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A trial of topiramate for patients with hereditary spinocerebellar ataxia

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Abstract

In an open pilot trial, six patients with various hereditary forms of spinocerebellar ataxia (SCA) were assigned to topiramate (50 mg/day) for 24 weeks. Four patients completed the protocol without adverse events. Of these four patients, topiramate was effective for three patients. Some patients with SCA could respond to treatment with topiramate.

KEYWORDS

drug repositioning, spinocerebellar ataxia, topiramate

1 | INTRODUCTION

Hereditary spinocerebellar ataxia (SCA) is a heterogeneous group of neurodegenerative disorders characterized by ataxia variably associated with other neurological features, including pyramidal signs, dystonia, peripheral neuropathy, and hearing loss.[1] Although some drugs, such as riluzole, varenicline, and amantadine, can be effective in the treatment of hereditary ataxias,[2] there is a need for additional treatments for patients with hereditary SCA.

Drug repositioning (i.e., the identification of new therapeutic effects of existing drugs) has been recognized as a useful strategy for drug discovery.[3–5] Due to the large quantity of information on existing drugs (e.g., pharmacokinetics, safety in humans, manufacturing processes), the drug repositioning approach can enable a dramatic reduction in the cost of developing the drug in terms of time and expenditure. Recently, a variety of computational drug repositioning methods have been developed based on statistical analyses of biomedical big data.[6–14] These methods have the potential to find new drug candidates that may be useful for the treatment of SCA.

In this study, we searched for new drug candidates effectively for SCA using a computational drug repositioning approach on the basis of the large-scale data analysis of existing drugs, genes, proteins, molecular interactions,

and diseases. We administered a repositioned drug candidate to six patients with autosomal dominant cerebellar ataxia to examine the effect on ataxia symptoms.

2 | METHODS

2.1 | Computational drug repositioning

We attempted to find new drug candidates that may be useful for SCA by applying a computational drug repositioning approach. Drug phenotypic effects are basically derived from their interactions with proteins, including the primary target and off-target proteins. Thus, we used a target-based drug repositioning method.[14] First, we estimated the potential target proteins of each drug using target estimation with similarity search (TESS). Then, we selected potential drug candidates by performing an indication prediction by supervised classification (IPSC). In TESS and IPSC, we used the chemical similarity, side-effect similarity, and gene-expression similarity of drugs based on their chemical substructure profiles,[14] clinical side-effect profiles,[13] and drug-induced gene-expression profiles.[6]

Figure 1 shows an illustration of the target-based drug repositioning used in this study. Panel (A) in Figure 1 shows the TESS procedure in which all potential target proteins of each drug were estimated by performing a similarity search with chemical structure similarity, side-effect similarity, and gene-expression similarity against drugs with target information. Panel (B) in Figure 1 shows the IPSC procedure in which new indications of each drug are predicted by the supervised classification of drug-disease pairs into applicable class or nonapplicable class. The details of each process have been described previously.[14]

2.2 | Protocol

We obtained written informed consent from all individuals examined. Efficacy was determined using the ICARS[15] assessed every 8 weeks. Namely, at week zero just before topiramate treatment (0w), 8, 16, and 24 weeks after topiramate treatment, 25 mg twice a day (8w, 16w, and 24w, respectively), and 8, 16, and 24 weeks after stopping topiramate treatment (p8w, p16w, and p24w, respectively). Combination medicine and rehabilitation were not changed during the clinical trial period. We defined the condition such that the total ICARS score at 24w was lower than at baseline as "effective".

3 | RESULTS

We performed a screening of 8274 drugs registered in Japan, the United States, and Europe using the computational drug repositioning methods: TESS and IPSC. We constructed three kinds of target-protein profiles of drugs based on their chemical, side-effect, and gene-expression similarities by TESS. We calculated the prediction scores of all the drugs from their target-protein profiles by IPSC for SCA and took the average of the IPSC prediction scores associated with chemical, side-effect, and gene-expression similarities. Topiramate had the highest prediction score for SCA; thus, we selected topiramate as a drug candidate for SCA.

Then, we performed a pilot study consisting of an open-label, self-controlled clinical trial. Six patients with hereditary cerebellar ataxia were recruited from the Department of Neurology, Kurume University Hospital. The sex, age, disease duration, and genetic diagnosis of the patients are shown in Table 1. The details of the six participating patients were as follows: SCA type 6 (SCA6), SCA8, SCA27,[16]
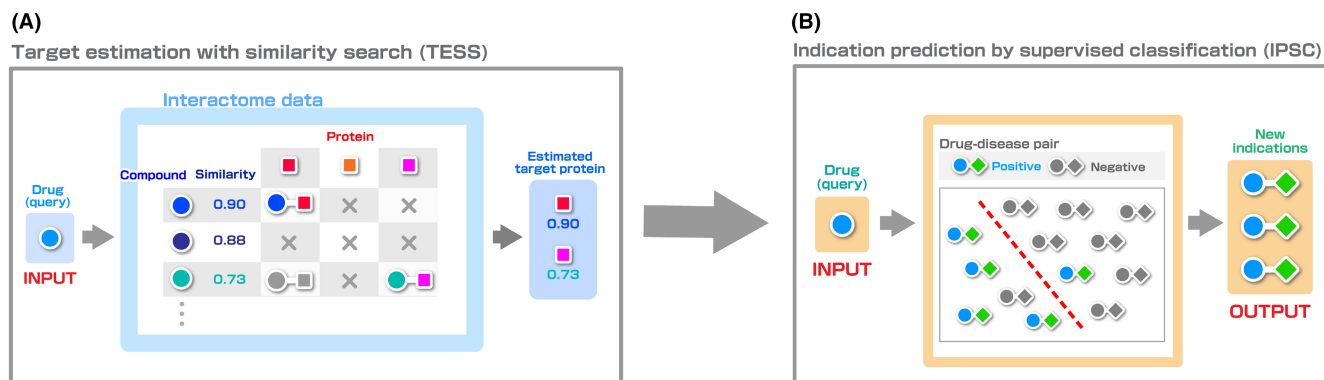
FIGURE 1 An illustration of the target-based drug repositioning method. (A) All potential target proteins of each drug were estimated by performing a similarity search with drug similarity against drugs with target information. (B) New indications for each drug were predicted by the supervised classification of drug-disease pairs into applicable class or nonapplicable class.

TABLE 1 Characteristics of the participating patients.

	Age (year)	Sex	Disease duration (year)	Initial symptom	Genetic diagnosis	Medical history
Case 1	61	Female	18	Limb ataxia	SCA6	None
Case 2	65	Female	13	Gait disturbance	Not examined (CCA type)	NA
Case 3	63	Female	26	Gait disturbance	SCA36	Hypertension, deafness
Case 4	61	Male	8	Gait disturbance	Unknown (CCA type)	None
Case 5	44	Female	18	Gait disturbance	SCA8	None
Case 6	62	Male	15	Gait disturbance	SCA27	Hypertension, dyslipidemia, chronic hepatitis C

Abbreviations: CCA, cerebellar cortical atrophy; NA, not available; SCA, spinocerebellar ataxia.

TABLE 2 ICARS score dynamics.

	0w	8w	16w	24w	p8w	p16w	p24w	Interpretation
Case 1	46	45	45	45	50	52	47	Effective
Case 2	20	21	16	17	18	18	18	Effective
Case 3	53	45	50	44	47	48	53	Effective
Case 4	38	44	52	49	46	50	50	Ineffective
Case 5	38	42	39	35	37	40	42	Effective[a]
Case 6	39	Dropout[b]						

Note: 0w: week zero just before topiramate treatment. 8w, 16w, 24w: 8, 16, and 24 weeks after topiramate treatment. p8w, p16w, p24w: 8, 16, and 24 weeks after stopping topiramate treatment.

[a]Reduced dose from 50 to 25 mg/day because of sleepiness at 16 weeks.

[b]Case 6 dropped out because of anorexia and worsening gait instability at 2 weeks.

SCA36, genetically unknown cerebellar cortical atrophy (CCA),[17] and CCA without genetic examination. The ICARS score dynamics are shown in Table 2. One patient (Case 6) dropped out because of anorexia and worsening gait instability at 2 weeks. Another patient (Case 5) had a dose reduction from 50 to 25 mg/day because of sleepiness at 16 weeks. The other four patients completed the protocol without adverse events. Of these four patients, topiramate was effective for three patients (75%).

4 | DISCUSSION

In this study, we investigated new drug candidates for SCA by computational drug repositioning on the basis of large-scale data on the drugs, genes, proteins, molecular interactions, and diseases. This study is the first attempt to suggest potential drug candidates for SCA by a data-driven approach. This is also the first report on the evaluation of the therapeutic effect of topiramate for hereditary SCA. The usual dose of topiramate for epilepsy in Japan is 100–200 mg a day, taken in two doses. In this study, we set a lower dose from the viewpoint of safety. Although one patient had a reduced daily dose of topiramate because of

daytime sleepiness, four out of five patients taking topiramate for 24 weeks showed both a decrease in the total ICARS score from baseline (0w) to 24w and an increase in the total ICARS score from 24w to the final visit (48w). These results indicate that topiramate was effective for some SCA patients.

Topiramate is a voltage-gated sodium channel blocker and has been shown to regulate voltage-gated sodium channel function in cerebellar granule cells.[18,19] Lamotrigine, which is also a voltage-gated sodium channel blocker, has been reported to reduce ataxic gait in Machado-Joseph disease/SCA type 3.[19,20] Both topiramate and lamotrigine also inhibit glutamate release.[19] Modulating glutamate release is important because the type 1 metabotropic glutamate receptor signaling cascade is thought to play a key role in the development of SCA.[21] In addition, the efficacy of topiramate for cerebellar ataxia and tremor in a patient with multiple sclerosis has been reported.[22] Thus, according to the results of these previous studies and the present study, topiramate could be effective for some patients with SCA. However, it has been reported that topiramate (50 mg/day) worsened ataxia in a patient with SCA type 17.[23] In that report, reducing the dosage of topiramate from 50 to 25 mg/day eliminated the

ataxia.[23] Similarly, in our study, Case 6 dropped out from our study because of anorexia and worsening gait instability induced by 50 mg/day of topiramate. Thus, there might be some patients with SCA whose symptoms are exacerbated by 50 mg/day of topiramate. In fact, 100 mg/day for 4 weeks of topiramate worsened instability in a patient with SCA type 42.[24]

In conclusion, this pilot study suggests that topiramate could be effective for some patients with hereditary cerebellar ataxia. However, in our study, the number of participating patients was low and the study design was open-label observations so both the optimal dose and the specificity of the effects of topiramate on ataxia must be further investigated in larger studies.

AUTHOR CONTRIBUTIONS

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FUNDING INFORMATION

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ETHICAL APPROVAL

This study was approved by the Ethics Committees of Kurume University School of Medicine in 2015.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's consent policy.

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