cell can be used for clarification of a development mechanism of the intractable Dravet syndrome, and for the development in medicament for Dravet syndrome. For example, it is possible to suitably use this for screening of a drug for treating Dravet syndrome. Namely, this cell can also be said as a screening cell for a drug for treating Dravet syndrome. Accordingly, the present invention also encompasses a screening cell of a drug for treating Dravet syndrome (hereinafter, simply called "screening cell"), and its production method

[0227] (4-2. Production Method of Cell According to Present Invention)

[0228] A method of producing a cell according to the present invention is a method of producing a cell that has the foregoing properties, and includes: introducing a mutation on a sodium ion channel  $\alpha$  1 subunit; and introducing a mutation on a calcium ion channel  $\alpha$  1 subunit. More specifically, the following three embodiments can be raised. The following three embodiments are described specifically below, however the present invention is not limited to these.

[0229] (1) Method of Using Expression Vector Etc.

[0230] This method produces a cell that expresses a mutant voltage-gated sodium ion channel Na $_{\nu}1.1$  and mutant voltage-gated calcium ion channel Ca $_{\nu}2.1$ , with use of an expression vector or the like. More specifically described, in order to make a cell express the mutant voltage-gated sodium ion channel Na $_{\nu}1.1$ , for example, a sodium ion channel a 1 subunit gene having a mutation that causes a change in an amino acid is coexpressed, in a culture cell that serves as a host, with a wild-type gene ( $\beta_1$  subunit gene and  $\beta_2$  subunit gene) making up the voltage-gated sodium ion channel Na $_{\nu}1.1$ , which wild-type gene encodes a subunit other than the  $\alpha1$  subunit ( $\beta_1$  subunit and  $\beta_2$  subunit), with use of an expression vector or the like. This enables the cell to express the mutant voltage-gated sodium ion channel Na $_{\nu}1.1$  that includes the mutant sodium ion channel  $\alpha$  1 subunit.

[0231] Similarly, in order to make the cell express the mutant voltage-gated calcium ion channel  $Ca_{\nu}2.1$ , for example, a calcium ion channel  $\alpha$  1 subunit gene having a mutation that causes a change in an amino acid is coexpressed, in a culture cell that serves as a host, with a wild-type gene ( $\beta$  subunit gene,  $\gamma$  subunit gene, and  $\alpha 2\delta$  subunit gene) making up a voltage-gated calcium ion channel  $Ca_{\nu}2.1$ , which wild-type gene encodes a subunit other than the  $\alpha$  1 subunit ( $\beta$  subunit,  $\gamma$  subunit, and  $\alpha 2\delta$  subunit), with the expression vector or the like. This hence enables the cell to express a mutant voltage-gated calcium ion channel  $Ca_{\nu}2.1$  that includes the mutant calcium ion channel  $\alpha$  1 subunit.

**[0232]** At this time, it is preferable that the culture cell serving as a host is a cell from which no voltage-gated sodium ion channel  $Na_{\nu}1.1$  and the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  is expressed. With use of such a cell, no effect is caused by the residing voltage-gated sodium ion channel  $Na_{\nu}1.1$  and residing voltage-gated calcium ion channel  $Ca_{\nu}2.1$ 

[0233] (2) Method of Using Artificial Mutation Introduction

**[0234]** This method introduces mutation for both of the sodium ion channel  $\alpha$  1 subunit and the calcium ion channel a 1 in a culture cell expressing both the voltage-gated sodium ion channel Na<sub>V</sub>1.1 and the voltage-gated calcium ion channel Ca<sub>V</sub>2.1.

[0235] The method of introducing the mutation on the culture cell is not particularly limited, and a conventionally known gene manipulation technique is used in combination as appropriate.

[0236] (3) Method of Using Model Animal of Dravet Syndrome According to the Present Invention

[0237] This method extracts a tissue from the model animal of Dravet syndrome according to the present invention as described above, and prepares a culture cell from that tissue. The model animal of Dravet syndrome according to the present invention is as described in "3. Model animal of Dravet syndrome according to the present invention and its production method", and so therefore specific description thereof has been omitted here. Of course, the "tissue" that is extracted is intended to mean a tissue in which both the sodium ion channel  $\alpha$  1 subunit on which a mutation is introduced and the calcium ion channel  $\alpha$  1 subunit on which a mutation is introduced are expressed.

[0238] This hence allows for easy production of a cell that has a mutation on both the sodium ion channel  $\alpha$  1 subunit and the calcium ion channel  $\alpha$  1 subunit. The kinds of tissues extracted from the model animal of Dravet syndrome is not limited in particular, and may be selected as appropriate depending on its purpose.

[0239] The method according to the present invention of producing a cell may include steps other than the steps described above. Specific steps, materials, conditions, used devices, used equipment and the like are not limited in particular.

[0240] 5. Screening Method of Drug for Treating Dravet Syndrome

[0241] The model animal of Dravet syndrome according to the present invention and the cell according to the present invention can be used in development of a new treatment method and drug for treating Dravet syndrome. Hence, the present invention encompasses a screening method of a drug for treating Dravet syndrome, which screens a drug for treating Dravet syndrome (hereinafter, also called "screening method according to the present invention").

[0242] In the specification, an embodiment using a model animal of Dravet syndrome according to the present invention and an embodiment using a screening cell have been explained as embodiments of the screening method according to the present application. However, the present invention is not limited to these embodiments.

**[0243]** Namely, for example, the embodiment may use another model animal of Dravet syndrome instead of the model animal of Dravet syndrome according to the present invention.

[0244] (1) Case of using model animal of Dravet syndrome according to the present invention

[0245] The method is sufficient as long as it includes administering a candidate agent to the model animal of Dravet syndrome according to the present invention, and assessing whether or not Dravet syndrome shows improvement or is cured in the model animal of Dravet syndrome to which the candidate agent is administered.

[0246] Namely, according to the screening method of the drug for treating Dravet syndrome according to the present invention, a candidate agent is administered to the model animal of Dravet syndrome, to assess whether or not that candidate agent can serve as a drug for treating Dravet syndrome in the model animal of Dravet syndrome to which the candidate agent is administered, by having the improvement or curing of Dravet syndrome serve as an indicator.

[0247] The method of assessing whether or not Dravet syndrome is improved or cured in the model animal of Dravet syndrome to which the candidate agent is administered is not limited in particular, and is sufficiently assessed by use of characteristic symptoms of Dravet syndrome as indicators. For example, it is possible to determine whether Dravet syndrome is improved or cured by comparing a control animal not having a mutation that causes an amino acid change on the sodium ion channel al subunit gene and the calcium ion channel  $\alpha$  1 subunit gene (i.e. an animal not having a mutation on both of  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>ν</sub>1.1 and α-subunit type 1 of voltage-gated calcium ion channel  $Ca_{\nu}2.1$ ) with the model animal of Dravet syndrome according to the present invention, in terms of "body temperature at convulsion onset (convulsion threshold)", "severity score", "duration of convulsion", and the like each shown in the Examples later described.

**[0248]** The candidate agent is not limited in particular, however it is preferable that it is a compound expectable of giving effect on the expression of voltage-gated sodium ion channel  $Na_{\nu}1.1$  and/or expression of voltage-gated calcium ion channel  $Ca_{\nu}2.1$ , or a compound expectable of giving effect on the activity of the voltage-gated sodium ion channel  $Na_{\nu}1.1$  and/or the activity of voltage-gated calcium ion channel  $Ca_{\nu}2.1$  (e.g. an inhibitor or candidate substance of an inhibitor, or an agonist or a candidate substance of an agonist, each of which has effect on both the voltage-gated sodium ion channel  $Na_{\nu}1.1$  and the voltage-gated calcium ion channel  $Ca_{\nu}2.1$ ).

[0249] Moreover, the candidate agent may be an expression plasmid vector or a virus vector that includes a polynucleotide made of a sodium ion channel  $\alpha$  1 subunit gene or a part of its nucleotide sequence. Moreover, the candidate agent may be an expression plasmid vector or a virus vector that includes a polynucleotide made of the calcium ion channel  $\alpha$  1 subunit gene or a part of its nucleotide sequence.

**[0250]** The method of administering such a candidate agent to the Dravet syndrome model animal according to the present invention is not limited in particular, and a suitable method is sufficiently selected from conventionally known methods in accordance with physical properties of that candidate agent.

[0251] (2) Case of Using Screening Cell According to the Present Invention

**[0252]** The method at least includes administering a candidate agent to a screening cell according to the present invention, and assessing whether or not activity of voltage-gated sodium ion channel  $\mathrm{Na}_{\nu}1.1$  and/or activity of voltage-gated calcium ion channel  $\mathrm{Ca}_{\nu}2.1$  in the screening cell of a drug for treating Dravet syndrome to which the candidate agent was administered, is changed.

[0253] Namely, with the screening method according to the present embodiment, it is possible to assess whether a candidate agent can serve as a drug for treating Dravet syndrome, by administering the candidate agent to the screening cell according to the present invention, based on an indicator of whether the activity of the voltage-gated sodium ion channel  $Na_{\nu}1.1$  and/or the activity of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  in the screening cell to which the candidate agent is administered, is changed.

[0254] Moreover, the method of assessing, in the screening cell to which the candidate agent is administered, whether or not the activity of the voltage-gated sodium ion channel  $\mathrm{Na}_{\nu}1.1$  is changed and whether or not the activity of the

voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$  is changed are not limited in particular, and the assessments are sufficiently carried out by use of an electrophysiologic measurement device, fluorescence observation device, or the like.

[0255] The candidate agent is not limited in particular, and similar substances as those described in the foregoing "(1) Case of using model animal of Dravet syndrome according to the present invention" may be used.

[0256] The method of administering such a candidate agent to a cell according to the present invention is not limited in particular, and a suitable method based on the physical properties and the like of that candidate agent is selected and used from conventionally known methods.

[0257] It is preferable in the assessment method according to the present invention that the mutation on  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel Na<sub> $\nu$ </sub>1.1 is at least one of a mutation shown in Table 1, and

[0258] the mutation on  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel Ca  $_{\nu}2.1$  is at least one of a mutation shown in Table 2.

[0259] It is preferable in the assessment method according to the present invention to further include:

[0260] detecting a change in activity of the voltage-gated sodium ion channel  $Na_{\nu}1.1$ ; and

[0261] detecting a change in activity of the voltage-gated calcium ion channel Ca<sub>v</sub>2.1.

**[0262]** The present invention is not limited to the description of the embodiments above, but may be altered by a skilled person within the scope of the claims. An embodiment based on a proper combination of technical means disclosed in different embodiments is encompassed in the technical scope of the present invention.

# **EXAMPLES**

[0263] The following describes more specifically of the present invention with use of Examples, however the present invention is not limited to the Examples.

# Example 1

Identification of Risk Factors for Predicting Development of Dravet Syndrome

[0264] DNA were extracted from peripheral blood of 47 Dravet syndrome patients who visited Okayama University Hospital and/or its related hospitals, and mutations on various genes were analyzed. This study was performed upon receiving approval from Okayama University, Institutional Review Board of Human Genome and Gene Analysis Research.

[0265] More specifically, a genomic DNA was extracted from peripheral blood of a patient with use of a DNA extraction kit (WB kit; Nippon gene, Tokyo, Japan), and all exons were amplified by PCR. In PCR, a reaction solution of 25 μl was used, which includes 50 ng of human genomic DNA, 20 μmol of various primers, 0.8 mM of dNTPs, 1 reaction buffer, 1.5 mM of MgCl<sub>2</sub>, and 0.7 units of AmpliTaq Gold DNA polymerase (Applied Biosystems, Foster City, Calif., USA). As to the nucleotide sequence (SEQ ID NOs.: 9-62) of the primer pair used, see "Sequence of primers" described later. [0266] An obtained PCR product was purified with use of PCR products pre-sequencing kit (Amersham Biosciences, Little Chalfont, Buckinghamshire, England). Subsequently, with use of Big Dye Terminator FS ready-reaction kit (Ap-

plied Biosystems), a sequence reaction was performed, and

with use of a fluorescence sequencer (ABI PRISM3100 sequencer; Applied Biosystems), a nucleotide sequence of the obtained PCR product was determined.

[0267] First, mutation analysis was performed of SCN1A gene that encodes  $\alpha$ -subunit type 1 (also called "\$\alpha\$1 subunit") making up the voltage-gated sodium ion channel Na\$\_\text{1.1}\$, for the 47 Dravet syndrome patients. As a result, a mutation in the SCN1A gene was found in 38 patients out of the 47 Dravet syndrome patients. For the 9 patients in which no mutation was detected, a further analysis was performed on the number of gene copies of the SCN1A gene, with use of Multiplex Ligation-dependent Probe Amplification (MLPA; MRC-Holland; SALSA MLPA kit P137). As a result, a deletion of exon 10 was detected in 1 patient. The number of patients in which no mutation of the SCN1A gene was found was 8. The mutation detected in the SCN1A gene is as shown in Table 1.

[0268] Next, with use of the DNA of the 47 patients, gene analysis was performed for GABRG2 gene, CACNA1A gene, CACNB4 gene, SCN1B gene, and SCN3A gene. These genes encode proteins as follows:

[0269] GABRG2: GABAA receptor γ2 subunit gene

[0270] CACNA1A:  $\alpha$ 1 subunit of voltage-gated calcium ion channel Ca $_{\nu}$ 2.1

[0271] CACNB4:  $\beta4$  subunit of voltage-gated calcium ion channel

[0272] SCN1B:  $\beta$ 1 subunit of voltage-gated sodium ion channel

[0273] SCN3A:  $\alpha$ 3 subunit of voltage-gated sodium ion channel Na $_{\nu}$ 1.3

[0274] The nucleotide sequence (SEQ ID NOs.: 63-143) of the primer pair used for the gene analysis of the CACNA1A gene is shown in "Sequence of primers" described later.

[0275] As a result, various kinds of gene mutations were found in the CACNA1A gene that encodes  $\alpha$ -subunit type 1 (also called " $\alpha$ 1 subunit") making up the voltage-gated calcium ion channel Ca<sub>v</sub>2.1 (see Table 2 and FIG. 12).

[0276] Table 3 shows the gene mutations of SCN1A and CACNA1A that were detected in the Dravet syndrome patients.

TABLE 3

SC	CN1A and CACNA1A	gene mutations of patients	letected in	Dravet syn	idrome
P. No.	SCN1A gene		CACNA1A	gene	
1	G177R	G266S			
2	W738fsX746	K472R			
3	V1390M	A924G			
4	V212A	E921D	E996V		
5	R377L	E921D	E996V		
6	Deletion of exon 10	E921D	E996V		
	(Exon10*)				
7	P707fsX714	E921D	E996V		
8	R865X	E921D	E996V		
9	F902C	E921D	E996V		
10	T1082fsX1086	E921D	E996V		
11	Q1277X	E921D	E996V		
12	Q1450R	E921D	E996V		
13	A1685D	E921D	E996V		
14	T1909I	E921D	E996V	R1126H	R2201Q
15	G163E	R1126H	R2201Q		
16	K547fsX570	R1126H	R2201Q		
17	S1574X	R1126H	R2201Q		
18	R712X	G1108S			
19	R1648C	G1108S			
20	negative	G1108S			
21	negative	Del2202-2205			
22	R501fsX543	negative			

TABLE 3-continued

SCN1A and CACNA1A gene mutations detected in Dravet syndrome patients

P. No.	SCN1A gene	CACNA1A gene
23	S607fsX622	negative
24	E788K	negative
25	R931C	negative
26	R931C	negative
27	L990F	negative
28	A1002fsX1009	negative
29	K1027X	negative
30	K1057fsX1073	negative
31	L1265P	negative
32	W1271X	negative
33	1289delF	negative
34	Intron 21 splicing	negative
	error	
35	A1429fsX1443	negative
36	W1434R	negative
37	T1539R	negative
38	S1574X	negative
39	G1674R	negative
40	A1662V	negative
41	G1880fsX1881	negative
42	negative	negative
43	negative	negative
44	negative	negative
45	negative	negative
46	negative	negative
47	negative	negative

P. No. Patient Number

Exon10\* exon deletion detected by MPLA

[0277] The following mutations are mutations of the CACNA1A gene detected this time. These mutations were mutations that cause an amino acid substitution, mutations that cause no amino acid substitution, and intron mutations.

#### (1) Missense Mutations

[0278]

G266S	1 case
K472R	1 case
E921D	11 cases
A924G	1 case
E996V	11 cases
G1108S	3 cases
R1126H	4 cases
R2201Q	4 cases

# (2) Deletion of Amino Acids

[0279] 4 amino acid deletions (deletion 2202-2205) 1 case (3) Gene Mutation Causing No Amino Acid Change in Exon E292E (rs16006), E394E (rs2248069), 15251 (rs16010), T698T (rs16016), R1023R (rs16025), F1291F (rs16030), T1458T (new SNP or mutation), S1472S (new SNP or mutation), V1890V (rs17846921), H2225H (rs16051)

## (4) Gene Mutation in Intron

[0280] exon 1 upstream (rs16000), intron 1 (rs16003), intron 3 (rs17846942), intron 8 (rs2306348), intron 11 (rs10407951), intron 17 (rs16018), intron 39 (rs3816027), intron 40 (rs17846925), intron 42 (new SNP or mutation).

**[0281]** The missense mutations and deletion mutations detected in coding regions of the CACNA1A gene shown in the foregoing (1), and (2) are shown in Table 4.

TABLE 4

Sumn	nary of mutatio	ns detected in codin Coding Regio		CNA1A gene
	Exon No.	Amino acid	Mutation type	SNP Reg. No.
1	Exon 6	G266S	Missense	_
2	Exon 11	K472R	Missense	_
3	Exon 19	E921D	Missense	rs16022
4	Exon 19	A924G	Missense	_
5	Exon 19	E996V	Missense	rs16023
6	Exon 20	G1108S	Missense	rs16027
7	Exon 20	R1126H	Missense	_
8	Exon 47	R2201Q	Missense	_
9	Exon 47	Del 2202-2205	Deletion	_

SNP Reg. No.: Single Nucleotide Polymorphism Registration Number

**[0282]** These mutations were compared and studied with a gene polymorphism (Single Nucleotide Polymorphism; SNP) database of NCBI (National Center for Biotechnology Information). As a result, it was found that 3 kinds of the mutations out of the 9 kinds of mutations were registered in the SNP database as gene polymorphism (Single Nucleotide Polymorphism; SNP).

[0283] The gene mutation shown in (3) and (4) were either a gene polymorphism registered in the SNP database, or a new gene polymorphism or mutation. The registered number in the SNP database is shown in the brackets.

**[0284]** Out of the SNP already reported, the mutations which caused a change in the amino acid were considered probably that although no seizure occurs just by that individual case having the CACNA1A gene SNP, but when an abnormality of SCN1A gene is simultaneously present, this is somewhat involved in the worsening of the symptom.

[0285] A comparison of patients having a mutation in either of the SCN1A gene and the CACNA1A gene or both of the SCN1A gene and CACNA1A gene, out of the 47 Dravet syndrome patients, resulted as follows.

[0286] Patients having a mutation on both SCN1A and CACNA1A: 19 cases

[0287] Patients having a mutation on just SCN1A: 20 cases [0288] Patients having a mutation on just CACNA1A: 2 cases

[0289] Patients having no mutation on either of SCN1A or CACNA1A: 6 cases.

[0290] No reports whatsoever have been made regarding abnormalities in the CACNA1A gene of the patients of Dravet syndrome, until now. The result of the present study shows that Dravet syndrome patients highly frequently has a mutation in SCN1A, i.e. a  $\alpha$ 1 subunit gene of the voltage-gated sodium ion channel Na $_{\nu}$ 1.1, and in CACNA1A, i.e. a  $\alpha$ 1 subunit gene of the voltage-gated calcium ion channel Ca $_{\nu}$ 2.1.

[0291] A literature disclosing that a mutation on a  $\beta 4$  subunit of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  (hereinafter, simply referred to as "calcium ion channel  $\beta 4$  subunit") is involved with Dravet syndrome (Iori Ohmori et al., Neurobiology of Disease 32 (2008) 349-354) describes that out of 38 patients in which a mutation was detected in the sodium ion channel  $\alpha 1$  subunit, 1 Dravet syndrome patient had a mutation on both the sodium ion channel  $\alpha 1$  subunit and the calcium ion channel  $\beta 4$  subunit.

[0292] In comparison, out of 39 patients in which a mutation was detected on the sodium ion channel  $\alpha$  1 subunit, the patients of Dravet syndrome having a mutation on both the sodium ion channel  $\alpha$  1 subunit and the calcium ion channel  $\alpha$ 1 subunit were 19 patients (6 patients when excluding patients having registered SNP that cause a change in an amino acid in an exon). This result shows that by detecting the mutation for both the sodium ion channel  $\alpha$  1 subunit and the calcium ion channel  $\alpha$  1 subunit, the detection sensitivity of Dravet syndrome patients dramatically increase as compared to detecting the mutation for both the sodium ion channel a 1 subunit and the calcium ion channel  $\alpha$ 4 subunit.

[0293] In the present specification, a nucleotide number in mRNA of the SCN1A gene and an amino acid number in a protein of SCN1A were made to be in line with GenBank accession No. AB093548; methionine, encoded by the initiation codon (ATG), was numbered as the first amino acid, and the initial A of the initiation codon was numbered as the first nucleotide.

[0294] Moreover, a genome sequence of the CACNA1A gene was in line with the GenBank accession number NC\_000019. The number of the nucleotide in mRNA of CACNA1A gene and the number of the amino acid in CACNA1A protein was made to be in line with the GenBank accession number NM 023035; methionine, encoded by the initiation codon (ATG), was numbered as the primacy amino acid, and the initial A of the initiation codon was numbered as the primacy nucleotide.

# Example 2

## Study of Gene Mutation in Benign Febrile Seizure Patient

[0295] A study was performed of a SCN1A gene and CACNA1A gene abnormality in a benign febrile seizure patient. DNA was extracted from peripheral blood of 50 patients of benign generalized epilepsy with febrile seizure plus (GEFS+), who visited Okayama University Hospital and/or its related hospitals, and mutations on various genes were analyzed. The DNA extraction, PCR amplification of the gene, and sequencing reactions were performed by the methods described above.

[0296] First, mutation analysis of voltage-gated sodium ion channel SCN1A gene was performed, which resulted in detecting gene mutation that caused amino acid changes in 6 patients. Next, mutation analysis was performed for 9 kinds of mutations of missense mutations and deletion mutations that were detected in the coding region of the CACNA1A gene, which resulted in detecting a mutation in 16 patients. Each of the mutations are shown in Table 5.

TABLE 5

SCN1A and CACNA1A gene mutations detected in benion febrile seizure

SCINIA and CACIN	SCNTA and CACNATA gene indiations detected in benign feorme seizure							
Patient No.	SCN1A	CACN	JA1A					
1								
2	M1856T							
3		del 2202-2205						
4								
5		del 2202-2205						
6	R1575C							
7		E921D	E996V					
8		E921D	E996V					
9		E921D	E996V					

TABLE 5-continued

SCN1A and CACN.	A1A gene mutat	ions detected in ben	ign febrile seizure
Patient No.	SCN1A	CAC	NA1A
10			
11	74.64.677		
12	I1616T		
13 14			
15			
16			
17			
18		E921D	E996V
19			
20			
21			
22		E921D	E996V
23		E921D	E996V
24			
25		E021D	E00 CLZ
26 27		E921D	E996V
28		E921D	E996V
28 29		A924G	E990 V
30		E921D	E996V
31		27212	23301
32			
33		E921D	E996V
34		G1108S	
35			
36	I1616T		
37	I1616T		
38			
39	Y1769H	E021D	E00 CL
40 41		E921D	E996V
42			
43			
44			
45			
46			
47			
48		E921D	E996V
49			
50			

[0297] Out of the 50 benign epilepsy patients, it was confirmed that no patient had mutations simultaneously on both SCN1A gene and CACNA1A gene.

[0298] The following shows a result of gene mutation analysis of a total of 97 patients, of 47 malignant Dravet syndrome cases and 50 benign febrile seizure patient cases.
[0299] (1) As a result of screening patients having a mutation on the SCN1A gene among the 97 patients, 39 Dravet syndrome patients (39 cases out of 47 cases) and 6 benign epilepsy patients (6 cases out of 50 cases) were detected.

[0300] (2) As a result of screening patients having a mutation on both the SCN1A gene and CACNA1A gene out of the 97 patients, 19 Dravet syndrome patients (19 cases out of 47) were detected, and no (0) benign epilepsy patients were detected.

[0301] These results suggest that by examining both the SCN1A gene mutation and the CACNA1A gene mutation, it is possible to eliminate the false positive (benign febrile seizure patients) better than examining just the SCN1A gene mutation, and suggest a possibility of detecting the Dravet syndrome patients with higher accuracy.

# Example 3

## Study of Gene Mutation in a Healthy Person

[0302] To investigate whether the remaining 6 kinds of gene mutations excluding the registered 3 kinds out of the 9 kinds of missense mutations and deletion mutations detected in the coding region of the CACNA1A gene are of the gene polymorphism (SNP), gene mutation of the CACNA1A gene was similarly analyzed for DNA extracted from blood of 190 healthy persons. Results of the 9 kinds of the missense mutations and deletion mutations detected in the coding region of the CACNA1A gene are shown in Table 6. As a result, one kind of the CACNA1A gene mutation (G266S) was not detected from the healthy persons. From this result, it was found that the CACNA1A gene mutation of G266S is not an SNP, and is a novel gene mutation (gene abnormality) not found in the 190 healthy persons, which neither is in the NCBI SNP database.

TABLE 6

	CACNA1A gene mutation detected in healthy persons and Dravet syndrome								
Exon	Nucleotide Substitution	Amino Acid Substitution	Dravet	(n = 47)	Co (n = 1	p-value			
				Frequenc	cy of varia	nts	_		
6	A876G	G266S	1/47	2.1%	0/188	0%	0.20		
11	A1415G	K472R	1/47	2.1%	1/188	0.53%	0.36		
19	A2762C	E921D	11/47	23.4%	49/188	26.06%	0.71		
19	C2771G	A924G	1/47	2.1%	7/190	3.68%	1.00		
19	A2987T	E996V	11/47	23.4%	49/188	26.06%	0.71		
20	G3322A	G1108S	3/47	6.4%	16/189	8.46%	0.77		
20	G3377A	R1126H	4/47*	8.5%	1/188	0.53%	0.0061		
47	G6602A	R2201Q	4/47	8.5%	4/189	2.12%	0.052		
47	6605-6616del	DQER2202-	1/47	2.1%	3/190	1.58%	1.00		
		2205del							
				Free	uency of				
					ed mutation	ns			
							-		
19		E921D + E996V	11/47	23.4%	49/188	26.06%	0.71		
20 + 47		R1126H + R2201Q	4/47*	8.50%	0/188	0%	0.0014		

[0303] As a result of studying the comparison of frequencies in which mutations occur in healthy persons and Dravet syndrome patients, it was shown that the CACNA1A gene mutation R1126H was of a larger number with Dravet syndrome in terms of statistical significance (p=0.0061), and it was found that the CACNA1A gene mutation R2201Q also had a trend having a larger number with Dravet syndrome patients (p=0.052). The patients simultaneously having both mutations of R1126H and R2201Q on the CACNA1A gene were detected significantly in just the Dravet syndrome patients (4 cases out of 47 cases), and no healthy persons were detected (p=0.0014). Examination of DNA of the parents of these four patients revealed that the two mutations of R1126H and R2201Q were simultaneously present on one chromosome, i.e. within the same CACNA1A protein molecule, and that this double mutation was inherited from the parents.

#### Example 4

Study of Relation Between Genotype and Symptoms

[0304] A study was performed on how the 9 kinds of missense mutations and deletion mutations detected in the coding region of CACNA1A gene give effect on the worsening of symptoms of the disease. Out of Dravet syndrome patients whose seizure symptom data is managed in detail, the seizure symptoms under the age of 1 were compared between 20 patients who have just the SCN1A gene mutation and 19 patients who have a mutation on both the SCN1A gene and the CACNA1A gene. A result thereof is shown in Table 7. Note that "GTC" in Table 7 is an abbreviation of a generalized tonic-clonic seizure, and "CPS" is an abbreviation of a complex partial seizure.

#### Example 5

# Analysis on Functions of Mutant Voltage-Gated Calcium Ion Channel

[0306] An analysis was performed on functions of a mutant calcium ion channel and a normal (wild-type) calcium ion channel, with use of culture cells. First, cDNA of a human CACNA1A gene (SEQ ID NO.: 4) was used to prepare an expression vector having a mutant CACNA1A (double mutation of G266S; R1126H; R2201Q; deletion 2202-2205; double mutation of R1126H and R2201Q) gene. After obtaining DNA fragments including the mutated parts by PCR, regions of a normal cDNA corresponding to those fragments were substituted with those fragments, to prepare the mutant cDNA. As a control, an expression vector (pMO14×2-CACNA1A) having a normal (wild-type) CACNA1A gene was used.

[0307] Analysis was performed on functions of the mutant calcium ion channel and the normal calcium ion channel, with use of the culture cells. A  $\alpha$ -subunit type 1 of the voltagegated calcium ion channel  $Ca_{\nu}2.1$ , which is a CACNA1A gene product, had been subjected to function adjustment by the  $\alpha2\delta$  subunit and  $\beta4$  subunit that similarly configure the voltage-gated calcium ion channel  $Ca_{\nu}2.1$ . Hence, an expression vector having a CACNA1A gene that encodes a  $\alpha$ -subunit type 1, and an expression vector having a human CACNB4 gene (GenBank accession No. U95020) (SEQ ID NO.: 151) encoding a P4 subunit and a rabbit  $\alpha2\delta$  gene (GenBank accession No. NM\_001082276) (SEQ ID NO.: 152) encoding a  $\alpha2\delta$  subunit. were coexpressed on a human

TABLE 7

			-	Total no.	of 1 with genotype  Type of Seizures			
Genotype	N	Seizure onset (months)	Total no. of seizures	prolonged (>10 min) seizures	GTC (%)	CPS (%)	Hemi- convulsion (%)	Myoclonic seizure (%)
SCN1A mutation + No CACNA1A variants	20	5.6 ± 0.3	10.2 ± 1.2	2.4 ± 0.4	95	45	50	15
SCN1A mutation + CACNA1A variants	19	4.6 ± 0.4*	10.7 ± 1.3	4.4 ± 0.7*	95	26	84*	11

GTC: generalized tonic-clone seizure.

CPS: complex partial seizure

p < 0.05

[0305] It was found that the patients having a CACNA1A variant, as compared to the patients having no CACNA1A variant, are (i) significantly quicker in seizure onset (p=0.049), (ii) significantly greater in the number of times prolonged seizures occur, which prolonged seizure is a convulsion seizure that continues for 10 or more minutes (p=0.019), and (iii) significantly higher in the frequency that a hemiconvulsion occurs (p=0.041). This indicates that when there is a variation of the CACNA1A gene including the polymorphism in addition to a SCN1A gene abnormality, there is a possibility that the symptom may worsen.

renal cell HEK293 with use of a transfection reagent. Electrophysiologic properties were studied by patch clamping of a whole cell record.

[0308] More specifically, recording of a calcium ion channel current was carried out at room temperature of 22° C. to 24° C., 72 hours after transfection. With use of a multistage P-97 Flaming-Brown micropipette puller, a patch electrode was prepared from borosilicate glass.

[0309] The composition of intracellular fluid was 110 mM CsOH, 20 mM CsCl, 5 mM MgCl<sub>2</sub>, 10 mM EGTA, 5 mM MgATP, 5 mM creatine-phosphate, and 10 mM HEPES. On

the other hand, the composition of the used extracellular fluid was 5 mM BaCl, **150** mM TEA-Cl, 10 mM glucose, and 10 mM HEPES. The amplifier used was Axopatch200B (Axon Instruments).

[0310] Electrophysiologic properties of the mutation channel were compared with those of a normal channel, by studying voltage-gated channel activation, inactivation, recovery from inactivation, and duration current. The activation curve and the inactivation curve were analyzed by Boltzmann function, to find a half-maximal activation/inactivation ( $V_{1/2}$ ) and a slope factor (k). The recovery curve from the inactivation was analyzed by a two exponential function. Statistics used the unpaired Student's t test. Clampfit 8.2 software and OriginPro 7.0 (OriginLab) were used for data analysis.

[0311] FIG. 13 and FIG. 14 are views illustrating results of performing function analysis of the calcium ion channel, by patch clamping. In the graphs in FIG. 13 and FIG. 14, the normal calcium ion channel is shown as "WT", and the mutant calcium ion channels are shown as "R266S", "R1126H", "R2201Q", "De12202", and "RH+RQ". The mutation "De12202" means the mutation "Deletion 2202-2205", and the mutation "RH+RQ" means the mutation "R1126H+R2201Q".

[0312] Illustrated in (a) of FIG. 13 is a barium current record in accordance with a change in potential of the normal calcium ion channel and the mutant calcium ion channel. Illustrated in (b) is a current-voltage relationship, and illustrated in (c) are a peak current value (pA), a total charge (pF), and a peak current density (pA/pF).

[0313] More specifically, (a) of FIG. 13 illustrates a current record of measuring barium current that is depolarized by changing a depolarizing stimulus by 10 mV each from -40 mV to +60 mV and is flowed therein. The current-voltage relationship illustrated in (b) of FIG. 13 is a graph obtained by (i) measuring a flowing barium current for every membrane potential while having a holding potential, being deeper than a resting membrane potential, as -100 mV, and a depolarizing stimulus being changed by 10 mV each from -40 mV to +60 mV, and (ii) plotting the membrane potential on a horizontal axis and a current value on a vertical axis. The view illustrated on the lower right of the graph in (b) of FIG. 13 shows that in this experiment, "the depolarizing stimulus was changed by 10 mV each from -40 mV to +60 mV for 30 ms (milliseconds), with the holding potential being -100 mV, which holding potential is deeper than the resting membrane potential".

[0314] As a result, it was found that the mutant calcium ion channel "Deletion2202-2205" and "R1126H+R2201Q" significantly increased in its flowed current amount, peak current value, and peak current density, as compared to the normal calcium ion channel.

[0315] Next, in order to specifically study the electrophysiologic properties of the calcium ion channel, a voltage-gated activity of the calcium ion channel ((a) of FIG. 14), a time constant ( $\tau$ ) at activation ((b) and (c) of FIG. 14), inactivation of the calcium ion channel ((d) of FIG. 14), and a time constant ( $\tau$ ) at inactivation ((e) FIG. 14) were measured.

[0316] The activation curve illustrated in (a) of FIG. 14 shows a barium current value flowing per membrane potential as a relative value, by having a maximum sodium current value obtained from the graph of (b) of FIG. 13 be 1, and an obtained curve was analyzed by Boltzmann function to find a half-maximal activation ( $V_{1/2}$ ) and a slope factor (k). The view provided on the lower right of the graph in (a) of FIG. 14 represents that, in this experiment, "the depolarizing stimulus

was changed by 10~mV each from -40~mV to +60~mV for 30~ms (milliseconds), with the holding potential being -100~mV, which holding potential is deeper than the resting membrane potential".

[0317] As a result of analyzing the voltage-gated activity of the calcium ion channel, it was found that (i) the mutant calcium ion channel "G266S" and "R1126H" show a significant hyperpolarization shift as compared to the normal channel, and that (ii) the mutant calcium ion channel "R1126H" and "Deletion2202-2205" significantly increased in the voltage-gated property as compared to the normal channel, by comparing the slope factor (k) (see (a) of FIG. 14 and Table 8). This means that the mutant calcium ion channel "G266S", "R1126H" and "Deletion2202-2205" are easily activated even in a low membrane potential, thereby tending to cause excess hyperexcitability of nerve cells.

[0318] Table 8 shows electrophysiologic properties of the calcium ion channel. Statistical comparison of the normal CACNA1A and the mutant CACNA1A were performed by the Student's t test. The asterisk (\*) in Table 8 indicates that there is a significant difference between the normal CACNA1A and the mutant CACNA1A when a critical rate is under 5%, and the double asterisk (\*\*) indicates that there is a significant difference between the normal CACNA1A and the mutant CACNA1A when the critical rate is under 1%.

TABLE 8

Electrophysiologic properties of calcium ion channel								
	Activation							
	$V_{1/2}$			Inactivation				
	(mV)	k (mV)	n	$V_{1/2} \left( mV \right)$	k (mV)	n		
WT- CACNA1A	6.3 ± 1.3	4.3 ± 0.2	16	$-16.9 \pm 1.5$	-4.5 ± 0.6	10		
G266S	1.0 ±	$4.3 \pm 0.4$	11	$-13.8 \pm 1.6$	$-5.5 \pm 0.3$	10		
R1126H	0.4 ± 1.6**	$3.3 \pm 0.3*$	10	$-18.9 \pm 0.6$	$-6.1 \pm 0.7$	8		
R2201Q	6.4 ± 1.5	$4.1 \pm 0.2$	8	$-13.4 \pm 1.7$	$-5.7 \pm 0.4$	10		
Deletion2202- 2205	1.3 ±	$3.4 \pm 0.2*$	8	$-13.3 \pm 1.2$	$-4.7 \pm 0.6$	9		
R1126H + R2201Q	2.6 ± 1.1	$3.5 \pm 0.2$	10	$-15.2 \pm 0.9$	$-5.4 \pm 0.1$	10		

 $V_{1/2}$ , half-maximal voltage activation and inactivation;

k, slope factor

Statistical coparison between WT-CACNA1A and mutant channels was performed by Student's t test (\*P < 0.05 and \*\*P < 0.01 versus WT-CACNA1A).

[0319] Illustrated in (b) of FIG. 14 is a time constant of channel voltage-gated activation, that is to say, a time required for each current to reach 66.7%. Moreover, (c) of FIG. 14 illustrates a time constant of voltage-gated activation at 20 mV. From (b) and (c) of FIG. 14, it was demonstrated that the mutant calcium ion channel "G266S" was significantly small in the time constant of voltage-gated activation at 20 mV, as compared to a normal channel. Since this point is considered as that the mutant calcium ion channel "G2665" is made so as to flow a lot of current within a short depolarization, this means that there is a trend of causing hyperexcitement in the nerve cells.

[0320] Illustrated in (d) of FIG. 14 is a voltage-gated inactivation curve of the calcium ion channel, which was measured upon changing a membrane potential to activate the calcium ion channel and thereafter providing a depolarizing stimulus to measure how much barium current was flown. Note that the view illustrated on the lower left of the graph

illustrated in (d) of FIG. 14 shows that, in this experiment, "the depolarizing stimulus was changed by 20 mV each from  $-120~\mathrm{mV}$  to  $+60~\mathrm{mV}$  for 2 s (seconds), and subsequently be changed to 20 mV, with the holding potential being  $-100~\mathrm{mV}$ , which holding potential is deeper than the resting membrane potential".

[0321] The voltage-gated inactivation curve of the calcium ion channel showed no recognizable significant difference, in either of the mutant channel or the normal channel.

[0322] Illustrated in (e) of FIG. 14 is a result of studying an inactivation time constant  $(\tau)$ . There are two kinds of inactivation: inactivation of a fast component and inactivation of a slow component. The " $\tau_{fast}$ " in the left graph of (e) of FIG. 14 is a constant representing a time required until the inactivation of the fast component reaches 33.3%, and the " $\tau_{slow}$ " in the right graph is a constant representing a time required until the inactivation of the slow component reaches 33.3%. These inactivation time constants were, more specifically, calculated by analyzing the inactivation curve with use of Clampfit 8.2 software.

[0323] As a result, there was no significant difference in the inactivation time constant between that of the normal calcium ion channel and that of the mutant calcium ion channel. Table 9 shows physiological properties of the mutant calcium ion channel. The arrow pointing upwards (\^) in Table 9 indicates that an increase in channel activity was recognized, and the hyphen "-" indicates that no change was recognized in the channel activity.

TABLE 9

Summary of electrophysiological properties of mutant calcium ion channel

	CACNA1A						
Biophysical property	G266S	R1126H	R2201Q	Del 2202-2205	R1126H + R2201Q		
Peak current density Activation V <sub>1/2</sub> Activation slop	<u>†</u>		_	<u>†</u>	<u>†</u> †		
Activation time constants	1	_	_	_	_		
Inactivation V <sub>1/2</sub>	_	_	_	_	_		
Inactivation slope factor	_	_	_	_	_		

<sup>↑,</sup> predicted gain of channel activity.

[0324] It was found that the mutations other than "R2201Q" in the calcium ion channel were mutations of a gain of function kind, and tends to cause excitement of the nerve cells.

# Example 6

#### Production of Dravet Syndrome Model Rat

[0325] From the foregoing findings, it was considered that having some kind of mutation on both of SCN1A and CACNA1A is important in the development of Dravet syndrome. Accordingly, a rat was produced which has both of the mutation on  $\alpha$ 1-subunit gene Scn1a of the voltage-gated sodium ion channel Na<sub> $\nu$ 1.1 and the mutation on  $\alpha$ 1-subunit gene Cacna1a of the voltage-gated calcium ion channel Ca $_{\nu}$ 2.1, to study the worsening of symptoms (human genes are represented as SCN1A and CACNA1A, and rat genes are represented as Scn1a and Cacna1a).</sub>

[0326] More specifically, a rat having a mutation on the Scn1a gene (F344-Scn1a<sup>Kyo811</sup>) and a rat having a mutation on the Cacna1a gene (GRY (groggy rat, Cacna1a<sup>gry</sup>)) were used as parent rats. Each of these mice is described below.

[0327] <F344-Scn1a $^{Kyo811}>$ 

[0328] A rat produced by ENU mutagenesis, having a missense mutation on a  $\alpha 1$  subunit gene (Scn1a) of the voltagegated sodium channel Na $_{\nu} 1.1$ . Asparagine (N), which is an amino acid at position 1417, was mutated to histidine (H) (represented as "N1417H"). This rat served as a model animal of human generalized epilepsy febrile seizure plus (GEFS+). Background genealogy is F344/NS1c rat. This rat was provided from the Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University.

[0329] <GRY (Groggy Rat, Cacnala<sup>gry</sup>)>

[0330] A mutant rat produced by administering methyl nitrosourea to Scl: Wistar, whose main symptoms are ataxia and absence-like seizure. This rat has an autosomal recessive mode of inheritance, and has a missense mutation on the  $\alpha$ 1-subunit of the voltage-gated calcium ion channel Ca $_{\nu}$ 2.1. Methionine (M), which is an amino acid at position 251, is mutated to lysine (K) (M251K). This rat was provided from the Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University.

[0331] FIG. 11 is a view showing an amino acid sequence of a protein encoded by a human CACNA1A gene and an amino acid sequence of a protein encoded by a rat Cacna1a gene. The upper line of the amino acid sequence shown in FIG. 11 represents an amino acid sequence of the protein encoded by the rat Cacna1a gene (GenBank accession No. NM\_012918) (SEQ ID NO.: 147), and the lower line is the amino acid sequence of the protein encoded by the human CACNA1A gene (GenBank accession No. NM\_023035) (SEQ ID NO.: 3). Moreover, the squared amino acid "M" in FIG. 11 is an amino acid that is mutated from the amino acid "M" to an amino acid "K" in the human mutant CACNA1A (M249K) protein (SEQ ID NO.: 148) and the rat mutant Cacna1a (M251K) protein (SEQ ID NO.: 149).

[0332] As illustrated in FIG. 11, the mutation (M251K) on the  $\alpha$ 1 subunit of the rat voltage-gated calcium ion channel Ca<sub> $\nu$ 2.1 corresponds to the mutation (M249K) on the al subunit of the human voltage-gated calcium ion channel Ca<sub> $\nu$ 2.1.</sub></sub>

[0333] The F344-Scn1a $^{Kyo811}$  and GRY (groggy rat, Cacna1a $^{gry}$ ) as described above were mated to produce a rat having each of the gene mutations.

[0334] (1. Analysis on Functions of Mutant Voltage-Gated Sodium Ion Channel)

[0335] An analysis was performed with use of culture cells, on functions of a mutant sodium ion channel and normal sodium ion channel, before tests using the rats were performed. The rat having a mutation on the Scn1a gene (F344-Scn1a<sup>Kyo811</sup>) has asparagine (AAT), which is an amino acid at position 1417 of a protein encoded by the Scn1a gene, was changed to histidine (CAT) (N1417H). The asparagine at position 1417 is located in a pore formation region that is related to ionic permeation of sodium ion channel third domain. On this account, first, the function analysis of the mutant voltage-gated sodium ion channel included in F344-Scn1a<sup>Kyo811</sup> was performed.

[0336] More specifically, an expression vector having a mutant SCN1A (N1417H) gene (SEQ ID NO.: 150) including a missense mutation was prepared with use of cDNA of

<sup>-,</sup> no predicted change in channel activity.

human SCN1A gene. As control, an expression vector having a normal (wild-type) SCN1A gene (SEQ ID NO.: 2) was prepared.

[0337] FIG. 1 is a view showing an amino acid sequence of a protein encoded by the human SCN1A gene and an amino acid sequence of a protein encoded by the rat Scn1a gene. The upper line in the amino acid sequence shown in FIG. 1 represents an amino acid sequence of a protein that is encoded by the human SCN1A gene (SEQ ID NO.: 1), and the lower line represents an amino acid sequence of a protein that is encoded by the rat Scn1a gene (SEQ ID NO.: 144). Moreover, the squared amino acid "N" in FIG. 1 is an amino acid on which a mutation from an amino acid "N" to an amino acid "H" occurs, of the human mutant SCN1A (N1417H) protein (SEQ ID NO.: 145) and the rat mutant SCN1A (N1417H) protein (SEQ ID NO.: 146).

[0338] An analysis was performed with use of culture cells, on functions of the mutant sodium ion channel and the normal sodium ion channel. The  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel  $Na_{\nu}1.1$ , which is a SCN1A gene product, was adjusted in its function by  $\beta_1$  subunit and  $\beta_2$  subunit that similarly make up the voltage-gated sodium ion channel  $Na_{\nu}1.1$ . Hence, an expression vector having the SCN1A gene that encodes the  $\alpha$ -subunit type 1 was coexpressed with an expression vector having the SCN1B gene that encodes the  $\beta_1$  subunit and the SCN2B gene that encodes the  $\beta_2$  subunit in a human renal cell HEK293, with use of a transfection reagent. The electrophysiologic properties were studied by patch clamping based on whole cell recording.

[0339] More specifically, recording of the sodium ion channel current was carried out at room temperature of 22° C. to 24° C., 24 hours to 48 hours after transfection. A patch electrode was prepared from borosilicate glass by use of multistage P-97 Flaming-Brown micropipette puller.

[0340] Composition of intracellular fluid was 110 mM CsF, 10 mM NaF, 20 mM CsCl, 2 mM EGTA, and 10 mM HEPES. On the other hand, the composition of extracellular fluid was 145 mM NaCl, 4 mM KCl, 1.8 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, and 10 mM HEPES. Axopatch200B (Axon Instruments) was used as the amplifier.

[0341] Electrophysiologic properties of the mutation channel were compared with those of a normal channel, by studying voltage-gated channel activation, inactivation, recovery from inactivation, and duration current. The activation curve and the inactivation curve were analyzed by Boltzmann function, to find a half-maximal activation/inactivation ( $V_{1/2}$ ) and a slope factor (k). The recovery curve from the inactivation was analyzed by a two exponential function. Durable Na current was found by a difference in the duration current when depolarized at -10~mV for 100 ms, before and after addition of  $10~\text{\mu M}$  of tetrodotoxin (TTX). Statistics used were unpaired Student's t test. Clampfit 8.2 software and Origin-Pro 7.0 (OriginLab) were used for data analysis.

[0342] FIGS. 2 to 4 are views illustrating results of performing function analysis of the sodium ion channel by patch clamping. The graphs of FIGS. 2 to 4 show the normal sodium ion channel as "WT" or "WT-SCN1A", and show the mutant sodium ion channel as "N1417H".

[0343] Illustrated in (a) of FIG. 2 is a typical example of a sodium current in response to a change in potential of the normal sodium ion channel and the mutant sodium ion channel. More specifically, a depolarizing stimulus was changed 10 mV each from -80 mV to +60 mV for depolarization, and sodium current that flowed in was measured. As a result, both

of the normal sodium ion channel and the mutant sodium ion channel function as a channel, and there was no significant difference between the two.

[0344] Illustrated in (b) of FIG. 2 is a result of studying the inactivation time constant  $(\tau)$ . There are two types of inactivation; an inactivation of a fast component and an inactivation of a slow component. The " $\tau$ 1" in (b) of FIG. 2 is indicative of a constant indicative of a time required for the inactivation of the fast component to reach 33.3%, and the " $\tau$ 2" is indicative of a constant indicative of a time required for the inactivation of the slow component to reach 33.3%. These inactivation time constants, more specifically, were calculated by analyzing the inactive curve with use of the Clampfit 8.2 software. As a result, there was no significant difference in the inactivation time constant between that of the normal sodium ion channel and that of the mutant sodium ion channel.

[0345] Next, in order to specifically study the electrophysiologic properties of the sodium ion channel, a current-voltage relationship ((a) of FIG. 3), an activation of the sodium ion channel ((b) of FIG. 3), an inactivation of the sodium ion channel ((c) of FIG. 3), and recovery from the inactivation of the sodium ion channel ((d) of FIG. 3) were measured.

[0346] More specifically, the current-voltage relationship illustrated in (a) of FIG. 3 was obtained by (i) measuring a flowing sodium current for every membrane potential while having a holding potential, being deeper than a resting membrane potential, as -120 mV, and a depolarizing stimulus being changed by 10 mV each from -80 mV to +60 mV, and (ii) plotting the membrane potential on a horizontal axis and a current value on a vertical axis. The view illustrated on the lower left of the graph in (a) of FIG. 3 shows that in this experiment, "the depolarizing stimulus was changed by 10 mV each from -80 mV to +60 mV for 20 ms (milliseconds), with the holding potential being -120 mV, which holding potential is deeper than the resting membrane potential".

[0347] The activation curve illustrated in (b) of FIG. 3 shows a sodium current value flowing per membrane potential as a relative value, by having a maximum sodium current value obtained from the graph of (a) of FIG. 3 be 1, and an obtained curve was analyzed by Boltzmann function to find a half-maximal activation ( $V_{1/2}$ ) and a slope factor (k). The view provided on the lower right of the graph in (b) of FIG. 3 represents that in this experiment, "the depolarizing stimulus was changed by 10 mV each from -80 mV to +60 mV, for 20 ms (milliseconds), with the holding potential being -120 mV, which holding potential is deeper than the resting membrane potential".

[0348] The inactive curve illustrated in (c) of FIG. 3 was obtained by similarly changing the membrane potential to activate the channel and thereafter providing depolarizing stimulus and measuring how much the sodium current flows, to find the half-maximal inactivation  $(V_{1/2})$  and the slope factor (k). Note that the view provided on the lower left of the graph of (c) of FIG. 3 represents that in this experiment, "the depolarizing stimulus was changed by  $10\,\mathrm{mV}$  each from  $-140\,\mathrm{mV}$  to  $+0\,\mathrm{mV}$  for  $100\,\mathrm{ms}$  (milliseconds) and subsequently changed to  $-10\,\mathrm{mV}$ , with the holding potential being  $-120\,\mathrm{mV}$ ".

[0349] The recovery curve from the inactivation illustrated in (d) of FIG. 3 was obtained as follows. When a depolarizing stimulus was provided with pulse 1 (P1), the channel became inactive upon opening. When the depolarizing stimulus was returned to the original -120 mV, the sodium ion channel returned to its resting state, and upon stimulation of pulse 2

(P2), the channel opened again. The recovery time of this pulse 1 and pulse 2 were changed to obtain the recovery curve from the inactivation. This curve was analyzed by a two exponential function. It was determined whether the function of the channel was made easily excited or in the opposite was made difficult to be excited, depending on whether the recovery was quicker or slower as compared to the normal channel. The view provided on the lower right of the graph of (d) of FIG. 3 indicates that in this experiment, "a holding potential was mV, -10 mV was provided for 100 ms (milliseconds) as the depolarizing stimulus and thereafter was returned to -120 mV, and after elapse of each of the times (milliseconds) shown on the x-axis, -10 mV was provided for 20 ms (milliseconds)".

[0350] As a result, no significant difference was recognized in the current-voltage relationship and the channel activation, between the normal sodium ion channel and the mutant sodium ion channel (see (a) and (b) of FIG. 3). Meanwhile, a significant test was performed regarding the channel inactivation, on a point that the normal sodium ion channel and the mutant sodium ion channel are inactivated by 50%, whereby resulted in finding that the mutant sodium ion channel had shifted significantly to the depolarization side (p<0.05)((c)) of FIG. 3).

[0351] As to the recovery from the channel inactivation, it was found that the recovery was significantly slow in the mutant sodium ion channel ((d) of FIG. 3). In (d) of FIG. 3, a part in which a period of recovery (Recovery period (ms)) from the inactivation was 1 ms to 8 ms corresponds to a "fast component", and a part in which the period of recovery from the inactivation was 10 ms to 100 ms corresponds to a "slow component".

**[0352]** More specifically, upon comparison between the normal sodium ion channel and an abnormal sodium ion channel based on a time required for the fast component in recovering from the inactivation to recover from the inactivation to 33.3%, it was found that the recovery was significantly slow for the mutant sodium ion channel (normal:  $\tau_f$ =1.7±0.1 ms, n=14; mutant:  $\tau_f$ =2.5±0.2 ms (P<0.01), n=12).

[0353] Similarly, upon comparison of the normal sodium ion channel with the abnormal sodium ion channel based on the time required for the slow component in recovering from the inactivation to recover from the inactivation to 33.3%, it was found that the mutant sodium ion channel was significantly slow in recovering (normal:  $\tau_r$ =40.3±5.3 ms, n=14; mutant:  $\tau_s$ =60.9±7.9 ms (P<0.05), n=12).

[0354] FIG. 4 shows that, even if the sodium ion channel was made inactivated after the potential was changed to activate the sodium ion channel, the baseline of the mutant sodium channel does not return back in the whole cell record, which indicates clearly that the sodium current was persistently flowing into the mutant sodium ion channel. The persistent sodium current is considered as an obstruction of an inactivation gate. From the view of (a) of FIG. 4, it was confirmed that even after the elapse of time, the inactivation was insufficient in the mutant sodium ion channel as compared to that of the normal sodium ion channel.

[0355] So as to find the persistent sodium current shown in (a) of FIG. 4, a relative value (%) was found by dividing, with a maximum current amount, a final current amount that flowed between 80 milliseconds to 100 milliseconds when a depolarizing stimulus of 100 milliseconds was given. Results thereof are shown in (b) of FIG. 4. From these results, it was found that the mutant sodium ion channel had properties that the persistent sodium current increases.

**[0356]** This data show that the function of the voltage-gated sodium ion channel Na $_{\nu}1.1$  became abnormal by the mutation. Namely, this means that by having the mutation, the nerve cells are easily excessively excited, that is to say, more easily causes the occurrence of a convulsion.

[0357] Literature (Satoko Tokuda et. al., BRAINRE-SEARCH 1133 (2007) 168-177; Kenta Tanaka et. al., Neuroscience Letters 426 (2007) 75-80) discloses that the function of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  of a rat becomes abnormal due to a mutation (M251K) on the  $\alpha$ 1 subunit of the voltage-gated calcium ion channel  $Ca_{\nu}2.1$  of the rat.

[0358] Therefore, with a rat having the mutation on both the Scn1a gene and Cacna1a gene described later, it can be considered that the functions of both the voltage-gated sodium ion channel Na $_{\nu}1.1$  and the voltage-gated calcium ion channel Ca $_{\nu}2.1$  are abnormal.

[0359] (2. Confirmation of Gene Mutation in Dravet Syndrome Model Rat)

[0360] The foregoing F344-Scn1a<sup>Kyo81</sup> and the GRY (groggy rat, Cacna1a<sup>gry</sup>) were mated as parent rats (P) to produce F1 (first filial generation) rats, and these F1 rats were mated to produce F2 (second filial generation) rats. FIG. 5 is a view showing genotypes of the parent rats (P), the F1 rats and the F2 rats. As illustrated in (a) of FIG. 5, the F1 rats have the heterozygous mutation on both the Scn1a gene and the Cacna1a gene (referred to as "Scn1a mutant (hetero)+ Cacna1a mutant (hetero)"). Moreover, as illustrated in (b) of F1G. 5, rats showing 9 types of genotypes were born from the F2 rats. The genotypes of each of the rats were identified by extracting a tip tissue of the tail of the rats and extracting its DNA, to perform DNA sequencing with the extracted DNA and detect its gene mutation, or by detecting a digested pattern with use of a restriction enzyme.

[0361] (Method of Confirming Gene Mutation by DNA Sequencing)

[0362] Confirmation of gene mutation by DNA sequencing was performed as follows. First, a genomic DNA was amplified with use of a primer pair that sandwiches a mutation point (a nucleotide sequence of a Scn1a amplification primer pair is represented by SEQ ID NO.: 5 and SEQ ID NO.: 6, and a nucleotide sequence of a Cacna1a amplification primer pair is represented by SEQ ID NO.: 7 and SEQ ID NO.: 8), and thereafter, an obtained PCR product was purified with use of a PCR products pre-sequencing kit (Amersham Biosciences, Little Chalfont, Buckinghamshire, England). See the item "Sequence of primers" later described for the nucleotide sequence of the used primer pairs.

[0363] Next, sequence reaction was performed with use of a Big Dye Terminator FS ready-reaction kit (Applied Biosystems), to determine a nucleotide sequence with a fluorescence sequencer (ABI PRISM3100 sequencer; Applied Biosystems)

[0364] FIG. 6 is a view illustrating a method of identifying a genotype of the Scn1a gene and the Cacna1a gene of the F2 rats, by sequencing. As illustrated in FIG. 6, a wild-type Scn1a gene has a nucleotide at position 4249 be "A". In comparison, a mutant Scn1a gene (N1417H) has a nucleotide at position 4249 that is mutated from "A" to "C". As a result, a codon "AAT" that designates asparagine (N) being an amino acid at position 1417 in the wild-type Scn1a gene, is mutated to a codon "CAT" which designates histidine (H), in the mutant Scn1a gene (N1417H).

[0365] Moreover, the wild-type Cacnala gene has a nucleotide at position 752 be "T". In comparison, the mutant Cacnala gene (M251K) has a nucleotide at position 752 that is mutated from "T" to "A". As a result, a codon "ATG" that designates methionine, which is an amino acid at position 251, is mutated to a codon "AAG" that designates lysine.

[0366] (Method of Confirming Gene Mutation by Restriction Enzyme Digestion)

[0367] The method of confirming gene mutation by the restriction enzyme digestion was performed as follows. When detecting mutation in the Scn1a gene, a genomic DNA was amplified with use of a primer pair (SEQ ID NOs.: 5 and 6) that sandwich a mutation point in the Scn1a gene, and thereafter an obtained PCR product was reacted for three hours at 50° C., with use of a restriction enzyme BcII. Thereafter, the PCR product reacted with the restriction enzyme was subjected to electrophoresis with use of 4% agarose gel, and the size of the band was detected. FIG. 7 is a view illustrating a method of identifying the genotype of the Scn1a gene of the F2 rats, by restriction enzyme digestion.

[0368] As shown in (a) and (b) of FIG. 7, the wild-type Scn1a gene was not digested with BM so the size of the band remained as the size of the PCR product (nucleotide of 380 bp). On the other hand, the mutant Scn1a gene (N1417H) was digested with BM so two fragments (nucleotides of 276 bp and 104 bp) were detected. In a case of a heterozygous rat of the wild-type Scn1a gene and the mutant Scn1a gene (N1417H), three fragments (nucleotides of 380 bp, 276 bp, and 104 bp) were detected. Illustrated in (c) of FIG. 7 shows a result of electrophoresis.

[0369] In a case of detecting the mutation on the Cacna1a gene, a genomic DNA was amplified with use of a primer pair (SEQ ID NOs.: 7 and 8) that sandwich a mutation point of the Cacna1a gene, and thereafter, an obtained PCR product was reacted for hour at 37° C. with use of a restriction enzyme PciI. Thereafter, the PCR product reacted with the restriction enzyme was subjected to electrophoresis with use of 4% agarose gel, to detect the size of a band.

[0370] FIG. 8 is a view illustrating a method of identifying a genotype of the Cacnala gene of the F2 rats, by restriction enzyme digestion. As illustrated in (a) and (b) of FIG. 8, a wild-type Cacnala gene was not digested with PciI, so hence the size of the band remained as the size of the PCR product (nucleotide of 352 bp). On the other hand, the mutant Cacnala gene (M251K) was digested with PciI, and thus two fragments (nucleotides of 219 by and 133 bp) were detected. With a heterozygous rat of the wild-type Cacnala gene and an abnormal Cacnala gene (M251K), three fragments (nucleotides of 352 bp, 219 bp, and 133 bp) were detected. Illustrated in (c) of FIG. 8 is a result of electrophoresis.

### Example 7

#### Analysis of Dravet Syndrome Model Rat

[0371] A study was performed on what kind of (worsening) effect was given on the seizure when a mutation on the Cacnala gene was added to a mutation on the Scnla gene, with use of a Dravet syndrome model rat. More specifically, comparison was made regarding symptoms when a convulsion seizure was induced by heat load, between a rat having a homozygous mutation on the Scnla gene (referred to as "Scnla mutant (homo)+Cacnala wild-type (homo)") and a rat having a homozygous mutation on the Scnla gene and a heterozygous mutation on the Cacnala gene (referred to as "Scnla mutant (homo)+Cacnala mutant (hetero)").

[0372] The Scn1a mutant (homo)+Cacna1a wild-type (homo) and the Scn1a mutant (homo)+Cacna1a mutant (hetero) both have a homozygous mutation on the Scn1a gene (N1417H). Hence, comparison is made between the wild-type Cacna1a gene and the mutant Cacna1a gene (M251K), under the condition of the homozygous mutation of the Scn1a gene.

[0373] Moreover, a rat having a wild-type Scn1a gene and a wild-type Cacna1a gene (referred to as "Scn1a wild-type (homo)+Cacna1a wild-type (homo)") and a rat having a wild-type homozygous mutation on the Scn1a gene and a heterozygous mutation on the Cacna1a gene (referred to as "Scn1a wild-type (homo)+Cacna1a mutation (hetero)") were used as control. The following lists the genotypes of the rats used in the experiment. The following numbers (1) to (4) correspond to the numbers in (b) of FIG. 5.

[0374] (1) Scn1a<sup>wt/wt</sup>Cacna1a<sup>wt/wt</sup> (Scn1a wild-type (homo)+Cacna1a wild-type (homo)) 14 males

[0375] (2) Scn1 $a^{mut/mut}$  Cacna1 $a^{wt/wt}$  (Scn1a mutant (homo)+Cacna1a wild-type (homo)) 7 males

[0376] (3) Scn1a<sup>mut/mut</sup> Cacnala<sup>wt/mut</sup> (Scn1a mutant (homo)+Cacnala mutant (hetero)) 17 males

[0377] (4) Scn1a<sup>wt</sup>/<sup>wt</sup> Cacna1a<sup>wt</sup>/<sup>mut</sup> (Scn1a wild-type (homo)+Cacna1a mutant (hetero)) 12 males.

[0378] Hot bath load (45° C.) were given on male rats of 5 weeks old of the groups (1) to (4) described above, to compare their body temperatures at a time when a convulsion is induced, their duration of the convulsion, and their severity score of the convulsion. A rectal temperature at the time when the seizure started was measured, to serve as the body temperature at the time when the convulsion was induced. The seizure severity score of the convulsion were evaluated as follows: 0=no seizure, 1=facial convulsion, 2=clonic convulsion of both arms while maintaining posture, 3=sprint or jump, 4=generalized convulsion unable to maintain posture, and 5=death caused by persistent convulsion.

[0379] The results were as shown in FIG. 9. FIG. 9 is a view showing a result of the effect caused by the mutation on the Cacnala gene in the Scnla gene-mutated rat. In the graphs of (a) to (c) in FIG. 9, Scnla<sup>mut/mut</sup>Cacnala<sup>wt/vt</sup> (the foregoing rat (2)) is shown as "Scnla mutant (homo)". Scnla<sup>mut/mut</sup>Cacnala<sup>wt/mut</sup> (the foregoing rat (3)) is shown as "Scnla mutant (homo)+Cacnala mutant (hetero)". Moreover, control Scnla<sup>wt/vt</sup>Cacnala<sup>wt/vt</sup> (foregoing rat (1)) is shown as "WT", and control Scnla<sup>wt/vt</sup>Cacnala<sup>wt/mut</sup> (foregoing rat (4)) is shown as "Cacnala mutant (hetero)".

[0380] As a result of analysis, the group (3) rats (Scn1a mutant (homo)+Cacna1a mutant (hetero)) had no large difference in the body temperatures at the time of convulsion onset (convulsion threshold) ((a) of FIG. 9) and severity scores ((b) of FIG. 9), from those of the group (2) rats (Scn1a mutant (homo)+Cacna1a wild-type (homo)). However, it was found that the duration of the convulsion ((c) of FIG. 9) became significantly long. This result demonstrates that the mutation of the Cacna1a gene relates to the worsening of the symptoms of convulsion.

[0381] Furthermore, FIG. 10 shows a part of an electroencephalogram during a seizure of a group (3) rat (Scn1a mutant (homo)+Cacna1a mutant (hetero)). It was considered from this result that a rat having a mutation on the Scn1a gene and the Cacna1a gene could serve as a model rat of the intractable Dravet syndrome. The model rat is expected to be usefully used in the future for clarification of the onset mechanism of the intractable Dravet syndrome, development of medicament for Dravet syndrome, and like uses.

[0382] Moreover, these results are considered as supporting the gene analysis data of Example 1, that a variation of the CACNA1A gene was detected in addition to a mutation on the SCN1A gene, in a patient of Dravet syndrome which is an intractable epilepsy. Namely, the method according to the present invention of obtaining data for assessing the potential for development of Dravet syndrome can be said as a technique supported by the gene analysis results of the Examples, a mutant channel function analysis result, and animal experiment results.

#### CONCLUSION

[0383] The present invention was developed based on a molecular foundation of development of the intractable Dravet syndrome; the assessment method according to the present invention can be said as useful as an early detection method of Dravet syndrome patients. By use of the assessment method according to the present invention, it is possible to find Dravet syndrome, which has an unfavorable prognosis, in high accuracy and at an early stage. This allows for an epilepsy specialist to prepare a treatment management system for the patient of Dravet syndrome from an early stage. As a result, this leads to improvement in therapeutic intervention of the patient, reduction of mental load on the family, and reduction of economical burden. Moreover, it is possible to

carry out appropriate treatment to the Dravet syndrome patient, so therefore is considered as contributive to the reduction of medical fees.

[0384] Furthermore, with use of the kit according to the present invention, it is possible to easily detect the mutation for both the SCN1A gene and CACNA1A gene. Consequently, the kit according to the present invention is useful for a general pediatrician to distinguish a patient of Dravet syndrome who requires treatment by a specialist out of the benign febrile epilepsies, during the initial stage of the disease under the age of one.

[0385] By use of the assessment method and the kit according to the present invention, it is possible to detect with high accuracy a patient of Dravet syndrome at the point in time of under the age of one, which was difficult to detect until now. Moreover, by examining gene abnormalities upon sending the blood taken to an examination center, it is possible to detect Dravet syndrome patients in high accuracy even for a remote personal hospital or the like.

[0386] Moreover, the model animal and cell according to the present invention may be usefully used in the clarification of an onset mechanism of the intractable Dravet syndrome, the development of medicament for Dravet syndrome, and like uses

[0387] <Primer Sequences>

[0388] Table 10 shows a nucleotide sequence of a primer pair used for amplifying the Scn1a gene and amplifying the Cacna1a gene.

TABLE 10

Scnla amplification	Sense primer: Antisense primer:					SEQ ID NO.: 5 SEQ ID NO.: 6
Cacnala amplification	Sense primer: Antisense primer:	5'-TCT 5'-GTG	 	 	 	SEQ ID NO: 7 SEQ ID NO.: 8

[0389] Tables 11 and 12 show nucleotide sequences of primer pairs used for detecting SCN1A gene genomes.

TABLE 11

Exon 1 amplification	Sense primer: Antisense primer:	5'-tcatggcacagttcctgtatc-3' 5'-gcagtaggcaattagcagcaa-3'	SEQ ID NO.: 9 SEQ ID NO.: 10
Exon 2 amplification	Sense primer: Antisense primer:	5'-tggggcactttagaaattgtg-3' 5'-tgacaaagatgcaaaatgagag-3'	SEQ ID NO.: 11 SEQ ID NO.: 12
Exon 3 amplification	Sense primer: Antisense primer:	5'-gcagtttgggcttttcaatg-3' 5'-tgagcattgtcctcttgctg-3'	SEQ ID NO.: 13 SEQ ID NO.: 14
Exon 4 amplification	Sense primer: Antisense primer:	5'-agggctacgtttcatttgtatg-3' 5'-tgtgctaaattgaaatccagag-3'	SEQ ID NO.: 15 SEQ ID NO.: 16
Exon 5 amplification	Sense primer: Antisense primer:	5'-CAGCTCTTCGCACTTTCAGA-3' 5'-TCAAGCAGAGAAGGATGCTGA-3'	SEQ ID NO.: 17 SEQ ID NO.: 18

TABLE 11 -continued

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Exon 6 amplification	Sense primer: Antisense primer:	5'-agcgttgcaaacattcttgg-3' 5'-gggatatccagcccctcaag-3'	SEQ ID NO.: 19 SEQ ID NO.: 20
Exon 7 amplification	Sense primer:	5'-gacaaatacttgtgcctttgaatg-3' 5'-acataatctcatactttatcaaaaacc-3'	SEQ ID
Exon 8 amplification	Sense primer: Antisense primer:	5'-gaaatggaggtgttgaaaatgc-3' 5'-aatccttggcatcactctgc-3'	SEQ ID NO.: 23 SEQ ID NO.: 24
Exon 9 amplification	Sense primer: Antisense primer:	5'-agtacagggtgctatgaccaac-3' 5'-tcctcatacaaccacctgctc-3'	SEQ ID NO.: 25 SEQ ID NO.: 26
Exon 10 amplification	Sense primer: Antisense primer:	5'-tetecaaaageetteattagg-3' 5'-ttetaatteteeceetetetee-3'	SEQ ID NO.: 27 SEQ ID NO.: 28
Exon 11 amplification	Sense primer: Antisense primer:	5'-tcctcattctttaatcccaagg-3' 5'-gccgttctgtagaaacactgg-3'	SEQ ID NO.: 29 SEQ ID NO.: 30
Exon 12 amplification	Sense primer: Antisense primer:	5'-gtcagaaatatctgccatcacc-3' 5'-gaatgcactattcccaactcac-3'	SEQ ID NO.: 31 SEQ ID NO.: 32
Exon 13 amplification	Sense primer: Antisense primer:	5'-tgggctctatgtgtgtgtctg-3' 5'-ggaagcatgaaggatggttg-3'	SEQ ID NO.: 33 SEQ ID NO.: 34
Exon 14 amplification	Sense primer: Antisense primer:	5'-tacttcgcgtttccacaagg-3' 5'-gctatgcaagaaccctgattg-3'	SEQ ID NO.: 35 SEQ ID NO.: 36

### TABLE 12

Exon 15 amplification	Sense primer: Antisense primer:	5'-atgageetgagaeggttagg-3' 5'-atacatgtgeeatgetggtg-3'	SEQ ID NO.: 37 SEQ ID NO.: 38
Exon 16 amplification	Sense primer: Antisense primer:	5'-tgctgtggtgtttccttctc-3' 5'-tgtattcataccttcccacacc-3'	SEQ ID NO.: 39 SEQ ID NO.: 40
Exon 17 amplification	Sense primer: Antisense primer:	5'-aaaagggttagcacagacaatg-3' 5'-attgggcagatataatcaaagc-3'	SEQ ID NO.: 41 SEQ ID NO.: 42
Exon 18 amplification	Sense primer: Antisense primer:	5'-cacacagetgatgaatgtge-3' 5'-tgaagggetacaetttetgg-3'	SEQ ID NO.: 43 SEQ ID NO.: 44
Exon 19 amplification	Sense primer: Antisense primer:	5'-tctgccctcctattccaatg-3' 5'-gcccttgtcttccagaaatg-3'	SEQ ID NO.: 45 SEQ ID NO.: 46

TABLE 12 -continued

Exon 20	Sense	5'-aaaaattacatcctttacatcaaactg-3	
amplification	primer: Antisense primer:	5'-ttttgcatgcatagattttcc-3'	NO.: 47 SEQ ID NO.: 48
Exon 21 amplification	Sense primer:	5'-tgaaccttgcttttacatatcc-3'	SEQ ID
	Antisense primer:	5'-acccatctgggctcataaac-3'	SEQ ID NO.: 50
Exon 22 amplification	Sense primer:	5'-tgtcttggtccaaaatctgtg-3'	SEQ ID NO.: 51
	Antisense primer:	5'-ttggtcgtttatgctttattcg-3'	SEQ ID NO.: 52
Exon 23 amplification	Sense primer:	5'-ccctaaaggccaatttcagg-3'	SEQ ID NO.: 53
-	Antisense primer:	5'-atttggcagagaaaacactcc-3'	SEQ ID NO.: 54
Exon 24 amplification	Sense primer:	5'-gagatttgggggtgtttgtc-3'	SEQ ID NO.: 55
-	Antisense primer:	5'-ggattgtaatggggtgcttc-3'	SEQ ID NO.: 56
Exon 25 amplification	Sense primer:	5'-caaaaatcagggccaatgac-3'	SEQ ID NO.: 57
•	Antisense primer:	5'-tgattgctgggatgatcttg-3'	SEQ ID NO.: 58
Exon 26(1) amplification	Sense primer:	5'-aggactctgaaccttaccttgg-3'	SEQ ID NO.: 59
-	Antisense primer:	5'-ccatgaatcgctcttccatc-3'	SEQ ID NO.: 60
Exon 26(2) amplification	Sense primer:	5'-tgtgggaacccatctgttg-3'	SEQ ID NO.: 61
	Antisense primer:	5'-gtttgctgacaaggggtcac-3'	SEQ ID NO.: 62

[0390] Tables 13 and 14 show nucleotide sequences of primer pairs used for detecting the CACNA1A gene genome. In Tables 13 and 14, for example, E1F indicates an Exon 1 amplification sense primer, and E1Rv indicates an Exon 1 amplification antisense primer.

#### TABLE 13

Exon 1 amplification	CACNA1A-E1F: CACNA1A-E1Rv:	5'-teteegeagtegtageteeag-3' 5'-agagattettteacacteetee-3'		ID NO.:	
Exon 2 amplification	CACNA1A-E2F: CACNA1A-E2Rv:	5'-tttagaagtcacctgatctggg-3' 5'-gacagagcgagactctggttca-3'	_	ID NO.:	
Exon 3 amplification	CACNA1A-E3F: CACNA1A-E3RV:	5'-gacaagagaactctgcaagagg-3' 5'-atacagctgagacatggaggtg-3'	~	ID NO.:	
Exon 4 amplification	CACNA1A-E4F: CACNA1A-E4Rv:	5'-tttatcccgtgaggcaggtactg-3' 5'-cctcctgagatgctctgcatag-3'		ID NO.:	
Exon 5 amplification	CACNA1A-E5F: CACNA1A-E5Rv:	5'-tgtggtgcttccttcaccattg-3' 5'-cagaggctatttcactcactgc-3'		ID NO.:	
Exon 6 amplification	CACNA1A-E6F: CACNA1A-E6Rv:	5'-ccccaaagccaaacattgatctc-3' 5'-actctgattgtccacacacactg-3'	~	ID NO.:	
Exon 7 amplification	CACNA1A-E7F: CACNA1A-E7Rv:	5'-cagaaaacgttcctccatttccc-3' 5'-aagcttcaatggcctctacttgg-3'	-	ID NO.:	
Exon 8 amplification	CACNA1A-E8F: CACNA1A-E8Rv:	5'-gccatactctggcttttctatgc-3' 5'-cgtgatgtcagatcctggcttc-3'		ID NO.:	
Exon 9 amplification	CACNA1A-E9F: CACNA1A-E9Rv:	5'-gttggctattgctactgttgcg-3' 5'-gatccttagaaccagtcacctg-3'		ID NO.:	

# TABLE 13 -continued

Exon 10 amplification	CACNA1A-E1OF: CACNA1A-E1ORv:	5'-tgatagtgccaccttgaacctc-3' 5'-tgatgtaatctgcccaggacac-3'		NO . :	
Exon 11 amplification	CACNA1A-E11F: CACNA1A-E11Rv:	5'-ctgcaacagagaactatcagcc-3' 5'-aagagaagtggaaaaagggtgtg-3'	~	NO . :	
Exon 12 amplification	CACNA1A-E12F: CACNA1A-E12Rv:	5'-gtagttctagcatgttggaggc-3' 5'-atctgtcattccaggcaagagc-3'	~	NO . :	
Exon 13~15 amplification	CACNA1A-E13F: CACNA1A-E15Rv:	5'-atggatgaatgagggggtcaag-3' 5'-agcaggcactttcatctgtgac-3'	~	NO . :	
Exon 13~15 amplification	CACNA1A-E13F2: CACNA1A-E15Rv:	5'-tccatttggagggaggagtttg-3' 5'-agcaggcactttcatctgtgac-3'	~	NO . :	
Exon 14~15 amplification	CACNA1A-E14F: CACNA1A-E15Rv:	5'-cctccagaaagttgggaaagtg-3' 5'-agcaggcactttcatctgtgac-3'		NO.:	
Exon 16~17 amplification	CACNA1A-E16F: CACNA1A-E17Rv:	5'-aaggagaagccaacacggagtc-3' 5'-ggtggtaactttgccagagaaac-3'	-	NO . :	
Exon 18 amplification	CACNA1A-E18F: CACNA1A-E18Rv:	5'-agcaggtacccattccaattgg-3' 5'-aatctgtgcctgggatagtgtg-3'	-	NO . :	
Exon 19 amplification (1)	CACNA1A-E19F: CACNA1A-E19Rv:	5'-cctgactcagatgctcacagac-3' 5'-acacagcacgtgctactttggc-3'		NO . :	
Exon 19 amplification (2)	CACNA1A-E19F2: CACNA1A-E19Rv:	5'-gaggactteeteaggaaacag-3' 5'-acacageaegtgetaetttgge-3'		NO . :	
Exon 20 amplification	CACNA1A-E20F: CACNA1A-E20Rv:	5'-agatggaatcttagctaggatcc-3' 5'-aattatctcactgaaccctccac-3'		NO . :	
Exon 21 amplification	CACNA1A-E21F: CACNA1A-E21Rv:	5'-agaaatgtcagccgcttcttgc-3' 5'-ggtggtcaacactcactcattg-3'		NO . :	
Exon 22 amplification	CACNA1A-E22F: CACNA1A-E22Rv:	5'-tttgttgtgtaggaggccttgg-3' 5'-aacatcccaccctacctatgag-3'	~	NO . :	

# TABLE 14

Exon 23	CACNA1A-E23F:	5'-cctgcgcaactgtatatagcag-3'	SEQ ID NO.: 104
amplification	CACNA1A-E23Rv:	5'-ctcaacctcctgatctcaagtg-3'	SEQ ID NO.: 105
Exon 24 amplification	CACNA1A-E24F:	5'-cccaaagtttggatctaagagcc-3'	SEQ ID NO.: 106
	CACNA1A-E24Rv:	5'-aaagccatcgaagctcttcctg-3'	SEQ ID NO.: 107
Exon 25	CACNA1A-E25F:	5'-caggtgaaatggaccactcttc-3'	SEQ ID NO.: 108
amplification	CACNA1A-E25Rv:	5'-tccttgagcagtgtacaacctg-3'	SEQ ID NO.: 109
Exon 26	CACNA1A-E26F:	5'-gaatgccaggattgagtccaac-3'	SEQ ID NO.: 110
amplification	CACNA1A-E26Rv:	5'-gaatgtgctggaaagtggagac-3'	SEQ ID NO.: 111
Exon 27	CACNA1A-E27F:	5'-cactgcttcccaagcagtctag-3'	SEQ ID NO.: 112
amplification	CACNA1A-E27Rv:	5'-attacaggcgtgagccaccatg-3'	SEQ ID NO.: 113
Exon 28	CACNA1A-E28F:	5'-tttccctctgttcctgttctgc-3'	SEQ ID NO.: 114
amplification	CACNA1A-E28Rv:	5'-ttcggttgggacaatgcttctg-3'	SEQ ID NO.: 115
Exon 29	CACNA1A-E29F:	5'-ctcaagcaactgtagctgttgg-3'	SEQ ID NO.: 116
amplification	CACNA1A-E29Rv:	5'-ttatcagggtagaggcaggaac-3'	SEQ ID NO.: 117
Exon 30	CACNA1A-E30F:	5'-gtgaaaagaagagcctagtccg-3'	SEQ ID NO.: 118
amplification	CACNA1A-E30Rv:	5'-atggtaacactcacaggttggg-3'	SEQ ID NO.: 119
Exon 31 amplification	CACNA1A-E31F:	5'-gcccttcgaacaaccataactg-3'	SEQ ID NO.: 120
	CACNA1A-E31Rv:	5'-cctacagccaagctttggttac-3'	SEQ ID NO.: 121
Exon 32	CACNA1A-E32F:	5'-cccattggttttttggcactgg-3'	SEQ ID NO.: 122
amplification	CACNA1A-E32Rv:	5'-ggacagacagacagaggagag-3'	SEQ ID NO.: 123

TABLE 14 -continued

Exon 33~35 amplification	CACNA1A-E33F: CACNA1A-E35Rv:	5'-tgttggttggcttcatgtaggg-3' 5'-cagaattatcagagcaggtccc-3'	~	ID NO.: ID NO.:	
Exon 36 amplification	CACNA1A-E36F: CACNA1A-E36Rv:	5'-teteageteccagtaaaaggag-3' 5'-caacagtgetgagtttgagaeg-3'	~	ID NO.: ID NO.:	
Exon 37 amplification	CACNA1A-E37F: CACNA1A-E37Rv:	5'-ggcctctgtgtacatgtctttg-3' 5'-gggtatgcaagggtgatgattc-3'	~	ID NO.: ID NO.:	
Exon 38 amplification	CACNA1A-E38F: CACNA1A-E38Rv:	5'-tgtttetecceaeetetette-3' 5'-aaaaaaaecceagtgeetggaeg-3'	~	ID NO.: ID NO.:	
Exon 39 amplification	CACNA1A-E39F: CACNA1A-E39Rv:	5'-agaaactgagtactgggacagg-3' 5'-ggaagagtgaatgaagatccgg-3'		ID NO.: ID NO.:	
Exon 40~41 amplification	CACNA1A-E40F: CACNA1A-E41Rv:	5'-aaagattggggtetegtteteg-3' 5'-ccctcatattccagttggttec-3'		ID NO.: ID NO.:	
Exon 42~44 amplification	CACNA1A-E42F: CACNA1A-E44Rv:	5'-gtgtgtgtgtgtgtatactggg-3' 5'-cagactgcttcagagactgaag-3'		ID NO.: ID NO.:	
Exon 45 amplification	CACNA1A-E45F: CACNA1A-E45Rv:	5'-cegatttetettgatgecagtg-3' 5'-agggtgegattgecaaagaaag-3'		ID NO.: ID NO.:	
Exon 46~47 amplification	CACNA1A-E46F: CACNA1A-E47Rv:	5'-acccagagccctgattgatcag-3' 5'-ttggatggggtatccccttctc-3'	-	ID NO.: ID NO.:	
Exon 48 amplification	CACNA1A-E48F: CACNA1A-E48Rv:	5'-tetetteeteecaateeegtg-3' 5'-tgeeeaggagggtetettttg-3'	-	ID NO.: ID NO.:	

#### INDUSTRIAL APPLICABILITY

[0391] As described above, by detecting the presence of a mutation on both  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na $_{\nu}$ 1.1 and  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca $_{\nu}$ 2.1, it is possible to obtain data for assessing a potential for development of Dravet syndrome of a subject who has not yet been subjected to onset of Dravet syndrome, with high accuracy. Hence, it is possible to distinguish a patient of Dravet syndrome that requires treatment by a specialist, out of benign febrile seizure patents, at an initial stage of disease under the age of one. Hence, it is possible to

use not only in the field of diagnosis medical treatment such as medical devices, diagnosis kits and the like, but broadly in the health science and medical field industry.

[0392] Moreover, in the present invention, by introducing a mutation on both of  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na $_{\nu}$ 1.1 and  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca $_{\nu}$ 2.1, it is possible to produce a model animal of Dravet syndrome. Such a model animal of Dravet syndrome can be used for development of medicament and treatment methods of Dravet syndrome. Hence, the present invention can be widely used in the industry of life science fields including the pharmaceutical field.

SEQUENCE LISTING

												COII	CIII	ueu	
Asp	Pro	Tyr	Tyr	Ile 85	Asn	Lys	Lys	Thr	Phe 90	Ile	Val	Leu	Asn	Lys 95	Gly
rys	Ala	Ile	Phe 100	Arg	Phe	Ser	Ala	Thr 105	Ser	Ala	Leu	Tyr	Ile 110	Leu	Thr
Pro	Phe	Asn 115	Pro	Leu	Arg	ГЛа	Ile 120	Ala	Ile	rya	Ile	Leu 125	Val	His	Ser
Leu	Phe 130	Ser	Met	Leu	Ile	Met 135	СЛа	Thr	Ile	Leu	Thr 140	Asn	Cys	Val	Phe
Met 145	Thr	Met	Ser	Asn	Pro 150	Pro	Asp	Trp	Thr	Lys 155	Asn	Val	Glu	Tyr	Thr 160
Phe	Thr	Gly	Ile	Tyr 165	Thr	Phe	Glu	Ser	Leu 170	Ile	Lys	Ile	Ile	Ala 175	Arg
Gly	Phe	Cys	Leu 180	Glu	Asp	Phe	Thr	Phe 185	Leu	Arg	Asp	Pro	Trp 190	Asn	Trp
Leu	Asp	Phe 195	Thr	Val	Ile	Thr	Phe 200	Ala	Tyr	Val	Thr	Glu 205	Phe	Val	Asp
Leu	Gly 210	Asn	Val	Ser	Ala	Leu 215	Arg	Thr	Phe	Arg	Val 220	Leu	Arg	Ala	Leu
Lys 225	Thr	Ile	Ser	Val	Ile 230	Pro	Gly	Leu	Lys	Thr 235	Ile	Val	Gly	Ala	Leu 240
Ile	Gln	Ser	Val	Lys 245	Lys	Leu	Ser	Asp	Val 250	Met	Ile	Leu	Thr	Val 255	Phe
CAa	Leu	Ser	Val 260	Phe	Ala	Leu	Ile	Gly 265	Leu	Gln	Leu	Phe	Met 270	Gly	Asn
Leu	Arg	Asn 275	Lys	CAa	Ile	Gln	Trp 280	Pro	Pro	Thr	Asn	Ala 285	Ser	Leu	Glu
Glu	His 290	Ser	Ile	Glu	Lys	Asn 295	Ile	Thr	Val	Asn	Tyr 300	Asn	Gly	Thr	Leu
Ile 305	Asn	Glu	Thr	Val	Phe 310	Glu	Phe	Asp	Trp	Lys 315	Ser	Tyr	Ile	Gln	Asp 320
Ser	Arg	Tyr	His	Tyr 325	Phe	Leu	Glu	Gly	Phe 330	Leu	Asp	Ala	Leu	Leu 335	CAa
Gly	Asn	Ser	Ser 340	Asp	Ala	Gly	Gln	Cys 345	Pro	Glu	Gly	Tyr	Met 350	Сув	Val
rys	Ala	Gly 355	Arg	Asn	Pro	Asn	Tyr 360	Gly	Tyr	Thr	Ser	Phe 365	Asp	Thr	Phe
Ser	Trp 370	Ala	Phe	Leu	Ser	Leu 375	Phe	Arg	Leu	Met	Thr 380	Gln	Asp	Phe	Trp
Glu 385	Asn	Leu	Tyr	Gln	Leu 390	Thr	Leu	Arg	Ala	Ala 395	Gly	Lys	Thr	Tyr	Met 400
Ile	Phe	Phe	Val	Leu 405	Val	Ile	Phe	Leu	Gly 410	Ser	Phe	Tyr	Leu	Ile 415	Asn
Leu	Ile	Leu	Ala 420	Val	Val	Ala	Met	Ala 425	Tyr	Glu	Glu	Gln	Asn 430	Gln	Ala
Thr	Leu	Glu 435	Glu	Ala	Glu	Gln	Lys 440	Glu	Ala	Glu	Phe	Gln 445	Gln	Met	Ile
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Ala Gly Gly 35	/ Ser Arg G	ln Gly Gly 40	Gln Pro Gly	Ala Gln Arg Met Tyr 45	
Lys Gln Ser 50	Met Ala G	ln Arg Ala 55	Arg Thr Met	Ala Leu Tyr Asn Pro 60	
Ile Pro Val	. Arg Gln A	_	Thr Val Asn 75	Arg Ser Leu Phe Leu 80	
Phe Ser Glu	ı Asp Asn V	al Val Arg	Lys Tyr Ala 90	Lys Lys Ile Thr Glu 95	
Trp Pro Pro	Phe Glu Ty	yr Met Ile	Leu Ala Thr 105	Ile Ile Ala Asn Cys 110	

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Суs 145	Phe	Glu	Ala	Gly	Ile 150	ГÀз	Ile	Ile	Ala	Leu 155	Gly	Phe	Ala	Phe	His 160
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Thr	Leu	Arg 195	Ala	Val	Arg	Val	Leu 200	Arg	Pro	Leu	Lys	Leu 205	Val	Ser	Gly
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Pro 225	Leu	Leu	Gln	Ile	Gly 230	Leu	Leu	Leu	Phe	Phe 235	Ala	Ile	Leu	Ile	Phe 240
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Pro	Tyr 290	Trp	Glu	Gly	Pro	Asn 295	Asn	Gly	Ile	Thr	Gln 300	Phe	Asp	Asn	Ile
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Glu	Trp	Leu 515	Ser	Asp	Phe	Leu	Tyr 520	Tyr	Ala	Glu	Phe	Ile 525	Phe	Leu	Gly
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tgggctctat gtgtgtgtct g
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ggaagcatga aggatggttg
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aaaaattaca tootttacat caaactg 27						
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agagattett teacaeteet ee
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthesized
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cctcctgaga tgctctgcat ag
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gccatactct ggcttttcta tgc
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ctgcaacaga gaactatcag cc
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<220> FEATURE:
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ràa	Ala	Lys 35	Asn	Pro	ГÀз	Pro	Asp 40	Lys	Lys	Asp	Asp	Asp 45	Glu	Asn	Gly
Pro	Lys 50	Pro	Asn	Ser	Asp	Leu 55	Glu	Ala	Gly	Lys	Asn 60	Leu	Pro	Phe	Ile
Tyr 65	Gly	Asp	Ile	Pro	Pro 70	Glu	Met	Val	Ser	Glu 75	Pro	Leu	Glu	Asp	Leu 80
Asp	Pro	Tyr	Tyr	Ile 85	Asn	Lys	Lys	Thr	Phe 90	Ile	Val	Leu	Asn	Lys 95	Gly
ГÀа	Ala	Ile	Phe 100	Arg	Phe	Ser	Ala	Thr 105	Ser	Ala	Leu	Tyr	Ile 110	Leu	Thr
Pro	Phe	Asn 115	Pro	Leu	Arg	Lys	Ile 120	Ala	Ile	ГÀв	Ile	Leu 125	Val	His	Ser
Leu	Phe 130	Ser	Met	Leu	Ile	Met 135	Cys	Thr	Ile	Leu	Thr 140	Asn	Cys	Val	Phe
Met 145	Thr	Met	Ser	Asn	Pro 150	Pro	Asp	Trp	Thr	Lув 155	Asn	Val	Glu	Tyr	Thr 160
Phe	Thr	Gly	Ile	Tyr 165	Thr	Phe	Glu	Ser	Leu 170	Ile	Lys	Ile	Ile	Ala 175	Arg
Gly	Phe	CÀa	Leu 180	Glu	Asp	Phe	Thr	Phe 185	Leu	Arg	Asp	Pro	Trp 190	Asn	Trp
		195					200					205		Val	
	210					215					220			Ala	
225					230		_		-	235			_	Ala	240
				245					250					Val 255	
			260					265					270	Gly	
		275					280					285		Leu	
	290					295				_	300		Ī	Thr	
305					310			Ī	_	315				Gln	320
				325					330					335	
-			340	_		_		345			-	-	350	C\ha	
-		355	_				360	_	_			365	_	Thr	
	370					375					380			Phe	
Glu 385	Asn	Leu	Tyr	Gln	Leu 390	Thr	Leu	Arg	Ala	Ala 395	Gly	Lys	Thr	Tyr	Met 400

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Leu	Ile	Leu	Ala 420	Val	Val	Ala	Met	Ala 425	Tyr	Glu	Glu	Gln	Asn 430	Gln	Ala
Thr	Leu	Glu 435	Glu	Ala	Glu	Gln	Lys 440	Glu	Ala	Glu	Phe	Gln 445	Gln	Met	Leu
Glu	Gln 450	Leu	Lys	Lys	Gln	Gln 455	Glu	Ala	Ala	Gln	Gln 460	Ala	Ala	Ala	Ala
Thr 465	Ala	Ser	Glu	His	Ser 470	Arg	Glu	Pro	Ser	Ala 475	Ala	Gly	Arg	Leu	Ser 480
Asp	Ser	Ser	Ser	Glu 485	Ala	Ser	Lys	Leu	Ser 490	Ser	Lys	Ser	Ala	Lys 495	Glu
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Glu	Glu	Lys 515	Asp	Asp	Asp	Glu	Phe 520	His	ГЛа	Ser	Glu	Ser 525	Glu	Asp	Ser
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Gly	Ser	Leu	Phe	Ser 565	Pro	Arg	Arg	Asn	Ser 570	Arg	Thr	Ser	Leu	Phe 575	Ser
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	Glu	595					600				_	605	_		
	Val 610			_		615		_	-		620				
625	Ser				630				_	635				_	640
	His			645	_	-		_	650					655	_
	Ser		660					665					670		
	Asp	675				_	680		_			685			
	Arg 690	-				695					700		_		
705	Aap				710		•			715					720
	Asn			725					730					735	
	Trp	_	740					745			_	_	750		
-	Trp	755	-				760					765		-	
	Val 770	-				775		-			780				
Met 785	Ala	Met	Glu	His	Tyr 790	Pro	Met	Thr	Glu	His 795	Phe	Asn	His	Val	Leu 800
Thr	Val	Gly	Asn	Leu	Val	Phe	Thr	Gly	Ile	Phe	Thr	Ala	Glu	Met	Phe

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Leu Lys Ile Ile	Ala Met Asp I	Pro Tyr Tyr Tyr	Phe Gln Glu Gly Trp
820		825	830
Asn Ile Phe Asp	•	al Thr Leu Ser	Leu Val Glu Leu Gly
835		340	845
Leu Ala Asn Val	Glu Gly Leu 8	Ser Val Leu Arg	Ser Phe Arg Leu Leu
850	855		860
Arg Val Phe Lys	Leu Ala Lys 8	Ser Trp Pro Thr	Leu Asn Met Leu Ile
865		875	880
Lys Ile Ile Gly	Asn Ser Val (	Gly Ala Leu Gly	Asn Leu Thr Leu Val
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900		905	910
Gly Lys Ser Tyr		al Cys Lys Ile	Ala Thr Asp Cys Lys
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Leu Pro Arg Trp 930	His Met Asn A	Asp Phe Phe His	Ser Phe Leu Ile Val 940
Phe Arg Val Leu	Cys Gly Glu 7	rp Ile Glu Thr	Met Trp Asp Cys Met
945		955	960
Glu Val Ala Gly	Gln Ala Met 0	Cys Leu Thr Val	Phe Met Met Val Met
	965	970	975
Val Ile Arg Asn	Leu Val Val I	eu Asn Leu Phe	Leu Ala Leu Leu
980		985	990
Ser Ser Phe Ser		eu Ala Ala Th	r Asp Asp Asp Asn Glu
995		.000	1005
Met Asn Asn Lev	ı Gln Ile Ala		et His Lys Gly Val
1010	1019		1020
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Leu Asn Asn Arg	J Lys Asp Asn	Cys Thr Ser A	sn His Thr Thr Glu
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Ile Gly Lys Asy	Deu Asp Cys	Leu Lys Asp V	al Asn Gly Thr Thr
1070	1079		1080
Ser Gly Ile Gly	y Thr Gly Ser		ys Tyr Ile Ile Asp
1085	1090		1095
Glu Ser Asp Tyr	r Met Ser Phe		ro Ser Leu Thr Val
1100	1109		1110
Thr Val Pro Ile	e Ala Val Gly 1120	Glu Ser Asp P	he Glu Asn Leu Asn 1125
Thr Glu Asp Phe	e Ser Ser Glu	-	lu Glu Ser Lys Glu
1130	1135		1140
Lys Leu Asn Glu	ı Ser Ser Ser		ly Ser Thr Val Asp
1145	1150		1155
Ile Gly Ala Pro	Ala Glu Glu		et Glu Pro Glu Glu
1160	1169		1170
Thr Leu Glu Pro	Glu Ala Cys 1180		ly Cys Val Gln Arg 1185

Tro	Trn	Λan	Lou	Λrα	λxα	Thr	Cva	Dho	Λrα	T10	17.2.1	Clu	Uia	7 an
irp	1205		ьeu	Arg		1210		Pne	Arg	шe	Val 1215		HIS	ASII
Trp	Phe 1220	Glu	Thr	Phe	Ile	Val 1225		Met	Ile	Leu	Leu 1230		Ser	Gly
Ala	Leu 1235	Ala	Phe	Glu	Asp	Ile 1240		Ile	Asp	Gln	Arg 1245	Lys	Thr	Ile
Lys	Thr 1250	Met	Leu	Glu	Tyr	Ala 1255		Lys	Val	Phe	Thr 1260		Ile	Phe
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Val	Ser 1295	Leu	Val	Ser	Leu	Thr 1300		Asn	Ala	Leu	Gly 1305		Ser	Glu
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CAa	Leu 1355	Ile	Phe	Trp	Leu	Ile 1360		Ser	Ile	Met	Gly 1365	Val	Asn	Leu
Phe	Ala 1370	Gly	ГÀв	Phe	Tyr	His 1375		Val	Asn	Thr	Thr 1380	Thr	Gly	Asp
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Asn	Phe 1415	Asp	Asn	Val	Gly	Phe 1420	Gly	Tyr	Leu	Ser	Leu 1425	Leu	Gln	Val
Ala	Thr 1430	Phe	Lys	Gly	Trp	Met 1435	Asp	Ile	Met	Tyr	Ala 1440	Ala	Val	Asp
Ser	Arg 1445	Asn	Val	Glu	Leu	Gln 1450		Lys	Tyr	Glu	Glu 1455	Ser	Leu	Tyr
Met	Tyr 1460	Leu	Tyr	Phe	Val	Ile 1465	Phe	Ile	Ile	Phe	Gly 1470		Phe	Phe
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Leu	Asp	Phe 195	Thr	Val	Ile	Thr	Phe 200	Ala	Tyr	Val	Thr	Glu 205	Phe	Val	Asp
Leu	Gly 210	Asn	Val	Ser	Ala	Leu 215	Arg	Thr	Phe	Arg	Val 220	Leu	Arg	Ala	Leu
Lys 225	Thr	Ile	Ser	Val	Ile 230	Pro	Gly	Leu	Lys	Thr 235	Ile	Val	Gly	Ala	Leu 240
Ile	Gln	Ser	Val	Lys 245	Lys	Leu	Ser	Asp	Val 250	Met	Ile	Leu	Thr	Val 255	Phe

												COII	CIII	<del>Jeu</del>	
CÀa	Leu	Ser	Val 260	Phe	Ala	Leu	Ile	Gly 265	Leu	Gln	Leu	Phe	Met 270	Gly	Asn
Leu	Arg	Asn 275	Lys	Cys	Val	Gln	Trp 280	Pro	Pro	Thr	Asn	Ala 285	Ser	Leu	Glu
Glu	His 290	Ser	Ile	Glu	ГÀз	Asn 295	Val	Thr	Thr	Asp	Tyr 300	Asn	Gly	Thr	Leu
Val 305	Asn	Glu	Thr	Val	Phe 310	Glu	Phe	Asp	Trp	Lys 315	Ser	Tyr	Ile	Gln	Asp 320
Ser	Arg	Tyr	His	Tyr 325	Phe	Leu	Glu	Gly	Val 330	Leu	Asp	Ala	Leu	Leu 335	Cys
Gly	Asn	Ser	Ser 340	Asp	Ala	Gly	Gln	Cys 345	Pro	Glu	Gly	Tyr	Met 350	Cys	Val
ГÀа	Ala	Gly 355	Arg	Asn	Pro	Asn	Tyr 360	Gly	Tyr	Thr	Ser	Phe 365	Asp	Thr	Phe
Ser	Trp 370	Ala	Phe	Leu	Ser	Leu 375	Phe	Arg	Leu	Met	Thr 380	Gln	Asp	Phe	Trp
Glu 385	Asn	Leu	Tyr	Gln	Leu 390	Thr	Leu	Arg	Ala	Ala 395	Gly	Lys	Thr	Tyr	Met 400
Ile	Phe	Phe	Val	Leu 405	Val	Ile	Phe	Leu	Gly 410	Ser	Phe	Tyr	Leu	Ile 415	Asn
Leu	Ile	Leu	Ala 420	Val	Val	Ala	Met	Ala 425	Tyr	Glu	Glu	Gln	Asn 430	Gln	Ala
Thr	Leu	Glu 435	Glu	Ala	Glu	Gln	Lys 440	Glu	Ala	Glu	Phe	Gln 445	Gln	Met	Leu
Glu	Gln 450	Leu	Lys	Lys	Gln	Gln 455	Glu	Ala	Ala	Gln	Gln 460	Ala	Ala	Ala	Ala
Thr 465	Ala	Ser	Glu	His	Ser 470	Arg	Glu	Pro	Ser	Ala 475	Ala	Gly	Arg	Leu	Ser 480
Asp	Ser	Ser	Ser	Glu 485	Ala	Ser	Lys	Leu	Ser 490	Ser	Lys	Ser	Ala	Lys 495	Glu
Arg	Arg	Asn	Arg 500	Arg	ГÀз	ГÀа	Arg	Lys	Gln	Lys	Glu	Gln	Ser 510	Gly	Gly
Glu	Glu	Lys 515	Asp	Asp	Asp	Glu	Phe 520	His	Lys	Ser	Glu	Ser 525	Glu	Asp	Ser
Ile	Arg 530	Arg	Lys	Gly	Phe	Arg 535	Phe	Ser	Ile	Glu	Gly 540	Asn	Arg	Leu	Thr
Tyr 545	Glu	ГЛа	Arg	Tyr	Ser 550	Ser	Pro	His	Gln	Ser 555	Leu	Leu	Ser	Ile	Arg 560
Gly	Ser	Leu	Phe	Ser 565	Pro	Arg	Arg	Asn	Ser 570	Arg	Thr	Ser	Leu	Phe 575	Ser
Phe	Arg	Gly	Arg 580	Ala	ГÀа	Asp	Val	Gly 585	Ser	Glu	Asn	Asp	Phe 590	Ala	Asp
Asp	Glu	His 595	Ser	Thr	Phe	Glu	Asp 600	Asn	Glu	Ser	Arg	Arg 605	Asp	Ser	Leu
Phe	Val 610	Pro	Arg	Arg	His	Gly 615	Glu	Arg	Arg	Asn	Ser 620	Asn	Leu	Ser	Gln
Thr 625	Ser	Arg	Ser	Ser	Arg 630	Met	Leu	Ala	Gly	Leu 635	Pro	Ala	Asn	Gly	Lys 640
Met	His	Ser	Thr	Val 645	Asp	CAa	Asn	Gly	Val 650	Val	Ser	Leu	Val	Gly 655	Gly
Pro	Ser	Val	Pro 660	Thr	Ser	Pro	Val	Gly 665	Gln	Leu	Leu	Pro	Glu 670	Val	Ile

Ile	Asp	Lys 675	Pro	Ala	Thr	Asp	Asp 680	Asn	Gly	Thr	Thr	Thr 685	Glu	Thr	Glu
Met	Arg 690	Lys	Arg	Arg	Ser	Ser 695	Ser	Phe	His	Val	Ser 700	Met	Asp	Phe	Leu
Glu 705	Asp	Pro	Ser	Gln	Arg 710	Gln	Arg	Ala	Met	Ser 715	Ile	Ala	Ser	Ile	Leu 720
Thr	Asn	Thr	Val	Glu 725	Glu	Leu	Glu	Glu	Ser 730	Arg	Gln	Lys	Cys	Pro 735	Pro
Cys	Trp	Tyr	Lys 740	Phe	Ser	Asn	Ile	Phe 745	Leu	Ile	Trp	Asp	Сув 750	Ser	Pro
Tyr	Trp	Leu 755	Lys	Val	Lys	His	Ile 760	Val	Asn	Leu	Val	Val 765	Met	Asp	Pro
Phe	Val 770	Asp	Leu	Ala	Ile	Thr 775	Ile	Cha	Ile	Val	Leu 780	Asn	Thr	Leu	Phe
Met 785	Ala	Met	Glu	His	Tyr 790	Pro	Met	Thr	Glu	His 795	Phe	Asn	His	Val	Leu 800
Thr	Val	Gly	Asn	Leu 805	Val	Phe	Thr	Gly	Ile 810	Phe	Thr	Ala	Glu	Met 815	Phe
Leu	Lys	Ile	Ile 820	Ala	Met	Asp	Pro	Tyr 825	Tyr	Tyr	Phe	Gln	Glu 830	Gly	Trp
Asn	Ile	Phe 835	Asp	Gly	Phe	Ile	Val 840	Thr	Leu	Ser	Leu	Val 845	Glu	Leu	Gly
Leu	Ala 850	Asn	Val	Glu	Gly	Leu 855	Ser	Val	Leu	Arg	Ser 860	Phe	Arg	Leu	Leu
Arg 865	Val	Phe	Lys	Leu	Ala 870	Lys	Ser	Trp	Pro	Thr 875	Leu	Asn	Met	Leu	Ile 880
Lys	Ile	Ile	Gly	Asn 885	Ser	Val	Gly	Ala	Leu 890	Gly	Asn	Leu	Thr	Leu 895	Val
Leu	Ala	Ile	Ile 900	Val	Phe	Ile	Phe	Ala 905	Val	Val	Gly	Met	Gln 910	Leu	Phe
Gly	Lys	Ser 915	Tyr	Lys	Asp	Cys	Val 920	Сув	Lys	Ile	Ala	Thr 925	Asp	Cys	Lys
Leu	Pro 930	Arg	Trp	His	Met	Asn 935	Asp	Phe	Phe	His	Ser 940	Phe	Leu	Ile	Val
Phe 945	Arg	Val	Leu	Cys	Gly 950	Glu	Trp	Ile	Glu	Thr 955	Met	Trp	Asp	Cys	Met 960
Glu	Val	Ala	Gly	Gln 965	Ala	Met	Cys	Leu	Thr 970	Val	Phe	Met	Met	Val 975	Met
Val	Ile	Arg	Asn 980	Leu	Val	Val	Leu	Asn 985	Leu	Phe	Leu	Ala	Leu 990	Leu	Leu
Ser	Ser	Phe 995	Ser	Ala	Asp	Asn	Leu 1000		a Ala	a Th:	r Ası	As;		sp A	sn Glu
Met	Asn 1010		ı Lev	ı Glr	ı Ile	e Ala 101		al As	sp A:	rg Me		is 020	Lys (	Gly '	Val
Ala	Tyr 1025		L Lys	a Arç	J Lys	103		yr G	lu Pl	ne I		ln 035	Gln s	Ser 1	Phe
Val	Arg 1040	_	Glr	ı Lys	3 Ile	e Let 104		sp GI	lu I	le Ly		ro 050	Leu <i>l</i>	Asp 1	Asp
Leu	Asn 1055		n Arg	g Lys	a Asp	Ası 100		ys Tl	nr Se	er A		is 065	Thr '	Thr (	Glu
Ile	Gly	Lys	a Asp	) Let	ı Asp	Cy:	∃ Le	eu Ly	ys A:	ap Va	al As	sn '	Gly :	Thr '	Thr

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	1070					1075					1080			
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Thr	Val 1115	Pro	Ile	Ala	Val	Gly 1120	Glu	Ser	Asp	Phe	Glu 1125	Asn	Leu	Asn
Thr	Glu 1130	Asp	Phe	Ser	Ser	Glu 1135		Asp	Leu	Glu	Glu 1140	Ser	Lys	Glu
ГÀа	Leu 1145	Asn	Glu	Ser	Ser	Ser 1150		Ser	Glu	Gly	Ser 1155	Thr	Val	Asp
Ile	Gly 1160	Ala	Pro	Ala	Glu	Glu 1165	Gln	Pro	Val	Met	Glu 1170	Pro	Glu	Glu
Thr	Leu 1175	Glu	Pro	Glu	Ala	Cys 1180		Thr	Glu	Gly	Cys 1185	Val	Gln	Arg
Phe	Lys 1190		CAa	Gln	Ile	Ser 1195		Glu	Glu	Gly	Arg 1200	Gly	Lys	Gln
Trp	Trp 1205	Asn	Leu	Arg	Arg	Thr 1210		Phe	Arg	Ile	Val 1215	Glu	His	Asn
Trp	Phe 1220		Thr	Phe	Ile	Val 1225		Met	Ile	Leu	Leu 1230	Ser	Ser	Gly
Ala	Leu 1235	Ala	Phe	Glu	Asp	Ile 1240		Ile	Asp	Gln	Arg 1245	Lys	Thr	Ile
Lys	Thr 1250		Leu	Glu	Tyr	Ala 1255	_	Lys	Val	Phe	Thr 1260	Tyr	Ile	Phe
Ile	Leu 1265	Glu	Met	Leu	Leu	Lys 1270		Val	Ala	Tyr	Gly 1275	Tyr	Gln	Thr
Tyr	Phe 1280		Asn	Ala	Trp	Сув 1285		Leu	Asp	Phe	Leu 1290	Ile	Val	Asp
Val	Ser 1295	Leu	Val	Ser	Leu	Thr 1300		Asn	Ala	Leu	Gly 1305	Tyr	Ser	Glu
Leu	Gly 1310	Ala	Ile	Lys	Ser	Leu 1315	Arg	Thr	Leu	Arg	Ala 1320	Leu	Arg	Pro
Leu	Arg 1325	Ala	Leu	Ser	Arg	Phe 1330	Glu	Gly	Met	Arg	Val 1335	Val	Val	Asn
Ala	Leu 1340	Leu	Gly	Ala	Ile	Pro 1345		Ile	Met	Asn	Val 1350	Leu	Leu	Val
Cya	Leu 1355	Ile	Phe	Trp	Leu	Ile 1360		Ser	Ile	Met	Gly 1365	Val	Asn	Leu
Phe	Ala 1370	Gly	Lys	Phe	Tyr	His 1375		Val	Asn	Thr	Thr 1380	Thr	Gly	Asp
Thr	Phe 1385	Glu	Ile	Thr	Glu	Val 1390	Asn	Asn	His	Ser	Asp 1395	Cys	Leu	Lys
Leu	Ile 1400	Glu	Arg	Asn	Glu	Thr 1405	Ala	Arg	Trp	Lys	Asn 1410	Val	ГÀв	Val
Asn	Phe 1415	Asp	His	Val	Gly	Phe 1420		Tyr	Leu	Ser	Leu 1425	Leu	Gln	Val
Ala	Thr 1430	Phe	Lys	Gly	Trp	Met 1435	Asp	Ile	Met	Tyr	Ala 1440	Ala	Val	Asp
Ser	Arg 1445	Asn	Val	Glu	Leu	Gln 1450		Lys	Tyr	Glu	Glu 1455	Ser	Leu	Tyr

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Gln	Lуз 1505		Tyr	Tyr	Asn	Ala 1510		Lys	Lys	Leu	Gly 1515	Ser	Lys	Lys
Pro	Gln 1520	-	Pro	Ile	Pro	Arg 1525		Gly	Asn	Lys	Phe 1530	Gln	Gly	Met
Val	Phe 1535	Asp	Phe	Val	Thr	Arg 1540		Val	Phe	Asp	Ile 1545	Ser	Ile	Met
Ile	Leu 1550		Cys	Leu	Asn	Met 1555		Thr	Met	Met	Val 1560	Glu	Thr	Asp
Asp	Gln 1565	Ser	Asp	Tyr	Val	Thr 1570		Ile	Leu	Ser	Arg 1575	Ile	Asn	Leu
Val	Phe 1580	Ile	Val	Leu	Phe	Thr 1585	-	Glu	Cys	Val	Leu 1590	-	Leu	Ile
Ser	Leu 1595	Arg	His	Tyr	Tyr	Phe 1600		Ile	Gly	Trp	Asn 1605	Ile	Phe	Asp
Phe	Val 1610	Val	Val	Ile	Leu	Ser 1615		Val	Gly	Met	Phe 1620		Ala	Glu
Leu	Ile 1625	Glu	Lys	Tyr	Phe	Val 1630		Pro	Thr	Leu	Phe 1635	Arg	Val	Ile
Arg	Leu 1640	Ala	Arg	Ile	Gly	Arg 1645		Leu	Arg	Leu	Ile 1650	ГÀа	Gly	Ala
Lys	Gly 1655	Ile	Arg	Thr	Leu	Leu 1660		Ala	Leu	Met	Met 1665	Ser	Leu	Pro
Ala	Leu 1670	Phe	Asn	Ile	Gly	Leu 1675		Leu	Phe	Leu	Val 1680	Met	Phe	Ile
Tyr	Ala 1685	Ile	Phe	Gly	Met	Ser 1690		Phe	Ala	Tyr	Val 1695	Lys	Arg	Glu
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Met	Ile 1715	CAa	Leu	Phe	Gln	Ile 1720		Thr	Ser	Ala	Gly 1725	Trp	Asp	Gly
	Leu 1730		Pro	Ile		Asn 1735		Lys	Pro		Asp 1740		Asp	Pro
Asn	Lys 1745	Val	Asn	Pro	Gly	Ser 1750		Val	Lys	Gly	Asp 1755	CAa	Gly	Asn
Pro	Ser 1760	Val	Gly	Ile	Phe	Phe 1765		Val	Ser	Tyr	Ile 1770		Ile	Ser
Phe	Leu 1775	Val	Val	Val	Asn	Met 1780		Ile	Ala	Val	Ile 1785	Leu	Glu	Asn
Phe	Ser 1790	Val	Ala	Thr	Glu	Glu 1795	Ser	Ala	Glu	Pro	Leu 1800	Ser	Glu	Asp
Asp	Phe 1805	Glu	Met	Phe	Tyr	Glu 1810		Trp	Glu	ГÀв	Phe 1815	Asp	Pro	Asp
Ala	Thr 1820	Gln	Phe	Met	Glu	Phe 1825		ГЛа	Leu	Ser	Gln 1830		Ala	Ala
Ala	Leu 1835	Glu	Pro	Pro	Leu	Asn 1840		Pro	Gln	Pro	Asn 1845	Lys	Leu	Gln

Leu Ile Ala Me 1850	t Asp Lei	Pro 1855	Met Va	al Ser (	Gly Asp 186		Ile	His
Cys Leu Asp Il 1865	e Leu Phe	Ala 1870	Phe Th	nr Lys I	Arg Val		Gly	Glu
Ser Gly Glu Me	t Asp Ala	Leu 1885	Arg Il	e Gln I	Met Glu 189		Arg	Phe
Met Ala Ser As 1895	n Pro Sei	Lys 1900	Val Se	er Tyr (	Gln Pro 190		Thr	Thr
Thr Leu Lys Ar 1910	g Lys Glr	1 Glu 1915	Glu Va	al Ser	Ala Val 192		Ile	Gln
Arg Ala Tyr Ar 1925	g Arg His	Leu 1930	Leu Ly	s Arg '	Thr Val 193		Gln	Ala
Ser Phe Thr Ty	r Asn Lys	1945	Lys Le	eu Lys (	Gly Gly 195		Asn	Leu
Leu Val Lys Gl 1955	u Asp Met	Ile 1960	Ile As	sp Arg	Ile Asn 196		Asn	Ser
Ile Thr Glu Ly 1970	s Thr Asp	Leu 1975	Thr Me	et Ser '	Thr Ala 198		CAa	Pro
Pro Ser Tyr As 1985	p Arg Val	Thr 1990	Lys Pr	o Ile '	Val Glu 199		His	Glu
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<pre>&lt;212&gt; TYPE: PRT &lt;213&gt; ORGANISM: &lt;400&gt; SEQUENCE: Met Ala Arg Phe 1 Gly Gly Ser Gly 20 Arg Gly Ala Gly 35 Met Tyr Lys Gln 50</pre> Asn Pro Ile Pro	Gly Asp Fro Ala Gly Ser Ser Met Val Arg 70	Glu Me Ala Gl Arg Gl 40 Ala Gl 55	et Pro Ly Val 25 Ln Gly Ln Arg sn Cys	10 Val Va Gly Gl Ala Arc Leu Th. 75	n Pro G 4 g Thr M 60 r Val A	la Ala 30 ly Ala 5 et Ala sn Arg	15 a Gly a Glr a Leu g Ser	Gly Arg Tyr Leu 80
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Leu	Arg	Thr	Leu	Arg	Ala	Val	Arg	Val	Leu	Arg	Pro	Leu	Lys	Leu	Val
Cor	C1**	195	Dro	Cor	Lou	Cln	200	v. l	Lou	Tria	Cor	205	Mo+	Lys	71.
ser	210	iie	PIO	ser	ьец	215	vai	vai	ьец	пув	220	116	мес	пув	Ala
Met 225	Ile	Pro	Leu	Leu	Gln 230	Ile	Gly	Leu	Leu	Leu 235	Phe	Phe	Ala	Ile	Leu 240
Ile	Phe	Ala	Ile	Ile 245	Gly	Leu	Glu	Phe	Tyr 250	Met	Gly	Lys	Phe	His 255	Thr
Thr	Сув	Phe	Glu 260	Glu	Gly	Thr	Asp	Asp 265	Ile	Gln	Gly	Glu	Ser 270	Pro	Ala
Pro	Cys	Gly 275	Thr	Glu	Glu	Pro	Ala 280	Arg	Thr	Cys	Pro	Asn 285	Gly	Thr	Lys
Cys	Gln 290	Pro	Tyr	Trp	Glu	Gly 295	Pro	Asn	Asn	Gly	Ile 300	Thr	Gln	Phe	Asp
Asn 305	Ile	Leu	Phe	Ala	Val 310	Leu	Thr	Val	Phe	Gln 315	Cys	Ile	Thr	Met	Glu 320
Gly	Trp	Thr	Asp	Leu 325	Leu	Tyr	Asn	Ser	Asn 330	Asp	Ala	Ser	Gly	Asn 335	Thr
Trp	Asn	Trp	Leu 340	Tyr	Phe	Ile	Pro	Leu 345	Ile	Ile	Ile	Gly	Ser 350	Phe	Phe
Met	Leu	Asn 355	Leu	Val	Leu	Gly	Val 360	Leu	Ser	Gly	Glu	Phe 365	Ala	Lys	Glu
Arg	Glu 370	Arg	Val	Glu	Asn	Arg 375	Arg	Ala	Phe	Leu	380 Tàa	Leu	Arg	Arg	Gln
Gln 385	Gln	Ile	Glu	Arg	Glu 390	Leu	Asn	Gly	Tyr	Met 395	Glu	Trp	Ile	Ser	Lys 400
Ala	Glu	Glu	Val	Ile 405	Leu	Ala	Glu	Asp	Glu 410	Thr	Asp	Val	Glu	Gln 415	Arg
His	Pro	Phe	Asp 420	Gly	Ala	Leu	Arg	Arg 425	Ala	Thr	Leu	Lys	Lys 430	Ser	Lys
Thr	Asp	Leu 435	Leu	Asn	Pro	Glu	Glu 440	Ala	Glu	Asp	Gln	Leu 445	Ala	Asp	Ile
Ala	Ser 450	Val	Gly	Ser	Pro	Phe 455	Ala	Arg	Ala	Ser	Ile 460	Lys	Ser	Ala	Lys
Leu 465	Glu	Asn	Ser	Thr	Phe 470	Phe	His	Lys	Lys	Glu 475	Arg	Arg	Met	Arg	Phe 480
Tyr	Ile	Arg	Arg	Met 485	Val	Lys	Thr	Gln	Ala 490	Phe	Tyr	Trp	Thr	Val 495	Leu
Ser	Leu	Val	Ala 500	Leu	Asn	Thr	Leu	Trp 505	Leu	Ala	Ile	Val	His 510	Tyr	Asn
Gln	Pro	Glu 515	Trp	Leu	Ser	Asp	Phe 520	Leu	Tyr	Tyr	Ala	Glu 525	Phe	Ile	Phe
Leu	Gly 530	Leu	Phe	Met	Ser	Glu 535	Met	Phe	Ile	Lys	Met 540	Tyr	Gly	Leu	Gly
Thr 545	Arg	Pro	Tyr	Phe	His 550	Ser	Ser	Phe	Asn	Cys 555	Phe	Asp	Cys	Gly	Val 560
Ile	Ile	Gly	Ser	Ile 565	Phe	Glu	Val	Ile	Trp 570	Ala	Val	Ile	Lys	Pro 575	Gly
Thr	Ser	Phe	Gly 580	Ile	Ser	Val	Leu	Arg 585	Ala	Leu	Arg	Leu	Leu 590	Arg	Ile
Phe	Lys	Val	Thr	Lys	Tyr	Trp	Ala	Ser	Leu	Arg	Asn	Leu	Val	Val	Ser

		595					600					605			
Leu	Leu 610	Asn	Ser	Met	Lys	Ser 615	Ile	Ile	Ser	Leu	Leu 620	Phe	Leu	Leu	Phe
Leu 625	Phe	Ile	Val	Val	Phe 630	Ala	Leu	Leu	Gly	Met 635	Gln	Leu	Phe	Gly	Gly 640
Gln	Phe	Asn	Phe	Asp 645	Glu	Gly	Thr	Pro	Pro 650	Thr	Asn	Phe	Asp	Thr 655	Phe
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Pro	Leu	Ser 755	Ala	Ala	Asn	Met	Ser 760	Ile	Ala	Val	ГÀа	Glu 765	Gln	Gln	Lys
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Lys	Thr	His	Leu 820	Asp	Arg	Pro	Leu	Val 825	Val	Asp	Pro	Gln	Glu 830	Asn	Arg
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Glu	Ser	Glu	Pro	Gln 885	Gln	Arg	Glu	His	Ala 890	Pro	Pro	Arg	Glu	His 895	Val
Pro	Trp	Asp	Ala 900	Asp	Pro	Glu	Arg	Ala 905	Lys	Ala	Gly	Asp	Ala 910	Pro	Arg
Arg	His	Thr 915	His	Arg	Pro	Val	Ala 920	Glu	Gly	Glu	Pro	Arg 925	Arg	His	Arg
Ala	Arg 930	Arg	Arg	Pro	Gly	Asp 935	Glu	Pro	Asp	Asp	Arg 940	Pro	Glu	Arg	Arg
Pro 945	Arg	Pro	Arg	Asp	Ala 950	Thr	Arg	Pro	Ala	Arg 955	Ala	Ala	Asp	Gly	Glu 960
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His	Asp	Asp	Arg 980	Glu	Arg	Arg	His	Arg 985	Arg	Arg	Lys	Glu	Ser 990	Gln	Gly
Ser	Gly	Val 995	Pro	Met	Ser	Gly	Pro 1000		ı Lev	ı Se	r Thi	r Th:		rg Pi	ro Ile

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Asp	Asn 1025		ГÀз	Asn	Asn	Lys 1030		Ala	Thr	Gly	Glu 1035	Pro	Ala	Ser
Pro	His 1040	Asp	Ser	Leu	Gly	His 1045		Gly	Leu	Pro	Pro 1050		Pro	Ala
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Val	Thr 1100		Pro	Ser	Ser	Thr 1105		Pro	Asn	Ser	Ala 1110	_	Thr	Ala
Arg	Lys 1115		Glu	His	Met	Ala 1120		Glu	Ile	Pro	Pro 1125		Cys	Pro
Pro	Leu 1130		His	Thr	Val	Val 1135		Val	Asn	Lys	Asn 1140		Asn	Pro
Asp	Pro 1145	Leu	Pro	ГÀа	ГÀа	Glu 1150		Glu	Lys	ГÀа	Glu 1155	Glu	Glu	Glu
Ala	Asp 1160		Gly	Glu	Asp	Gly 1165		Lys	Pro	Met	Pro 1170		Tyr	Ser
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His	Tyr 1190		Leu	Asn	Leu	Arg 1195		Phe	Glu	Met	Cys 1200		Leu	Met
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Gln	Pro 1220	Asn	Ala	Pro	Arg	Asn 1225		Val	Leu	Arg	Tyr 1230		Asp	Tyr
Val	Phe 1235	Thr	Gly	Val	Phe	Thr 1240		Glu	Met	Val	Ile 1245	ràa	Met	Ile
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Trp	Asn 1265	Ile	Leu	Asp	Phe	Ile 1270		Val	Ser	Gly	Ala 1275	Leu	Val	Ala
	Ala 1280		Thr	Gly		Ser 1285		Gly	Lys		Ile 1290		Thr	Ile
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Lys	Arg 1310	Leu	Pro	ГЛа	Leu	Lys 1315	Ala	Val	Phe	Asp	Cys 1320		Val	Asn
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Met	Phe 1340	Ile	Phe	Ala	Val	Val 1345	Ala	Val	Gln	Leu	Phe 1350	ГÀа	Gly	Lys
Phe	Phe 1355	His	СЛа	Thr	Asp	Glu 1360		ГЛа	Glu	Phe	Glu 1365	Arg	Asp	САв
Arg	Gly 1370		Tyr	Leu	Leu	Tyr 1375	Glu	ГЛа	Asn	Glu	Val 1380	Lys	Ala	Arg
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Trp	Ala 1400	Leu	Leu	Thr	Leu	Phe 1405	Thr	Val	Ser	Thr	Gly 1410	Glu	Gly	Trp
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Ala	Leu 1460	Ile	Ile	Ile	Thr	Phe 1465	Gln	Glu	Gln	Gly	Asp 1470	rys	Met	Met
Glu	Glu 1475	Tyr	Ser	Leu	Glu	Lys 1480	Asn	Glu	Arg	Ala	Cys 1485	Ile	Asp	Phe
Ala	Ile 1490	Ser	Ala	Lys	Pro	Leu 1495	Thr	Arg	His	Met	Pro 1500	Gln	Asn	Lys
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Cys	Val 1565	Leu	Lys	Val	Met	Ala 1570	Phe	Gly	Ile	Leu	Asn 1575	Tyr	Phe	Arg
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Phe	Phe 1655	Ile	Tyr	Ala	Ile	Ile 1660	Gly	Met	Gln	Val	Phe 1665	Gly	Asn	Ile
Gly	Ile 1670	Asp	Gly	Glu	Asp	Glu 1675	Asp	Ser	Asp	Glu	Asp 1680	Glu	Phe	Gln
Ile	Thr 1685	Glu	His	Asn	Asn	Phe 1690	Arg	Thr	Phe	Phe	Gln 1695	Ala	Leu	Met
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Leu	Ser 1715	Cys	Leu	Ser	Gly	Lys 1720	Pro	Cys	Asp	Lys	Asn 1725	Ser	Gly	Ile
Gln	Lys 1730	Pro	Glu	Cys	Gly	Asn 1735	Glu	Phe	Ala	Tyr	Phe 1740	Tyr	Phe	Val
Ser	Phe 1745	Ile	Phe	Leu	Cys	Ser 1750	Phe	Leu	Met	Leu	Asn 1755	Leu	Phe	Val
Ala	Val 1760	Ile	Met	Asp	Asn	Phe 1765	Glu	Tyr	Leu	Thr	Arg 1770	Asp	Ser	Ser
Ile	Leu	Gly	Pro	His	His	Leu	Asp	Glu	Tyr	Val	Arg	Val	Trp	Ala

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Tyr	Ser 1805	Leu	Leu	Arg	Val	Ile 1810	Ser	Pro	Pro	Leu	Gly 1815	Leu	Gly	Lys
ГÀа	Cys 1820	Pro	His	Arg	Val	Ala 1825	Cys	Lys	Arg	Leu	Leu 1830	Arg	Met	Asp
Leu	Pro 1835	Val	Ala	Asp	Asp	Asn 1840	Thr	Val	His	Phe	Asn 1845	Ser	Thr	Leu
Met	Ala 1850	Leu	Ile	Arg	Thr	Ala 1855	Leu	Asp	Ile	Lys	Ile 1860	Ala	Lys	Gly
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Met	Ala 1880	Ile	Trp	Pro	Asn	Leu 1885	Ser	Gln	Lys	Thr	Leu 1890	Asp	Leu	Leu
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Lys	Leu 1925	Gln	Ala	Met	Arg	Glu 1930	Glu	Gln	Asn	Arg	Thr 1935	Pro	Leu	Met
Phe	Gln 1940	Arg	Met	Glu	Pro	Pro 1945	Ser	Pro	Thr	Gln	Glu 1950	Gly	Gly	Pro
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Pro	Glu 2000	Arg	Gly	Pro	Pro	Ile 2005	Asp	Met	Pro	Asn	Ser 2010	Gln	Pro	Asn
Ser	Gln 2015	Ser	Val	Glu	Met	Arg 2020	Glu	Met	Gly	Thr	Asp 2025	Gly	Tyr	Ser
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Lys	Arg 2075	Ser	Ala	Ser	Val	Leu 2080	Gly	Pro	Lys	Ala	Arg 2085	Arg	Leu	Asp
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His	Gln 2105	Arg	Arg	Arg	Asp	Arg 2110	Gly	His	Arg	Thr	Ser 2115	Glu	Arg	Ser
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Ser	Met 2135	Thr	Thr	Gln	Ser	Gly 2140	Asp	Leu	Pro	Ser	Lys 2145	Asp	Arg	Asp
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His	His 2165		His	His	His	His 2170		Pro	Pro	Ala	Pro 2175	Asp	Arg	Glu
Arg	Tyr 2180		Gln	Glu	Arg	Pro 2185	_	Thr	Gly	Arg	Ala 2190	Arg	Ala	Arg
Glu	Gln 2195		Trp	Ser	Arg	Ser 2200		Ser	Glu	Gly	Arg 2205	Glu	His	Ala
Thr	His 2210		Gln	Gly	Ser	Ser 2215		Val	Ser	Gly	Ser 2220	Pro	Ala	Pro
Ser	Thr 2225		Gly	Thr	Ser	Thr 2230		Arg	Arg	Gly	Arg 2235	Arg	Gln	Leu
Pro	Gln 2240		Pro	Cys	Thr	Pro 2245	_	Pro	Leu	Val	Ser 2250	Tyr	Ser	Pro
Ala	Pro 2255		Arg	Pro	Ala	Ala 2260		Arg	Met	Ala	Gly 2265	Pro	Pro	Ala
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Pro	Ala 2285		Ala	Pro	Glu	Gly 2290		Arg	Pro	Arg	Gly 2295	Ala	Asp	Tyr
Thr	Glu 2300		Asp	Ser	Pro	Arg 2305		Pro	Pro	Gly	Gly 2310	Ala	His	Glu
Pro	Ala 2315		Arg	Ser	Pro	Arg 2320		Pro	Arg	Ala	Ala 2325	Gly	Cys	Ala
Ser	Pro 2330		His	Gly	Arg	Arg 2335		Pro	Asn	Gly	Tyr 2340	_	Ala	Gly
His	Gly 2345		Pro	Arg	Pro	Arg 2350		Ala	Arg	Arg	Gly 2355	Ala	His	Asp
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Cys     Phe     Glu     Ala     Gly     Ile     Lys     Ile     Ala     Leu     Ala       Lys     Gly     Ser     Tyr     Leu     Arg     Asn     Gly     Trp     Asn     Val     Met     Asp     Phe       Val     Leu     Thr     Gly     Ile     Leu     Ala     Thr     Arg     Fr     Ile     Arg     Pro     Leu     Leu     Phe     Asp       Ile     Pro     Ser     Leu     Gl     Val     Leu     Leu     Fr     Leu     Val       Pro     Leu     Ser     Leu     Gl     Val     Val     Leu     Lys     Ser     Ile     Lys     Ala       Pro     Leu     Ser     Leu     Gl     Leu     Leu<	Val Val 175 Leu Arg Ser Gly Met Ile Ile Phe 240 Thr Cys 255 Pro Cys Cys Gln
The   The	Leu Arg Ser Gly Met Ile Ile Phe 240 Thr Cys 255 Pro Cys Cys Gln
Thr       Leu       Arg 195       Val 200       Leu 200       Pro 210       Leu Lys 205	Ser Gly  Met Ile  Ile Phe 240  Thr Cys 255  Pro Cys  Cys Gln
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Phe Glu Glu Gly Thr Asp Asp Ile Gln Gly Glu Ser Pro Ala 260 265 270	255 Pro Cys Cys Gln
260 265 270	Cys Gln
Gly Thr Glu Glu Pro Ala Arg Thr Cys Pro Asn Gly Thr Lys 275 280 285	Asn Ile
Pro Tyr Trp Glu Gly Pro Asn Asn Gly Ile Thr Gln Phe Asp 290 295 300	
Leu Phe Ala Val Leu Thr Val Phe Gln Cys Ile Thr Met Glu 305 310 310	Gly Trp 320
Thr Asp Leu Leu Tyr Asn Ser Asn Asp Ala Ser Gly Asn Thr 325 330	Trp Asn 335
Trp Leu Tyr Phe Ile Pro Leu Ile Ile Ile Gly Ser Phe Phe 340 345 350	Met Leu
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Arg Val Glu Asn Arg Arg Ala Phe Leu Lys Leu Arg Arg Gln 370 375 380	Gln Gln
Ile Glu Arg Glu Leu Asn Gly Tyr Met Glu Trp Ile Ser Lys 385 390 395	Ala Glu 400
Glu Val Ile Leu Ala Glu Asp Glu Thr Asp Gly Glu Gln Arg $$405$$	His Pro 415
Phe Asp Gly Ala Leu Arg Arg Thr Thr Ile Lys Lys Ser Lys 420 425 430	Thr Asp
Leu Leu Asn Pro Glu Glu Ala Glu Asp Gln Leu Ala Asp Ile 435 440 445	Ala Ser
Val Gly Ser Pro Phe Ala Arg Ala Ser Ile Lys Ser Ala Lys 450 455 460	Leu Glu
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Arg Arg Met Val Lys Thr Gln Ala Phe Tyr Trp Thr Val Leu 485 490	Ser Leu 495
Val Ala Leu Asn Thr Leu Cys Val Ala Ile Val His Tyr Asn 500 505 510	Gln Pro
Glu Trp Leu Ser Asp Phe Leu Tyr Tyr Ala Glu Phe Ile Phe 515 520 525	Leu Gly
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Pro Tyr Phe His Ser Ser Phe Asn Cys Phe Asp Cys Gly Val 545 550 555	Ile Ile 560

Clv	Cor	T10	Dho	Clu	Wal.	T10	Trn	712	7727	T10	Lva	Pro	Clvr	Thr	Cor
GIY	Set	116	riie	565	vai	116	шр	AIA	570	116	пуъ	FIO	GIY	575	ser
Phe	Gly	Ile	Ser 580	Val	Leu	Arg	Ala	Leu 585	Arg	Leu	Leu	Arg	Ile 590	Phe	Lys
Val	Thr	Lys 595	Tyr	Trp	Ala	Ser	Leu 600	Arg	Asn	Leu	Val	Val 605	Ser	Leu	Leu
Asn	Ser 610	Met	Lys	Ser	Ile	Ile 615	Ser	Leu	Leu	Phe	Leu 620	Leu	Phe	Leu	Phe
Ile 625	Val	Val	Phe	Ala	Leu 630	Leu	Gly	Met	Gln	Leu 635	Phe	Gly	Gly	Gln	Phe 640
Asn	Phe	Asp	Glu	Gly 645	Thr	Pro	Pro	Thr	Asn 650	Phe	Asp	Thr	Phe	Pro 655	Ala
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Ala	Asn	Gln	Lys 740	Leu	Ala	Leu	Gln	Lys 745	Ala	ГЛа	Glu	Val	Ala 750	Glu	Val
Ser	Pro	Leu 755	Ser	Ala	Ala	Asn	Met 760	Ser	Ile	Ala	Val	Lys 765	Glu	Gln	Gln
Lys	Asn 770	Gln	Lys	Pro	Ala	Lys 775	Ser	Val	Trp	Glu	Gln 780	Arg	Thr	Ser	Glu
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Met	Asp	Pro	Asp	Glu 805	Arg	Trp	Lys	Ala	Ala 810	Tyr	Thr	Arg	His	Leu 815	Arg
Pro	Asp	Met	Lys 820	Thr	His	Leu	Asp	Arg 825	Pro	Leu	Val	Val	Asp 830	Pro	Gln
Glu	Asn	Arg 835	Asn	Asn	Asn	Thr	Asn 840	Lys	Ser	Arg	Ala	Ala 845	Glu	Pro	Thr
Val	Asp 850	Gln	Arg	Leu	Gly	Gln 855	Gln	Arg	Ala	Glu	Asp	Phe	Leu	Arg	Lys
Gln 865	Ala	Arg	Tyr	His	Asp 870	Arg	Ala	Arg	Asp	Pro 875	Ser	Gly	Ser	Ala	Gly 880
Leu	Asp	Ala	Arg	Arg 885	Pro	Trp	Ala	Gly	Ser 890	Gln	Glu	Ala	Glu	Leu 895	Ser
Arg	Glu	Gly	Pro 900	Tyr	Gly	Arg	Glu	Ser 905	Asp	His	His	Ala	Arg 910	Glu	Gly
Ser	Leu	Glu 915	Gln	Pro	Gly	Phe	Trp 920	Glu	Gly	Glu	Ala	Glu 925	Arg	Gly	Lys
Ala	Gly 930	Asp	Pro	His	Arg	Arg 935	His	Val	His	Arg	Gln 940	Gly	Gly	Ser	Arg
Glu 945	Ser	Arg	Ser	Gly	Ser 950	Pro	Arg	Thr	Gly	Ala 955	Asp	Gly	Glu	His	Arg 960
Arg	His	Arg	Ala	His	Arg	Arg	Pro	Gly	Glu	Glu	Gly	Pro	Glu	Asp	Lys

_				965				9'	70				97!	5
Ala	Glu	Arg	Arg 980		Arg :	His A				er A	rg Pr	o Al. 99	a Arç	
Gly		Gly 995	Glu	Gly	Glu		ro <i>i</i> 000	Aap (	Gly (	Gly (		rg . 005	Arg 1	Arg Arg
His	Arg 1010		Gly	Ala	Pro	Ala 1015		Tyr	Glu	Gly	Asp 1020	Ala	Arg	Arg
Glu	Asp 1025		Glu	Arg	g Arg	His 1030	_	Arg	Arg	ГÀа	Glu 1035	Asn	Gln	Gly
Ser	Gly 1040		Pro	Val	. Ser	Gly 1045	Pro	Asn	Leu	Ser	Thr 1050	Thr	Arg	Pro
Ile	Gln 1055		. Asp	Leu	ı Gly	Arg 1060	Gln	Asp	Pro	Pro	Leu 1065	Ala	Glu	Asp
Ile	Asp 1070		. Met	Lys	s Asn	Asn 1075		Leu	Ala	Thr	Ala 1080	Glu	Ser	Ala
Ala	Pro 1085		Gly	Ser	Leu	Gly 1090	His	Ala	Gly	Leu	Pro 1095	Gln	Ser	Pro
Ala	1100		Gly	Asr	ser	Thr 1105		Pro	Gly	Pro	Met 1110	Leu	Ala	Ile
Pro	Ala 1115		Ala	Thr	Asn	Pro 1120	Gln	Asn	Ala	Ala	Ser 1125	Arg	Arg	Thr
Pro	Asn 1130		Pro	Gly	/ Asn	Pro 1135		Asn	Pro	Gly	Pro 1140	Pro	ГÀа	Thr
Pro	Glu 1145		Ser	Leu	ı Ile	Val 1150	Thr	Asn	Pro	Ser	Gly 1155	Thr	Gln	Thr
Asn	Ser 1160		Lys	Thr	Ala	Arg 1165	ГÀа	Pro	Asp	His	Thr 1170	Thr	Val	Asp
Ile	Pro 1175		Ala	. Сув	Pro	Pro 1180	Pro	Leu	Asn	His	Thr 1185	Val	Val	Gln
Val	Asn 1190		Asn	Ala	. Asn	Pro 1195	Asp	Pro	Leu	Pro	Lys 1200	Lys	Glu	Glu
Glu	Lys 1205		Glu	. Glu	ı Glu	Glu 1210	Asp	Asp	Arg	Gly	Glu 1215	Asp	Gly	Pro
ГÀа	Pro 1220		Pro	Pro	Tyr	Ser 1225	Ser	Met	Phe	Ile	Leu 1230	Ser	Thr	Thr
Asn	Pro 1235		Arg	Arg	, Leu	Cys 1240		Tyr	Ile	Leu	Asn 1245	Leu	Arg	Tyr
Phe	Glu 1250		Cys	Ile	e Leu	Met 1255		Ile	Ala	Met	Ser 1260		Ile	Ala
Leu	Ala 1265		Glu	. Asp	Pro	Val 1270		Pro	Asn	Ala	Pro 1275		Asn	Asn
Val	Leu 1280	_	Tyr	Ph∈	a Asp	Tyr 1285		Phe	Thr	Gly	Val 1290		Thr	Phe
Glu	Met 1295		Ile	Lys	Met	Ile 1300		Leu	Gly	Leu	Val 1305	Leu	His	Gln
Gly	Ala 1310		Phe	Arg	l Yab	Leu 1315		Asn	Ile	Leu	Asp 1320	Phe	Ile	Val
Val	Ser 1325	_	Ala	Leu	ı Val	Ala 1330		Ala	Phe	Thr	Gly 1335	Asn	Ser	Lys
Gly	Lys 1340		Ile	Asr	1 Thr	Ile 1345	-	Ser	Leu	Arg	Val 1350		Arg	Val

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	1355					1360					1365			
Val	Phe 1370	Asp	CÀa	Val	Val	Asn 1375		Leu	Lys	Asn	Val 1380		Asn	Ile
Leu	Ile 1385	Val	Tyr	Met	Leu	Phe 1390		Phe	Ile	Phe	Ala 1395		Val	Ala
Val	Gln 1400	Leu	Phe	ГЛа	Gly	Lys 1405		Phe	His	CAa	Thr 1410	Asp	Glu	Ser
Lys	Glu 1415	Phe	Glu	Lys	Asp	Cys 1420		Gly	Lys	Tyr	Leu 1425		Tyr	Glu
Lys	Asn 1430	Glu	Val	Lys	Ala	Arg 1435		Arg	Glu	Trp	Lys 1440		Tyr	Glu
Phe	His 1445	Tyr	Asp	Asn	Val	Leu 1450		Ala	Leu	Leu	Thr 1455		Phe	Thr
Val	Ser 1460	Thr	Gly	Glu	Gly	Trp 1465		Gln	Val	Leu	Lys 1470		Ser	Val
Asp	Ala 1475	Thr	Phe	Glu	Asn	Gln 1480		Pro	Ser	Pro	Gly 1485	Tyr	Arg	Met
Glu	Met 1490	Ser	Ile	Phe	Tyr	Val 1495		Tyr	Phe	Val	Val 1500		Pro	Phe
Phe	Phe 1505	Val	Asn	Ile	Phe	Val 1510		Leu	Ile	Ile	Ile 1515		Phe	Gln
Glu	Gln 1520	Gly	Asp	Lys	Met	Met 1525		Glu	Tyr	Ser	Leu 1530	Glu	ГÀв	Asn
Glu	Arg 1535	Ala	CAa	Ile	Asp	Phe 1540		Ile	Ser	Ala	Lys 1545	Pro	Leu	Thr
Arg	His 1550	Met	Pro	Gln	Asn	Lys 1555		Ser	Phe	Gln	Tyr 1560	Arg	Met	Trp
Gln	Phe 1565	Val	Val	Ser	Pro	Pro 1570	Phe	Glu	Tyr	Thr	Ile 1575	Met	Ala	Met
Ile	Ala 1580	Leu	Asn	Thr	Ile	Val 1585	Leu	Met	Met	Lys	Phe 1590	Tyr	Gly	Ala
Ser	Val 1595	Ala	Tyr	Glu	Asn	Ala 1600		Arg	Val	Phe	Asn 1605	Ile	Val	Phe
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Val	Thr 1640	Val	Leu	Gly	Ser	Ile 1645		Asp	Ile	Leu	Val 1650		Glu	Phe
Gly	Asn 1655	Pro	Asn	Asn	Phe	Ile 1660		Leu	Ser	Phe	Leu 1665	Arg	Leu	Phe
Arg	Ala 1670	Ala	Arg	Leu	Ile	Lys 1675		Leu	Arg	Gln	Gly 1680	-	Thr	Ile
Arg	Ile 1685	Leu	Leu	Trp	Thr	Phe 1690		Gln	Ser	Phe	Lys 1695	Ala	Leu	Pro
Tyr	Val 1700	CAa	Leu	Leu	Ile	Ala 1705	Met	Leu	Phe	Phe	Ile 1710		Ala	Ile
Ile	Gly 1715	Met	Gln	Val	Phe	Gly 1720		Ile	Gly	Ile	Asp 1725	Val	Glu	Asp
Glu	Asp 1730	Ser	Asp	Glu	Asp	Glu 1735		Gln	Ile	Thr	Glu 1740	His	Asn	Asn

Phe	Arg 1745	Thr	Phe	Phe	Gln	Ala 1750	Leu	Met	Leu	Leu	Phe 1755	Arg	Ser	Ala
Thr	Gly 1760	Glu	Ala	Trp	His	Asn 1765	Ile	Met	Leu	Ser	Cys 1770	Leu	Ser	Gly
Lys	Pro 1775	Cys	Asp	Lys	Asn	Ser 1780	Gly	Ile	Leu	Thr	Arg 1785	Glu	CAa	Gly
Asn	Glu 1790	Phe	Ala	Tyr	Phe	Tyr 1795	Phe	Val	Ser	Phe	Ile 1800	Phe	Leu	Cys
Ser	Phe 1805	Leu	Met	Leu	Asn	Leu 1810	Phe	Val	Ala	Val	Ile 1815	Met	Asp	Asn
Phe	Glu 1820	Tyr	Leu	Thr	Arg	Asp 1825	Ser	Ser	Ile	Leu	Gly 1830	Pro	His	His
Leu	Asp 1835	Glu	Tyr	Val	Arg	Val 1840	Trp	Ala	Glu	Tyr	Asp 1845	Pro	Ala	Ala
Trp	Gly 1850	Arg	Met	Pro	Tyr	Leu 1855	Asp	Met	Tyr	Gln	Met 1860	Leu	Arg	His
Met	Ser 1865	Pro	Pro	Leu	Gly	Leu 1870	Gly	Lys	Lys	СЛа	Pro 1875	Ala	Arg	Val
Ala	Tyr 1880	Lys	Arg	Leu	Leu	Arg 1885	Met	Asp	Leu	Pro	Val 1890	Ala	Asp	Asp
Asn	Thr 1895	Val	His	Phe	Asn	Ser 1900	Thr	Leu	Met	Ala	Leu 1905	Ile	Arg	Thr
Ala	Leu 1910	Asp	Ile	Lys	Ile	Ala 1915	Lys	Gly	Gly	Ala	Asp 1920	Lys	Gln	Gln
Met	Asp 1925	Ala	Glu	Leu	Arg	Lys 1930	Glu	Met	Met	Ala	Ile 1935	Trp	Pro	Asn
Leu	Ser 1940	Gln	Lys	Thr	Leu	Asp 1945	Leu	Leu	Val	Thr	Pro 1950	His	ГÀа	Ser
Thr	Asp 1955	Leu	Thr	Val	Gly	Lys 1960	Ile	Tyr	Ala	Ala	Met 1965	Met	Ile	Met
Glu	Tyr 1970	Tyr	Arg	Gln	Ser	Lys 1975	Ala	Lys	Lys	Leu	Gln 1980	Ala	Met	Arg
Glu	Glu 1985	Gln	Asp	Arg	Thr	Pro 1990	Leu	Met	Phe	Gln	Arg 1995	Met	Glu	Pro
Pro	Ser 2000	Pro	Thr	Gln	Glu	Gly 2005	Gly	Pro	Gly	Gln	Asn 2010	Ala	Leu	Pro
Ser	Thr 2015	Gln	Leu	Asp	Pro	Gly 2020	Gly	Ala	Leu	Met	Ala 2025	His	Glu	Ser
Gly	Leu 2030	Lys	Glu	Ser	Pro	Ser 2035	Trp	Val	Thr	Gln	Arg 2040	Ala	Gln	Glu
Met	Phe 2045	Gln	Lys	Thr	Gly	Thr 2050	Trp	Ser	Pro	Glu	Gln 2055	Gly	Pro	Pro
Thr	Asp 2060	Met	Pro	Asn	Ser	Gln 2065	Pro	Asn	Ser	Gln	Ser 2070	Val	Glu	Met
Arg	Glu 2075	Met	Gly	Arg	Asp	Gly 2080	Tyr	Ser	Asp	Ser	Glu 2085	His	Tyr	Leu
Pro	Met 2090	Glu	Gly	Gln	Gly	Arg 2095	Ala	Ala	Ser	Met	Pro 2100	Arg	Leu	Pro
Ala	Glu 2105	Asn	Gln	Arg	Arg	Arg 2110	Gly	Arg	Pro	Arg	Gly 2115	Asn	Asn	Leu
Ser	Thr	Ile	Ser	Asp	Thr	Ser	Pro	Met	rys	Arg	Ser	Ala	Ser	Val

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	2120					2125					2130			
Leu	Gly 2135		Lys	Ala	Arg	Arg 2140	Leu	Asp	Asp	Tyr	Ser 2145		Glu	Arg
Val	Pro 2150		Glu	Glu	Asn	Gln 2155	Arg	His	His	Gln	Arg 2160	Arg	Arg	Asp
Arg	Ser 2165	His	Arg	Ala	Ser	Glu 2170	Arg	Ser	Leu	Gly	Arg 2175	_	Thr	Asp
Val	Asp 2180		Gly	Leu	Gly	Thr 2185		Leu	Ser	Met	Thr 2190	Thr	Gln	Ser
Gly	Asp 2195		Pro	Ser	ГЛа	Glu 2200	_	Asp	Gln	Glu	Arg 2205	-	Arg	Pro
Lys	Asp 2210		ГЛа	His	Arg	Gln 2215		His	His	His	His 2220	His	His	His
His	His 2225		Pro	Pro	Pro	Asp 2230		Asp	Arg	Tyr	Ala 2235		Glu	Arg
Pro	Asp 2240		Gly	Arg	Ala	Arg 2245	Ala	Arg	Asp	Gln	Arg 2250	_	Ser	Arg
Ser	Pro 2255	Ser	Glu	Gly	Arg	Glu 2260	His	Met	Ala	His	Arg 2265	Gln	Gly	Ser
Ser	Ser 2270	Val	Ser	Gly	Ser	Pro 2275	Ala	Pro	Ser	Thr	Ser 2280	Gly	Thr	Ser
Thr	Pro 2285	Arg	Arg	Gly	Arg	Arg 2290	Gln	Leu	Pro	Gln	Thr 2295	Pro	Ser	Thr
Pro	Arg 2300		His	Val	Ser	Tyr 2305	Ser	Pro	Val	Ile	Arg 2310		Ala	Gly
Gly	Ser 2315	Gly	Pro	Pro	Gln	Gln 2320	Gln	Gln	Gln	Gln	Gln 2325	Gln	Gln	Gln
Gln	Gln 2330		Ala	Val	Ala	Arg 2335	Pro	Gly	Arg	Ala	Ala 2340	Thr	Ser	Gly
Pro	Arg 2345	Arg	Tyr	Pro	Gly	Pro 2350	Thr	Ala	Glu	Pro	Leu 2355	Ala	Gly	Asp
Arg	Pro 2360	Pro	Thr	Gly	Gly	His 2365	Ser	Ser	Gly	Arg	Ser 2370	Pro	Arg	Met
Glu	Arg 2375	Arg	Val	Pro	Gly	Pro 2380	Ala	Arg	Ser	Glu	Ser 2385	Pro	Arg	Ala
CAa						Arg 2395					Gly 2400		His	Val
Ser	Glu 2405	Gly	Pro	Pro	Gly	Pro 2410	Arg	His	His	Gly	Tyr 2415	Tyr	Arg	Gly
Ser	Asp 2420	Tyr	Asp	Glu	Ala	Asp 2425	Gly	Pro	Gly	Ser	Gly 2430	Gly	Gly	Glu
Glu	Ala 2435	Met	Ala	Gly	Ala	Tyr 2440	Asp	Ala	Pro	Pro	Pro 2445	Val	Arg	His
Ala	Ser 2450	Ser	Gly	Ala	Thr	Gly 2455	Arg	Ser	Pro	Arg	Thr 2460	Pro	Arg	Ala
Ser	Gly 2465	Pro	Ala	Сув	Ala	Ser 2470	Pro	Ser	Arg	His	Gly 2475	Arg	Arg	Leu
Pro	Asn 2480	Gly	Tyr	Tyr	Pro	Ala 2485	His	Gly	Leu	Ala	Arg 2490	Pro	Arg	Gly
Pro	Gly 2495	Ser	Arg	Lys	Gly	Leu 2500	His	Glu	Pro	Tyr	Ser 2505	Glu	Ser	Asp

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Met	Leu	Asn 355	Leu	Val	Leu	Gly	Val 360	Leu	Ser	Gly	Glu	Phe 365	Ala	Lys	Glu
Arg	Glu 370	Arg	Val	Glu	Asn	Arg 375	Arg	Ala	Phe	Leu	180	Leu	Arg	Arg	Gln
Gln 385	Gln	Ile	Glu	Arg	Glu 390	Leu	Asn	Gly	Tyr	Met 395	Glu	Trp	Ile	Ser	Lys 400
Ala	Glu	Glu	Val	Ile 405	Leu	Ala	Glu	Asp	Glu 410	Thr	Asp	Val	Glu	Gln 415	Arg
His	Pro	Phe	Asp 420	Gly	Ala	Leu	Arg	Arg 425	Ala	Thr	Leu	Lys	Lys 430	Ser	Lys
Thr	Asp	Leu 435	Leu	Asn	Pro	Glu	Glu 440	Ala	Glu	Asp	Gln	Leu 445	Ala	Asp	Ile
Ala	Ser 450	Val	Gly	Ser	Pro	Phe 455	Ala	Arg	Ala	Ser	Ile 460	Lys	Ser	Ala	Lys
Leu 465	Glu	Asn	Ser	Thr	Phe 470	Phe	His	Lys	Lys	Glu 475	Arg	Arg	Met	Arg	Phe 480
Tyr	Ile	Arg	Arg	Met 485	Val	ГАз	Thr	Gln	Ala 490	Phe	Tyr	Trp	Thr	Val 495	Leu
Ser	Leu	Val	Ala 500	Leu	Asn	Thr	Leu	Trp 505	Leu	Ala	Ile	Val	His 510	Tyr	Asn
Gln	Pro	Glu 515	Trp	Leu	Ser	Asp	Phe 520	Leu	Tyr	Tyr	Ala	Glu 525	Phe	Ile	Phe
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Thr 545	Arg	Pro	Tyr	Phe	His 550	Ser	Ser	Phe	Asn	Сув 555	Phe	Asp	Cys	Gly	Val 560
Ile	Ile	Gly	Ser	Ile 565	Phe	Glu	Val	Ile	Trp 570	Ala	Val	Ile	Lys	Pro 575	Gly
Thr	Ser	Phe	Gly 580	Ile	Ser	Val	Leu	Arg 585	Ala	Leu	Arg	Leu	Leu 590	Arg	Ile
Phe	Lys	Val 595	Thr	Lys	Tyr	Trp	Ala 600	Ser	Leu	Arg	Asn	Leu 605	Val	Val	Ser
Leu	Leu 610	Asn	Ser	Met	Lys	Ser 615	Ile	Ile	Ser	Leu	Leu 620	Phe	Leu	Leu	Phe
Leu 625	Phe	Ile	Val	Val	Phe 630	Ala	Leu	Leu	Gly	Met 635	Gln	Leu	Phe	Gly	Gly 640
Gln	Phe	Asn	Phe	Asp 645	Glu	Gly	Thr	Pro	Pro 650	Thr	Asn	Phe	Asp	Thr 655	Phe
Pro	Ala	Ala	Ile 660	Met	Thr	Val	Phe	Gln 665	Ile	Leu	Thr	Gly	Glu 670	Asp	Trp
Asn	Glu	Val 675	Met	Tyr	Asp	Glu	Ile 680	ГÀа	Ser	Gln	Gly	Gly 685	Val	Gln	Gly
Gly	Met 690	Val	Phe	Ser	Ile	Tyr 695	Phe	Ile	Val	Leu	Thr 700	Leu	Phe	Gly	Asn
Tyr 705	Thr	Leu	Leu	Asn	Val 710	Phe	Leu	Ala	Ile	Ala 715	Val	Asp	Asn	Leu	Ala 720
Asn	Ala	Gln	Glu	Leu 725	Thr	Lys	Asp	Glu	Gln 730	Glu	Glu	Glu	Glu	Ala 735	Ala
Asn	Gln	Lys	Leu 740	Ala	Leu	Gln	ГÀв	Ala 745	Lys	Glu	Val	Ala	Glu 750	Val	Ser
Pro	Leu	Ser 755	Ala	Ala	Asn	Met	Ser 760	Ile	Ala	Val	Lys	Glu 765	Gln	Gln	Lys

Asn	Gln 770	Lys	Pro	Ala	Lys	Ser 775	Val	Trp	Glu	Gln	Arg 780	Thr	Ser	Glu	Met
Arg 785	Lys	Gln	Asn		Leu 790	Ala	Ser	Arg	Glu	Ala 795	Leu	Tyr	Gly	Asp	Ala 800
Ala	Glu	Arg	Trp	Pro 805	Thr	Thr	Tyr	Ala	Arg 810	Pro	Leu	Arg	Pro	Asp 815	
Lys	Thr	His	Leu 820	Asp	Arg	Pro	Leu	Val 825	Val	Asp	Pro	Gln	Glu 830		Arg
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Ala	Arg 850	Pro	Arg	Glu	Ser	Ala 855	Arg	Asp	Pro	Asp	Ala 860	Arg	Arg	Ala	Trp
Pro 865	Ser	Ser	Pro		Arg 870	Ala	Pro	Gly	Arg	Glu 875	Gly	Pro	Tyr	Gly	Arg 880
Glu	Ser	Glu	Pro	Gln 885	Gln	Arg	Glu	His	Ala 890	Pro	Pro	Arg	Glu	His 895	
Pro	Trp	Asp	Ala 900	Asp	Pro	Glu	Arg	Ala 905	Lys	Ala	Gly	Asp	Ala 910		Arg
Arg	His	Thr 915	His	Arg	Pro	Val	Ala 920	Glu	Gly	Glu	Pro	Arg 925	Arg	His	Arg
Ala	Arg 930	Arg	Arg	Pro	Gly	Asp 935	Glu	Pro	Asp	Asp	Arg 940	Pro	Glu	Arg	Arg
Pro 945	Arg	Pro	Arg	_	Ala 950	Thr	Arg	Pro	Ala	Arg 955	Ala	Ala	Asp	Gly	Glu 960
Gly	Asp	Asp	Gly	Glu 965	Arg	Lys	Arg	Arg	His 970	Arg	His	Gly	Pro	Pro 975	Ala
His	Asp	Asp	Arg 980	Glu	Arg	Arg	His	Arg 985	Arg	Arg	Lys	Glu	Ser 990		Gly
Ser	Gly	Val 995	Pro	Met	Ser	Gly	Pro 1000		ı Let	ı Se:	r Thi	r Th 10		rg P	ro Ile
Gln	Gln 1010	_	Leu	ı Gly	Arg	Gli 101		вр Це	eu Pi	ro Le		la 020	Glu	Asp	Leu
Asp	Asn 1025		Lys	Asn	Asr	103		eu Al	la Ti	nr G		lu 035	Pro	Ala	Ser
Pro	His 1040	_	Ser	Leu	. Gly	7 His		er G	ly Le	eu P		ro 050	Ser	Pro	Ala
Lys	Ile 1055	_	Asn	ser	Thr	106		co GI	ly Pi	ro A		eu . 065	Ala	Thr	Asn
Pro	Gln 1070		n Ala	ı Ala	. Ser	10°		g Tl	nr Pi	ro A		≅n 080	Pro	Gly	Asn
Pro	Ser 1085		Pro	Gly	Pro	Pro 109		/s Tl	nr Pi	ro G		∌n 095	Ser	Leu	Ile
Val	Thr 1100		Pro	Ser	Ser	Th:		ln Pi	ro As	sn Se		la 110	Lys	Thr	Ala
Arg	Lys 1115		Glu	. His	Met	112		al G	lu I	le P:		ro . 125	Ala	Cys	Pro
Pro	Leu 1130		His	Thr	Val	113		ln Va	al As	en Ly		en . 140	Ala	Asn	Pro
Asp	Pro 1145		Pro	. Lys	Lys	3 Glu 119		lu G	lu Ly	As ri		lu 155	Glu	Glu	Glu
Δla	Asp	Pro	Gly	Glu	Asp	Gly	y Pi	o Ly	ys Pi	ro Me	et Pi	ro	Pro	Tyr	Ser

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His	Tyr 1190	Ile	Leu	Asn	Leu	Arg 1195	Tyr	Phe	Glu	Met	Cys 1200	Ile	Leu	Met
Val	Ile 1205	Ala	Met	Ser	Ser	Ile 1210	Ala	Leu	Ala	Ala	Glu 1215	Asp	Pro	Val
Gln	Pro 1220	Asn	Ala	Pro	Arg	Asn 1225	Asn	Val	Leu	Arg	Tyr 1230	Phe	Asp	Tyr
Val	Phe 1235	Thr	Gly	Val	Phe	Thr 1240	Phe	Glu	Met	Val	Ile 1245	Lys	Met	Ile
Asp	Leu 1250	Gly	Leu	Val	Leu	His 1255	Gln	Gly	Ala	Tyr	Phe 1260	Arg	Asp	Leu
Trp	Asn 1265	Ile	Leu	Asp	Phe	Ile 1270	Val	Val	Ser	Gly	Ala 1275	Leu	Val	Ala
Phe	Ala 1280	Phe	Thr	Gly	Asn	Ser 1285	ГЛа	Gly	Lys	Asp	Ile 1290	Asn	Thr	Ile
ГÀа	Ser 1295	Leu	Arg	Val	Leu	Arg 1300	Val	Leu	Arg	Pro	Leu 1305	Lys	Thr	Ile
ГÀа	Arg 1310	Leu	Pro	Lys	Leu	Lys 1315	Ala	Val	Phe	Asp	Сув 1320	Val	Val	Asn
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480

540

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- 1. A method of obtaining data for assessing potential for development of Dravet syndrome, the method comprising: with use of a sample taken from a subject,
  - detecting whether or not a mutation exists on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na $_{\nu}1.1;$  and
  - detecting whether or not a mutation is on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub> $\nu$ </sub>2.1.
  - 2. The method according to claim 1, wherein
  - the mutation on the  $\alpha$ -subunit type 1 of the voltage-gated sodium ion channel Na $_{\nu}1.1$  is at least one of mutations recited in Table 1, and
  - the mutation on the  $\alpha$ -subunit type 1 of the voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$  is at least one of mutations recited in Table 2.
  - The method according to claim 1, further comprising: detecting a change in activity of the voltage-gated sodium ion channel Na<sub>ν</sub>1.1; and
  - detecting a change in activity of the voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$ .
- **4**. A kit for assessing a potential for development of Dravet syndrome, the kit comprising:
  - a polynucleotide being used for determining a mutation on  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub> $\nu$ </sub>1.1; and
  - a polynucleotide being used for determining a mutation on  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub>1</sub>2.1.
- **5**. A model animal of Dravet syndrome, having a mutation on both  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub> $\nu$ </sub>1.1 and  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub> $\nu$ </sub>2.1.

- **6**. A method of producing a model animal of Dravet syndrome as set forth in claim **5**, the method comprising:
  - introducing a mutation on a  $\alpha$ -subunit type 1 of the voltagegated sodium ion channel Na $_{\nu}$ 1.1; and
  - introducing a mutation on a  $\alpha$ -subunit type 1 of the voltagegated calcium ion channel Ca<sub>r</sub>2.1.
- 7. A cell, having a mutation on both  $\alpha$ -subunit type 1 of voltage-gated sodium ion channel Na<sub>v</sub>1.1 and  $\alpha$ -subunit type 1 of voltage-gated calcium ion channel Ca<sub>v</sub>2.1.
- **8**. A method of producing a cell as set forth in claim **7**, the method comprising:
  - introducing a mutation on a  $\alpha$ -subunit type 1 of the voltagegated sodium ion channel Na $_V$ 1.1; and
  - introducing a mutation on a  $\alpha$ -subunit type 1 of the voltagegated calcium ion channel  $Ca_{\nu}2.1$ .
- **9**. A screening method of a drug for treating Dravet syndrome, the method comprising:
  - administering a candidate agent to the model animal of Dravet syndrome as set forth in claim 5; and
  - assessing whether or not the administering of the candidate agent has made Dravet syndrome improve or cure in the model animal of Dravet syndrome.
- 10. A screening method of a drug for treating Dravet syndrome, the method comprising:
  - administering a candidate agent to the cell as set forth in claim 7; and
  - assessing whether or not the administering of the candidate agent has made activity of the voltage-gated sodium ion channel Na<sub>v</sub>1.1 and/or activity of the voltage-gated calcium ion channel Ca<sub>v</sub>2.1 change in the cell.
  - 11. The method according to claim 2, further comprising: detecting a change in activity of the voltage-gated sodium ion channel Na<sub>v</sub>1.1; and
  - detecting a change in activity of the voltage-gated calcium ion channel  $\text{Ca}_{\nu}2.1$ .

\* \* \* \* \*