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Proposal for a Prospective Registry for Moyamoya Disease in Japan

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Abstract

The number of clinical research papers published worldwide on moyamoya disease (MMD) has increased recently. However, the majority of the literature comprises retrospective single-center studies collecting data on small numbers of patients. Several multi-center studies are ongoing in Japan; however, the current data are insufficient for comprehensively outlining the various characteristics of MMD. To enhance our knowledge on epidemiologic, vascular, and genetic aspects of MMD, a prospective multicenter registry will be established in Japan that will help to streamline clinical research as well as improve clinical treatments and long-term outcomes. Patients with MMD or secondary moyamoya syndrome referred to the participating centers will be invited to the registry. Demographic and physiological parameters, along with neuroimaging data will be collected chronologically. Clinical events, including neurological, medical, and surgical interventions will be recorded. Whole blood samples will be collected. Extra- and intracranial vascular tissue, and/or cerebrospinal fluid will also be collected from patients who undergo surgical revascularization. These biospecimens will be stored at the repositories and utilized for genome-wide association studies for identifying genetic variants, as well as tissue-specific proteomic, and/or molecular analyses. Ethics approval will be obtained at all facilities collecting biospecimens. The registry will provide descriptive statistics on functional outcomes, surgical techniques used, medications, and neurological events stratified according to patients' clinical characteristics. We expect this study to provide novel insights in the management of MMD patients and design better therapies.

Key words: intractable diseases, registry, moyamoya disease, epigenetics, clinical research

Introduction

Moyamoya disease (MMD) has been included in the list of 56 diseases within the Specified Disease Treatment Research Program in Japan, which was established in 1972. Through this program, the national government and prefectures partially cover the patients' share of medical expenses. The number of patients with MMD who received the designated disease treatment in Japan was 17,436 in 2014 (http://www.nanbyou.or.jp/entry/209). In 2015, a new legislation was established to assign 306 intractable diseases in Japan. Notably, Japan Agency for Medical Research and Development (AMED) was established to facilitate clinical trials and development of therapies for intractable diseases including rare diseases such as MMD (http://www.amed.go.jp/). Thus, in support of these national initiatives, establishing a rare disease registry will further advance clinical research as well as facilitate the development of orphan drugs (http://www.eucerd.eu/).[1)]

There are several distinct characteristics of MMD that should be taken into account while collecting data for the disease registry. Emphasis is placed on early detection in most of the rare, intractable diseases, because once the disease advances, no treatment may be effective. Furthermore, some of these diseases covertly affect multiple organs without obvious clinical symptoms. In contrast, identifying early stage of MMD can be performed non-invasively

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by MRI. Importantly, patients with advanced arterial narrowing can be treated successfully with revascularization surgery. Nevertheless, many clinical questions remain unanswered with respect to the clinical diagnosis as well as the treatment of MMD. For example, clarifications are required from a pathological point of view to distinguish the morphological changes observed in MMD from those in secondary moyamoya syndrome.[2] A recent randomized controlled trial revealed that direct anastomosis reduced the rate of recurrent hemorrhage in adult patients with MMD. However, surgical treatment is not always feasible for suitable patients in a timely manner.

Several polymorphisms in the *RNF213* gene have been identified in association with cases of MMD in East Asian and Caucasian populations, including *RNF213* c.14576G>A, an SNP with high prevalence among East Asian Moyamoya patients, but no evidence in Caucasian Moyamoya patients.[3] RNF213 has been suggested to play a role in arterial wall remodeling and angiogenesis as demonstrated by *in vitro* and *in vivo* experiments. However, due to inconsistencies in these experiments, further studies are required to clarify the role of *RNF213* gene in the development of MMD.[4–7] Other studies have suggested that mechanisms involving epigenetic/environmental factors may also be associated with disease progression.[6,8–10] The Biobank system will effectively collect a large number of samples nationwide. In combination with blood samples, the longitudinal clinical data stratified according to demographics or neuroimaging data may elucidate novel genetic/epigenetic markers associated with the onset of disease, various clinical subtypes, and disease progression.

In Japan, nationwide clinical research initiatives such as the Japan Adult Moyamoya (JAM) trial, Asymptomatic Moyamoya Registry (AMORE), and Cognitive dysfunction Survey of Moyamoya disease (COSMO) have been conducted to investigate the preventative effects of direct bypass on re-bleeding, the long-term prognosis and risk factors contributing to ischemic and hemorrhagic stroke of asymptomatic patients with MMD, and to establish a standard diagnosis of the cognitive impairment in patients with MMD, respectively.[11–13] While these clinical trials performed with strict inclusion criteria would provide valuable evidence, more detailed information is necessary for assistance in daily clinical practice. Furthermore, as our treatment techniques and paradigm change, it will be necessary to update the clinical course for the entire MMD demographics. Hence, descriptive statistics from a nationwide registry may further compliment the evidence generated from multicenter nationwide studies.

Thus, the aims of the prospective multicenter registry are to (1) provide descriptive statistics with respect to the symptoms, outcome and both medical as well as surgical treatment, (2) facilitate genetic research by combining with the biobank system, and (3) streamlining the clinical research from different centers.

Methods

Study design

The Japan Moyamoya Disease Registry (JMDR) is a prospective multicenter registry, in which patients will be observed long term. The study will be an open registry, initiated by members of the Research Committee on Moyamoya Disease, and sponsored by the Ministry of Health, Labor, and Welfare of Japan. A total of seven neurosurgical departments have constituted a Steering Committee, which will be responsible for the scientific goals of the registry and assure the independence of the data analysis. The basic concepts of the JMDR are summarized in Table 1.

Participants

Diagnosis of MMD will be performed according to the consensus criteria and guidelines proposed by the Research Committee on Spontaneous Occlusion of the Circle of Willis. Patients with MMD and the secondary moyamoya syndrome will be included in the study. However, patients with internal carotid occlusive lesions consistent with arteriosclerosis, as well as those with a history of cranial irradiation will be excluded. It should be noted, however, some patients with border zone angiographical changes are difficult to distinguish from those with idiopathic MMD.

Informed consent

The data will include information regarding patient consent (or willingness) to participate in clinical

Table 1 Summary of Japan Moyamoya Disease Registry plan

1.	The Japan Moyamoya Disease Registry will be conducted prospectively. It will be a multicenter initiative and an open registry in which patients will be observed long term and open ended.
2.	The registry will include patients with not definitive MMD or secondary moyamoya syndrome.
3.	The registry will be incorporated with a biobank in which blood samples as well as patient's specimen are collected prospectively.
4.	A limitation of the study is that the JMDR is not a controlled trial. Specific treatment strategies will not be compared to each other.

research as well as trials. Written informed consent is necessary in patients who agree to provide biospecimens. The study will be conducted in accordance with the provisions of the Declaration of Helsinki.

Data and sample collection

The basic list of items (Minimum Data Set; MDS) is a mandatory data set which will be shared with other rare diseases. The MDS includes necessary information on personal identification, consent for the prospective data collection, and assessment of quality of life. Additional items of data are also integrated based on questionnaires used in ongoing clinical research programs such as JAM, AMORE, and the COSMO study.[11–13] In addition to the cross-sectional data, patients will be tracked by monitoring specific events such as transient ischemic attack (TIA) or stroke events as well as changes observed by neuroimaging. Sample collection (Figs. 1 and 2).

Bio-specimens such as blood, cerebrospinal fluid (CSF), or vascular tissue of the patients will be collected and prepared for future analyses. These samples will be stored in appropriate conditions at the clinical biobank in national centers or local biobank systems, in which each process such as collection, preparation, and storage of samples will

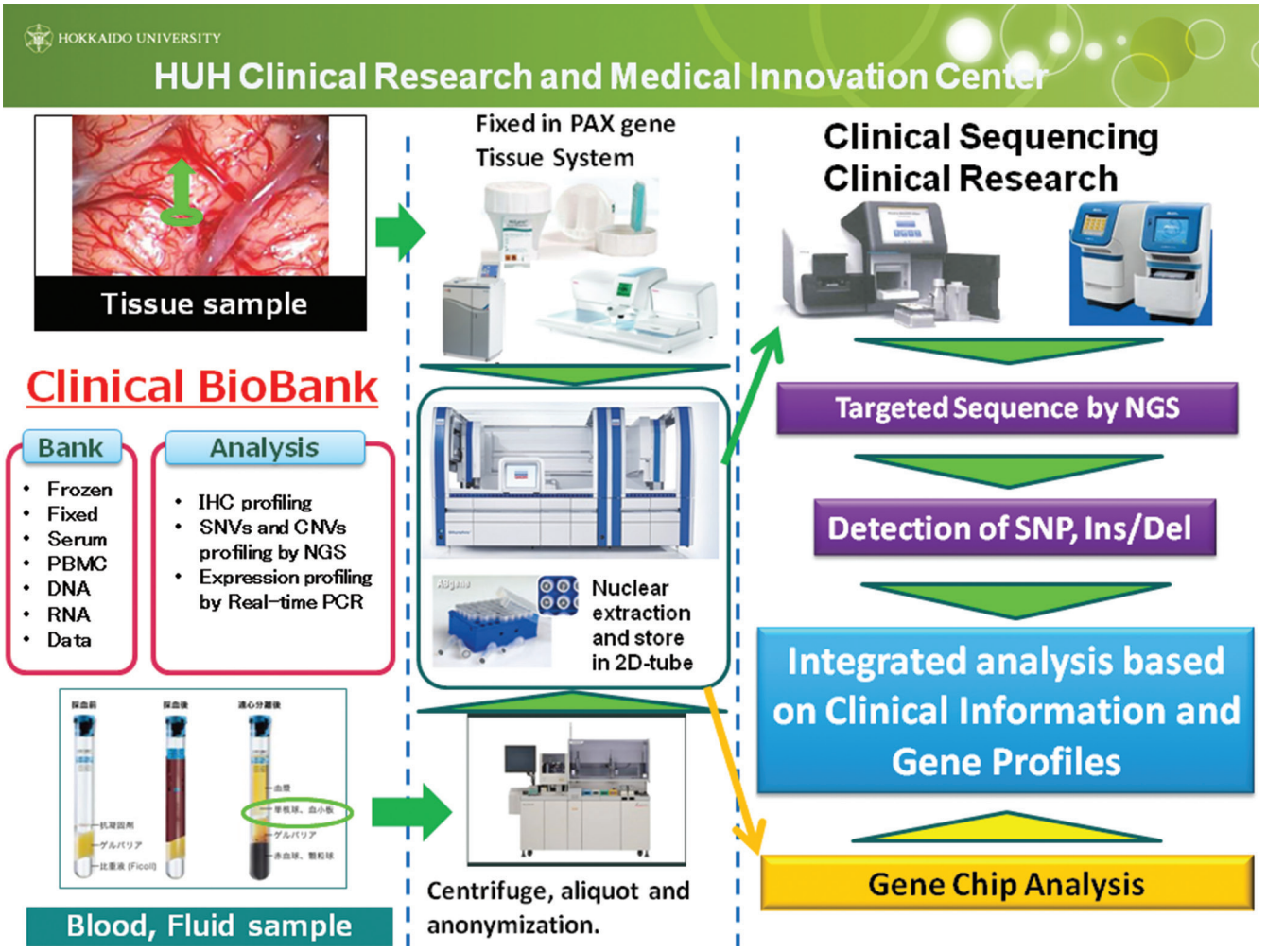

Fig. 1 Biobank system incorporated with registry. Biospecimens including blood and tissue samples will be stored in the Clinical Biobank of the Clinical Research and Medical Innovation Center at Hokkaido University Hospital. We employ PAXgeneTissue System (QIAGEN) for tissue fixation and preparation of PFPE (PAXgene Tissue fixed paraffin embedded) specimens for all tissue samples. High quality nucleic acids including DNA and RNA will be extracted by QIAsymphony (QIAGEN). Our banking system will be able to efficiently accept and label specimens from other medical facilities as well. Further, we will perform targeted gene sequencing using Mi-seq and GeneChip analysis to obtain the MMD-specific gene profile. Finally, we will perform integrative bioinformatics analysis based on multiple parameters such as the patients' familial and disease history or hydrodynamic data obtained from angiographic examination in addition to gene profiling to identify genetic alterations specific to MMD.

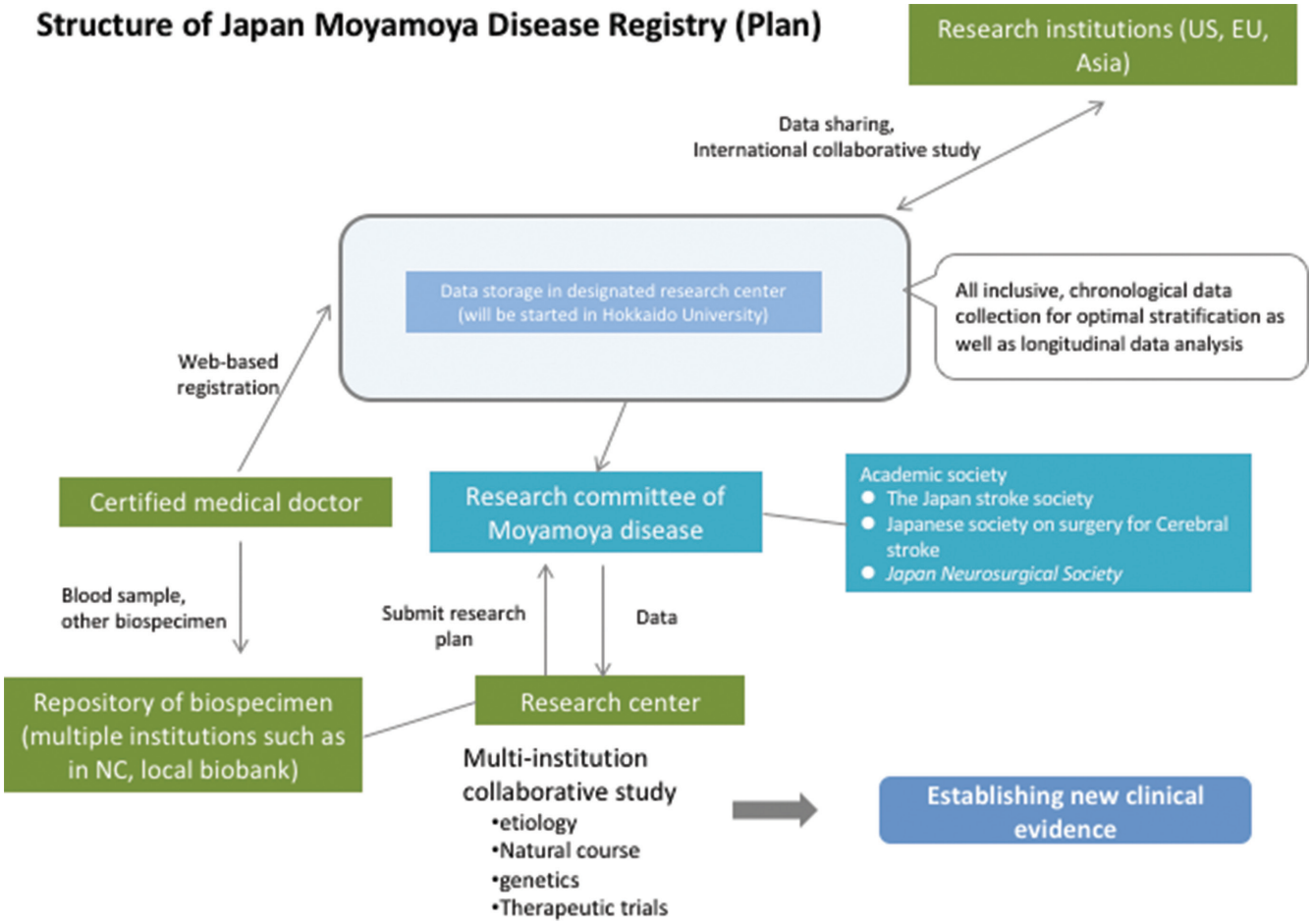

Fig. 2 The diagram outlines the structure of Japan Moyamoya Disease Registry collects clinical data focusing on mechanism of disease onset, progression as well as differential diagnosis. The information include the catalogue of biospecimen collected in multiple repositories such as National Center as well as local biobank.

be conducted using consistent protocols (Fig. 1). The catalogue of samples collected in each facility will be recorded in the registry and linked to detailed clinical information of the enrolled patients in a data linkage system with anonymity (Fig. 2).

Web-based data form

In addition to mandatory data items, the following information will be collected:

1. Basic information: The first part of the data items cover the date entered in the registry, date of birth, sex, race/s, weight, height, and blood pressure.
2. Life activity: In addition to the Barthel index, modified Rankin scale (mRS) score, occupation, marital status, and the higher education obtained.
3. Family history: Any family member known to be diagnosed with cerebrovascular diseases will be recorded.
4. Medical history: Common complications associated with arteriosclerosis (hypertension, arterial fibrillation, diabetes mellitus, dyslipidemia, coronary artery disease) will be recorded. In addition, diseases strongly associated with moyamoya phenomenon will be recorded.
5. Pregnancy and delivery: A history of pregnancy and delivery will be recorded.
6. Clinical presentations: Clinical presentations (TIA, infarction, intracranial bleeding, headache, seizure, asymptomatic, others) will be recorded.
7. Stroke history: History of stroke at the time entering JMDR will be recorded. Type of stroke, frequency of TIA, and most recent TIA will be recorded.
8. Cognitive function: Date of examination, full scale intelligence quotient (IQ), and neuro-psychological examinations performed in the patients will be recorded.
9. Neuroimaging: Conventional angiography and magnetic resonance arteriography (MRA)/computed tomography (CT) angiography will assist in identifying unilateral/bilateral involvement of the main cerebral arteries as well as moyamoya vessels.

The presence of acute/chronic infarctions/hemorrhage and micro-bleeds will be recorded. The findings of cerebral hemodynamics as determined by various modalities, such as MRI perfusion imaging, CT perfusion images, single photon emission computed tomography, and positron emission tomography, will be recorded.

10. Surgical treatment: Date/number and side of surgery, type/s of revascularization procedures (direct, indirect, or combined direct/indirect), and post-operative complications will be recorded.

11. Medications: Information on administered therapies including anti-platelets, anti-hypertensive drugs will be recorded along with the dates the therapies were started/discontinued.

12. Blood sampling: Patients' submission of blood samples, tissues, and CSF will be recorded.

13. Longitudinal follow-up data: TIA, infarction, intracranial bleeding will be recorded in addition to the neurological deficits attributed to the clinical events. Changes in neuroimaging data without the occurrence of stroke events/TIA will be also recorded. Silent infarctions, micro-bleeds, ivy signs, asymptomatic hemorrhage (parenchymal, intra-ventricular hemorrhage, subarachnoid hemorrhage) will be recorded. Steno-occlusive changes, even without neurological deterioration will be monitored. Treatment of neurological as well as radio-graphical deterioration will also be recorded.

Data management

Data collection for clinical research will be allowed when an optimal research plan has been submitted to the Ministry of Health, Labour and Welfare of Japan. An interim analysis will be planned in a few years and approximately 10 years after data collection, and we expect to include a large number of patients. All results of the JMDR, including epidemiological data, surgical techniques, complications, risk factors and long-term outcomes, will be published and/or reported at respective scientific meetings. Endpoints will be evaluated by using descriptive statistics. Univariate analyses will allow for a preliminary overview of potentially influential factors. Depending on the composition of the data, χ^2, Mann-Whitney *U*- and *t*-tests, Pearson or Spearman correlation coefficients will be calculated for evaluating the statistical significance of data. Relationships between multiple independent variables on the dependent variable(s) will be tested using multivariate regression analysis.

Registry reports

The results of the JMDR will be published by the Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor, and Welfare of Japan and distributed to all participating centers.

Dissemination of the registry

Dissemination of JMDR worldwide will contribute to the collection and sharing of data in an effective manner; it is vital for Japan to take this initiative for the advancement of both clinical and basic research in MMD.[14] JMDR can be introduced at a global academic meeting such as the International Moyamoya Meeting, which is held biannually (http://www.moyamoya2015.com/). Participants of this meeting come from Japan, Europe, North America, China and South Korea, representing key institutions for the treatment of MMD.[15,16]

Discussion

Nationwide registries and biospecimen repositories are considered to advance research initiatives in clarifying the pathogenesis of MMD, establishing treatment paradigms, and developing pharmaceutical products. Furthermore, establishing a patient registry may facilitate international collaborations for joint research. In 2012, the International rare disease research consortium (IRDiRC) was established to generate funding to accelerate research for development of novel therapies and diagnosis (http://www.irdirc.org/). In a majority of rare diseases, the main objective of the disease registry is to collect information on potential candidates for clinical trials. However, as an effective drug for MMD is not yet developed, the goal of establishing a disease registry is not clear. Data from prior registries is collected at each prefecture and gathered nationwide. Nonetheless, a lot of clinical data are left unregistered because input data to the electrical form is required at each prefecture. Besides, physicians tend to rate patients as more severe than they are, for the benefits associated with medical expenses, leading to inaccurate descriptions of the patients' QOL. As the benefits associated with medical expenses cannot be derived from patients with mild disease and those not requiring surgery, data is lacking for such patients. Furthermore, a longitudinal evaluation of QOL is difficult in the previous data sets, because information on patient IDs was not provided to the researchers.

The JMDR is designed as a multicenter, open access, prospective data resource for revealing outcomes stratified by the clinical as well as neuroimaging data. With the advent of clinical research, natural history as well as the surgical outcomes have been disclosed worldwide. As direct bypass became a standard technique for the treatment of adult MMD,

new complications such as hyper-perfusion have been recognized.[17] This lead to emphasis on optimizing surgical indications for re-vascularization surgery and thus, the original clinical evidence may not be relevant anymore. Medical treatments may also change the natural course and extend life expectancy, which may result in demographic changes in patients with MMD.

In general, collecting clinical data may reveal elements of disease progression, genetic and phenotypic heterogeneity, and endpoints that may be useful for development of novel therapeutics in the clinic. Part of the data items will be employed from the stroke version of (CDE) proposed by NINDS (NIN https://commondataelements.ninds.nih.gov/#page=Default), which will ensure that our disease registry meets with the international standards and will facilitate international co-operation.[18] It is also important to utilize the data from the past as well as ongoing clinical research; therefore, data items collected in JAM, AMORE and COSMO-Japan studies will be included in the registry, which will enable continuous follow-up of the patients who participated in these studies.[11–13] Open registry is ideal for collecting as much data as possible. The number of data items will be kept minimal to encourage registration from a broad range of medical institutions and doctors. The organization responsible for JMDR will need continuous funding. Approval for clinical research plans using JMDR should not be biased to limited institutions. Feasibility as well as clinical value of JMDR could be assessed, should descriptive statistics be published periodically.

A biobank that works in co-operation with the registry will facilitate genetic research. For example, in 2011, *RNF213* was identified as a disease susceptible gene in the Japanese population.[19] Nevertheless, the disease process is not sufficiently explained by mutations in *RNF213* alone. While 2% of the healthy Japanese population are estimated to be *RNF213* c.14576G>A carriers, only 5% of them may develop MMD.[20,21] Furthermore, the prevalence of *RNF213* c.14576G>A variant is different among races (i.e. Japanese: 90%; Korean: 80% and Caucasian: 0%).[3,20] Homozygosity of *RNF213* c.14576G>A has been found in 10% of Japanese patients and thus, is associated with early age onset and rapid progression of MMD.[22] However, the majority of the patients are heterozygous carriers and various other clinical courses or features are observed in their genotype. Therefore, other genetic variants, including *RNF213* rare variants, environmental factors, or epigenetic mechanisms may also be involved in the disease pathogenesis.[6,8–10] Circulating microRNAs (miRNAs) in blood have been reported to be differentially expressed in MMD patients and thus, are considered as potential factors involved in disease progression or modifications.[8,10] To facilitate such analyses, blood samples could be collected at several time points pertaining to the clinical events of patients. Therefore, combined with longitudinal clinical data in the registry, analysis of the epigenetic changes could be performed, which potentially could be used for prediction of disease progression.

To date, there has been no national open registry aimed at prospective data collection in neuro-surgical diseases. The current attempt may help to advance clinical research in a wide range of neurosurgical diseases. In conclusion, we propose to establish an open registry of moyamoya disease. The detailed design of this registry will be further evaluated by the members of the Research Committee on moyamoya disease and will be sponsored by the Ministry of Health, Labor, and Welfare of Japan as well as AMED.

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Conflicts of Interest Disclosure

None.

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