Karyotypic chromosomal analysis revealed a normal female karyotype. Array comparative genomic hybridization (aCGH) analysis was performed at 5 months of age and revealed duplication of 2q24.2q24.3 as mentioned below. This prompted us to change antiepileptic drugs. Phenobarbital and levetiracetam were substituted for valproate, and her seizures were completely controlled by 50 mg/kg of valproate (serum level, 69.1 μg/ml). Seizures provoked by fever had never been recognized, although she had several febrile illnesses. Her developmental milestones were severely delayed. Although social smile and eye following were recognized at 3 and at 4 months of age, respectively, head control or eye-hand coordination was not achieved at the last follow-up at 10 months of age. Marked generalized hypotonia was observed with normal deep tendon reflexes.

Methods

To investigate the chromosomal aberration, we performed aCGH analysis using Human Genome CGH Microarray 44A (Agilent Technologies, Palo Alto, CA, U.S.A.) with genomic DNA extracted from the patient's peripheral blood according to the method described elsewhere (Takatsuki et al., 2010). Metaphase or prometaphase chromosomes were prepared from phytohemagglutinin-stimulated peripheral blood lymphocytes for two-color fluorescence in situ hybridization (FISH) analysis using bacterial artificial chromosome (BAC) clones as probes as described previously (Takatsuki et al., 2010). BAC clones were selected from an in silico library (UCSC Human Genome Browser, March 2006 http://genome.ucsc.edu/).

Results

aCGH analysis identified an aberration in chr2(161,704,227-167,042,361) with average log2 ratio of 0.55, which indicated a 5.3-Mb duplication of 2q24.2q24.3 (Fig. 1). Physical positions referred to NCBI36/hg18. Similar variations were not identified in the Database of Genomic Variants (http://projects.tcag.ca/variation/). Two-color FISH analysis confirmed the duplication in the patient (Fig. 2), and parental FISH analysis showed normal results indicating de novo occurrence of the duplication in the patient. According to the UCSC genome browser, at least 22 genes and one noncoding RNA are included in the duplicated region of this patient, in which there is a cluster of SCN genes including *SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, and *SCN9A* (Fig. 2).

Discussion

In the literature, there are only two reports on epileptic patients with microduplication of 2q. The first is a family with neonatal seizures and intellectual disability caused by a

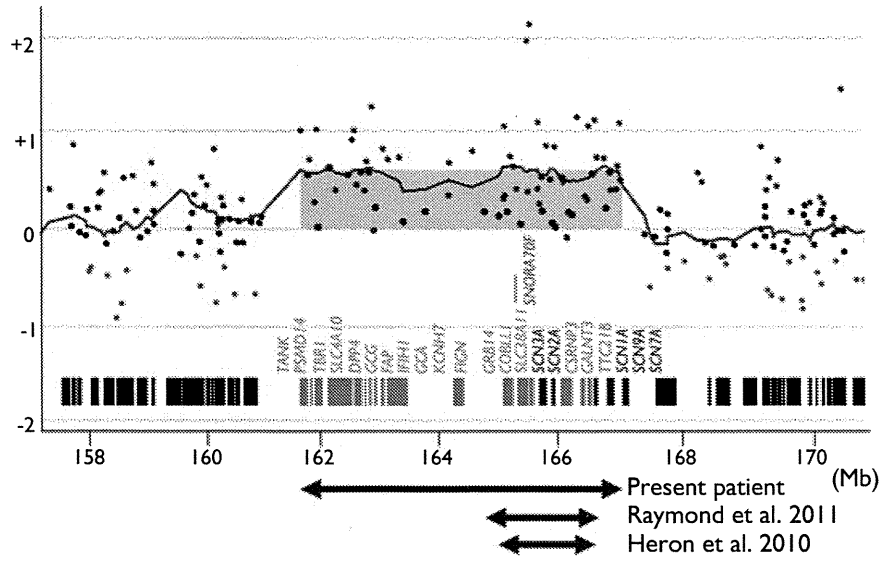

Figure 1.
The result of aCGH and the physical map around the duplicated region. aCGH revealed the duplication of 2q24.2q24.3, which is shown by gene view provided by Agilent Genomic Workbench (Agilent). Dots indicate the locations and log2 ratio of the probes in x axis and y axis, respectively. The identified duplication of our patient is shown by the red translucent rectangle, in which 22 genes and one noncoding RNA are included. Rectangles indicate the positions of RefSeq Genes. Gene symbols included in the duplicated region are shown in italic. Red and green indicate the voltage-gated sodium channel genes and non-coding RNA, respectively. The red bars with arrows on both edges indicate the duplicated regions of the previously reported patients and our patient.

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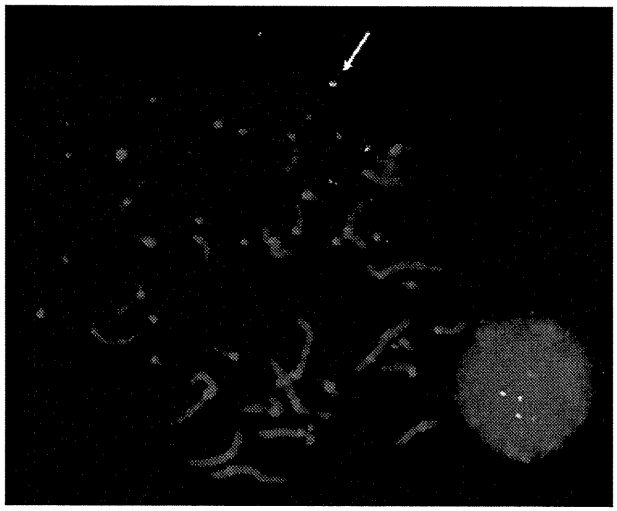

Figure 2.
FISH analysis to confirm the duplication of 2q24.2q24.3. Two BAC clones, RP11-214A4 (2q24.2:162,846,383-162,941,799) and RP11-297I3 (2p25.3:2,041,856-2,250,332), are labeled by spectrum green and red, respectively. RP11-297I3 labeled by red is used for the marker of chromosome 2. The targeted green signals of RP11-214A4 can be seen in tandem duplicated on one of the chromosome 2 of the metaphase (arrow), and 3 independent green signals are present on the same nucleus (lower right corner).

1.57 Mb microduplication of chromosome 2q24.3 containing *SCN2A*, *SCN3A*, and the 3′ end of *SCN1A* (Heron et al., 2010). This family comprised four individuals with neonatal onset seizures and learning difficulties. In three of them, seizures commenced on days 2–3 and settled by 5 months. In the remaining patient, seizures commenced on day 18 and ceased by 20 months. All of them had intellectual disability ranging from full-scale intelligence quotient (FSIQ) <40 to borderline intellect. The authors considered that the phenotype of the family is likely to be attributable to one or more of the duplicated (*SCN2A*, *SCN3A*) or partially duplicated (*SCN1A*) sodium channel subunit genes. The second is a girl with neonatal-infantile epilepsy and delayed development (Raymond et al., 2011). She had frequent seizures since 2–3 weeks of age and was unable to sit independently at 6 months of age. This patient had a 2.0 Mb microduplication at 2q24.3 including *SCN1A*, *SCN2A*, and *SCN3A*.

We identified another patient with severe seizures of neonatal onset and severe developmental delay. The size of the duplicated region in our patient was much larger than that in the previously reported patients, which may explain the more severe seizure prognosis and severe developmental delay. However, phenotype–genotype correlation is hard to establish because the patients reported by Raymond and by us are too young and the full spectrum of the phenotypic features have not been sufficiently understood. At least, what we can say is that SCNs in 2q24q25 are dose-sensitive in both loss and gain of genomic copy numbers and contribute to the severe seizure disorders.

Marini et al. (2009) reported microchromosomal copy number variations affecting *SCN1A* in Dravet syndrome, other epileptic encephalopathy, and generalized epilepsy with febrile seizures plus. They found a partial *SCN1A* duplication in two siblings with typical Dravet syndrome and a partial *SCN1A* amplification of five to six copies in another patient with Dravet syndrome. However, the phenotype of patients with chromosomal duplications including entire SCN gene clusters is different from that of the patients with Dravet syndrome, in terms of neonatal onset seizures, no seizures induced by fever, and focal seizures alone. This information would give us an important clue to help reveal the genetic mechanism of neonatal seizures.

At least 17 genes other than the SCN genes are present in the duplicated region of our patient. Some of them can contribute to seizures. *SLC4A10* encodes an electroneutral sodium bicarbonate exchanger. Gurnett et al. (2008) reported a patient with a disruption of *SLC4A10*, who had focal seizures with an onset of 7 years of age and moderate mental retardation. Krepischi et al. (2010) reported that aCGH revealed a common disruption of *SLC4A10* in two patients with epilepsy and mental retardation. One of them commenced refractory seizures since 2 months of age and had severe mental retardation. This phenotype is relatively similar to that of our patient. *KCNH7* encodes a pore-forming subunit of the voltage-gated potassium channel. Although some genes encoding voltage-gated potassium channel such as *KCNQ2* and *KCNQ3*, have been known to contribute to benign familial neonatal seizures (Schroeder et al., 1998), there have been no reports on contribution of *KCNH7* to seizures or epilepsies. There is a possibility that the duplication of these genes may affect the phenotype of our patient by the modification of neuronal excitability through the altered ion channel function. As to the other duplicated genes, there have been no reports on the relation to epilepsy, brain anomaly, or developmental disorder of the brain, although future studies may unveil some possible role that these genes will play.

The identification of microchromosomal copy number variations was useful to plan antiepileptic treatment of our patient. Our patient has neonatal-onset focal seizures. Phenobarbital and phenytoin has been generally considered to be preferable for the treatment of neonatal seizures, whereas valproate has been considered to be less appropriate (Wheless et al., 2007). We considered phenobarbital as a drug of choice in our patient. On the other hand, valproate is usually considered to be preferable for the treatment of Dravet syndrome (Dravet & Bureau, 2008). After the microchromosomal aberration including *SCN1A* was identified, we presumed that valproate will be more appropriate than phenobarbital and levetiracetam. Eventually, the alteration of antiepileptic drugs resulted in seizure freedom. This

indicates that aCGH may add useful information not only for the diagnosis of epilepsy but also for the determination of the treatment.

In conclusion, our findings show that the duplication of 2q24.2q24.3 including the whole SCN cluster will contribute to refractory neonatal epilepsy and severe mental retardation. This indicates that SCNs in this region are dose-sensitive in both loss and gain of genomic copy numbers.

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Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

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SCN1B is Not Related to Benign Partial Epilepsy in Infancy or Convulsions with Gastroenteritis

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Key words
- benign partial epilepsy in infancy
- convulsions with gastroenteritis
- SCN1B
- carbamazepine
- lidocaine

Abstract

We hypothesized that benign partial epilepsy in infancy (BPEI) and convulsions with gastroenteritis (CwG) may have a similar genetic background, because previous studies indicate that clinical features overlap between BPEI and CwG. As carbamazepine is effective for cessation of clustering seizures in children with BPEI and CwG, some genetic mutations regarding sodium channels may be related to the development of BPEI and/or CwG. We focused on *SCN1B* encoding the voltage-dependent sodium channel β subunit. We explored *SCN1B* mutation in 6 children with BPEI and 6 children with CwG. Genomic DNAs were extracted from peripheral blood samples accumulated from the patients and all 5 exons of *SCN1B* were amplified by standard PCR amplification. There were no *SCN1B* mutations or pathological single nucleotide polymorphisms in any of the patients, although the phenotypes of our patients were typical for BPEI or CwG. Our study demonstrated that *SCN1B* may not be related to the occurrence of BPEI or CwG.

Introduction

Benign partial epilepsy in infancy (BPEI) is an epileptic syndrome proposed by Watanabe et al. [23]. The clinical features of BPEI are clustering seizures, normal EEG and neuroimaging findings, excellent seizure and developmental outcome [14]. According to our previous studies, about 40% of the children with BPEI have a family history of BPEI [14]. The good response to carbamazepine (CBZ) is remarkable in children with BPEI [11].

Convulsions with gastroenteritis (CwG) is a situation-related seizure disorder, characterized by age at onset of 1–3 years, clustering seizures, normal interictal EEG and neuroimaging, and favorable outcome [19]. Our previous study showed that about 10% of children with BPEI also had CwG [14]. CBZ is also effective for cessation of clustering seizures in children with CwG [18]. These facts indicate that clinical features overlap between BPEI and CwG. Based on these observations, we hypothesized that BPEI and CwG may have a similar genetic background.

CBZ inhibits voltage-gated sodium channels in a voltage-dependent and frequency-dependent manner at clinically relevant concentrations. This attenuation of Na^+ current is thought to be the main mechanism of the antiepileptic efficacy [16]. Therefore, we considered that some genetic mutations regarding sodium channels may be related to the development of BPEI and/or CwG. We focused on *SCN1B*, which encodes the voltage-dependent sodium channel (Nav1.1) β subunit. The mutation of *SCN1B* gene had been reported in some epilepsies including generalized epilepsy with febrile seizures plus [21,22], febrile seizures plus and early-onset absence epilepsy [1], and Dravet syndrome [15]. However, there have been no reports on *SCN1B* mutation in children with BPEI or CwG. This prompted us to explore *SCN1B* mutation in children with BPEI or CwG.

Patients and Methods

We collected blood samples of children with BPEI or CwG from Juntendo University Hospital, Juntendo Nerima Hospital, and Hirakata City Hospital. According to our previous studies [12,14], BPEI was defined as epilepsy meeting all of the following conditions: (i) focal seizures and/or secondarily generalized seizures; (ii) normal psychomotor development and neurological findings until the last follow-up; (iii) normal interictal

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electroencephalograms (EEGs); (iv) normal cranial MRI; (v) no seizures during the first 4 weeks of life. CwG was defined as when a patient met the following 2 conditions: (i) seizures accompanied the symptoms of gastroenteritis without clinical signs of dehydration or electrolyte derangement and (ii) the body temperature remained less than 38.0 °C before and after the seizures [19]. Patients with meningitis, encephalitis/encephalopathy, or apparent history of epilepsy were excluded.

A total of 12 samples were obtained including 6 samples of children with BPEI and 6 samples of children with CwG.

This study was approved by the ethical committee of Juntendo University School of Medicine. Written informed consent was obtained from the parents of each child.

Methods

Genomic DNAs were extracted from peripheral blood samples accumulated from the patients by use of QIAamp DNA extraction kit (Qiagen, Hilden, Germany). All 5 exons of *SCN1B* were amplified by standard PCR amplification. Primers used for this study are listed in ○ **Table 1**. Subsequent cycle sequence reactions were performed using BiDye terminator, and the samples were electrophoresed by ABI7300 (Life Technologies, Carlsbad, California, USA). Acquired sequencing data were compared to the reference nucleotide sequence obtained from the in-silico library (http://www.ncbi.nlm.nih.gov/nucleotide/).

Results

Demographic features of the patients are shown on ○ **Table 2**. As to the patients with BPEI, the age at the onset ranged from 4 to 9 months. 3 of them were successfully treated with carbamazepine and 1 with valproate. The other 2 did not require antiepileptic drugs, because they had had only 3 or 4 seizures. All of them were followed-up until 2 years of age or older. Psychomotor development at the last follow-up was normal in all of them. As to the patients with CwG, the age at the onset ranged from 15 to 26 months. All of them had clustering seizures. Oral carbamazepine was administered in 3 patients and drip infusion of lidocaine in 2. After the administration of these drugs, no seizures were observed. In one patient, seizures disappeared spontaneously. They were followed-up for at least 1 year. No delay in psychomotor development was seen in all of them.

There were no *SCN1B* mutations or pathological single nucleotide polymorphisms in any of the patients.

Table 1 Primers for SCN1B used in this study.

	Forward	Reverse
Exon 1	CGCCTCTCGCCCCGCTATTA	CTCCCGCCGCCCCGCCAGTG
Exon 2	GTCTGCTGGTAATCATTGAGGG	ATCCAGGTCAGCAATCACAG
Exon 3	CAGAATCAGGGTCAGGTAAG	AACAGAGGCCAGAGCTGGAG
Exon 4	ATCACAGTGCATACACCAGGC	GTCTGACGACCCCTATCCTG
Exon 5	ACTAAGGAGCCCTGTGTACCTG	TTACGGCTGGCTCTTCCTTG

Table 2 Demoraphic features of the patients.BPEI: benign partial epilepsy in infancy, CwG: convulsions with gastroenteritis.

Patient	Diagnosis	Sex	Age at onset (Months)	Treatment	Psychomotor development
1	BPEI	F	4	carbamazepine	normal
2	BPEI	F	9	carbamazepine	normal
3	BPEI	M	4	carbamazepine	normal
4	BPEI	F	4	none	normal
5	BPEI	F	5	none	normal
6	BPEI	M	6	valproate	normal
7	CwG	F	16	none	normal
8	CwG	M	22	lidocaine	normal
9	CwG	M	26	lidocaine	normal
10	CwG	M	19	carbamazepine	normal
11	CwG	F	20	carbamazepine	normal
12	CwG	M	15	carbamazepine	normal

Discussion

Our study demonstrated that *SCN1B* may not be related to the occurrence of BPEI or CwG. No mutations or pathological single nucleotide polymorphisms were found in any children. The subjects of our study were considered to be typical children with BPEI or CwG. The age of onset, clinical manifestation, and response to the antiepileptic drugs were consistent with BPEI or CwG. Thus, the selection of subjects was made appropriately. According to the results of our study, *SCN1B* may not be a causative gene for BPEI or CwG.

There have been several studies on benign familial or non-familial infantile seizures, which will be analogous to BPEI, or other related conditions. Several gene loci related to benign familial infantile seizures have been mapped at chromosome 19q in 5 Italian families [7], at chromosome 16p12-q12 in more than 30 families worldwide [3,4,17,24], and at chromosome 2q24 in four additional Italian families [10]. The locus at chromosome 16 is also linked to the infantile convulsions and choreoathetosis syndrome [9]. The *ATP1A2* gene situated at chromosome 1q23 is mutated in familial hemiplegic migraine and co-segregation of benign familial infantile convulsions with familial hemiplegic migraine in one Dutch-Canadian family led to the identification of a p.R689Q missense mutation in *ATP1A2*–20]. Among children with benign familial neonatal infantile seizures, mutations have been found within the *SCN2A* gene, which is located at chromosome 2q24 and coding for the α-2 subunit of the voltage-gated sodium channel subunit [2,8]. As to CwG, few genetic studies have been reported. The mutations in the *SCN1A* gene have been investigated [25], but no mutation has been reported until now.

We targeted sodium channels as causative genes on the basis of good response to low-dose CBZ. CBZ is known to bind the inner pore of sodium channels and to block sodium currents with noticeable voltage dependence. Lidocaine is also effective for clustering seizures in CwG [13]. Lidocaine is usually used as a local anesthetic or antiarrhythmic drug. Voltage-gated sodium channels are targets for lidocaine which binds in the inner pore of the channels with affinities to the channel gating states. On the basis of the excellent efficacy of CBZ and lidocaine for seizures in BPEI and CwG, sodium channels have been considered to be involved in their pathogenesis. However, mutations in the genes encoding sodium channels have not been found in the majority of children with BPEI. Weng et al. explored *SCN1A* mutation in children with CwG and found no mutations in *SCN1A*–25]. Further studies on other genes encoding sodium channels should be performed in order to clarify the genetic causes of BPEI and CwG. However, the effectiveness of CBZ may not always indicate mutations in genes encoding sodium chan-

nels in themselves. It is generally accepted that CBZ is not effective for Dravet syndrome, in which *SCN1A* mutations are observed in the majority of the patients [5]. This may be explained by the results from a mouse model suggesting that the primary effect of *SCN1A* mutation is to decrease the activity of GABAergic inhibitory neurons. CBZ may more strongly worsen the function of inhibitory neurons which have already been affected by *SCN1A* mutation [6].

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平成23年度
3班合同ワークショッププログラム

稀少筋疾患　シナプトパチー・チャネロパチーの診断・病態から治療に向けて

厚生労働科学研究　難治性疾患克服研究事業
奨励研究分野　３班合同ワークショップ

Schwartz-Jampel症候群のわが国における診断システム確立とモデルマウスによる病態解明と治療研究班
（代表：平澤 恵理）

先天性筋無力症候群の診断・病態・治療法開発研究班
（代表：大野 欽司）

筋チャネル病および関連疾患の診断・治療指針作成および新規治療法開発に向けた基盤整備のための研究班
（代表：高橋 正紀）

日時　平成２４年１月２２日（日）　１４：３０～１７：００

会場　千里ライフサイエンスセンター　８階　８０１号室
大阪府豊中市新千里東町１－４－２

『次世代シークエンサを用いたエクソーム解析の実際と悩み –43例の解析経験–』
名古屋大学大学院医学系研究科　神経遺伝情報　教授　大野 欽司

『福山型筋ジストロフィーの新たなメカニズムと分子標的治療』
神戸大学大学院医学系研究科　神経内科・分子脳科学　教授　戸田 達史

『心筋イオンチャネル病：疾患群としての概要と発症機序』
滋賀医科大学　呼吸循環器内科　教授　堀江 稔

【事務局】
厚生労働科学研究費補助金　難治性疾患克服研究事業
「筋チャネル病および関連疾患の診断・治療指針作成および新規治療法開発に向けた基盤整備のための研究班」　研究代表者　高橋正紀
〒565-0871 大阪府吹田市山田丘2-2 D-4
大阪大学大学院医学系研究科　神経内科学教室内
FAX 06-6879-3579

厚生労働科学研究費補助金　難治性疾患克服研究事業

平成２３年度　奨励研究分野　３班合同ワークショップ

Schwartz-Jampel 症候群のわが国における診断システム確立とモデルマウスによる病態解明と治療研究班
（代表：平澤 恵理）
先天性筋無力症候群の診断・病態・治療法開発研究班
（代表：大野 欽司）
筋チャネル病および関連疾患の診断・治療指針作成および新規治療法開発に向けた基盤整備のための研究班
（代表：高橋 正紀）

日時　　平成２４年１月２２日（日）　１４：３０－１７：００

会場　　千里ライフサイエンスセンター　８階　８０１号室
大阪府豊中市新千里東町１－４－２
電話　06-6873-2010

事務局

厚生労働科学研究費補助金　難治性疾患克服研究事業
「筋チャネル病および関連疾患の診断・治療指針作成および新規治療法開発に向けた基盤整備のための研究班」事務局
〒565-0871 大阪府吹田市山田丘 2-2 D-4
大阪大学大学院医学系研究科　神経内科学教室内
TEL 06-6879-3571
FAX 06-6879-3579

プ ロ グ ラ ム

14:30-15:00
座長　順天堂大学大学院・老人性疾患病態・治療研究センター　平澤 恵理

『次世代シークエンサを用いたエクソーム解析の実際と悩み —43例の解析経験—』
名古屋大学大学院医学系研究科　神経遺伝情報　教授　大野 欽司

15:00-15:45
座長　名古屋大学大学院医学系研究科　神経遺伝情報　教授　大野 欽司

『福山型筋ジストロフィーの新たなメカニズムと分子標的治療』
神戸大学大学院医学系研究科　神経内科・分子脳科学　教授　戸田 達史

＜ 休 憩 ＞

16:00-16:45
座長　大阪大学大学院医学系研究科　神経内科学　高橋 正紀

『心筋イオンチャネル病：疾患群としての概要と発症機序』
滋賀医科大学　呼吸循環器内科　教授　堀江 稔

千里ライフサイエンスセンター

「新大阪」駅から約15分
大阪国際空港(伊丹空港)から約15分

● **地下鉄(北大阪急行電鉄)**

御堂筋線 千里中央行 終点・千里中央下車(北出口すぐ)

● **伊丹空港からお越しの方**

大阪モノレール 門真市行 千里中央下車(徒歩約5分)

● **関西空港からお越しの方**

(1) JR

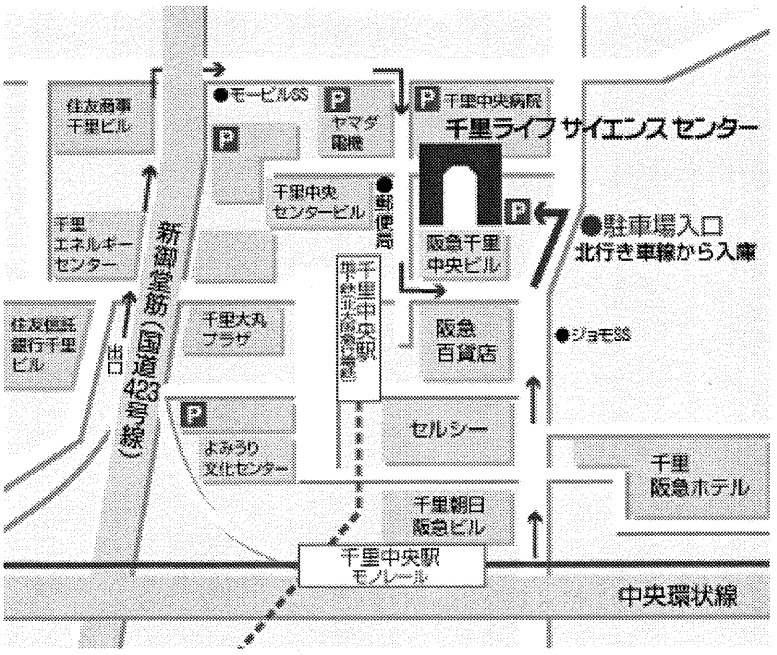
新大阪駅から地下鉄千里中央行にお乗り換えください。

(2) 南海電気鉄道

難波駅から地下鉄千里中央行にお乗り換えください。

● **お車でお越しの方**

新御堂筋(国道 423 号線)または、中央環状線をご利用ください。



厚生労働科学研究費補助金　難治性疾患克服研究事業

先天性筋無力症候群の診断・病態・治療法開発研究

平成23年度　総括･分担研究報告書

発行　　平成24年4月

発行所　先天性筋無力症候群の診断・病態・治療法開発研究班事務局
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