Development of Database and Genomic Medicine for von Hippel-Lindau Disease in Japan

Shunsaku Takayanagi,1 Akitake Mukasa,1 Hirofumi Nakatomi,1 Hiroshi Kanno,2 Jun-ichi Kuratsu,3 Ryo Nishikawa,4 Kazuhiko Mishima,4 Atushi Natsume,5 Toshihiko Wakabayashi,5 Kiyohiro Houkin,6 Shunsuke Terasaka,6 Masahiro YAO,7 Nobuo Shinohara,8 Taro Shuin,9 and Nobuhito Saito1

1Department of Neurosurgery, the University of Tokyo, Tokyo, Japan; 2Department of Neurosurgery, International University of Health and Welfare Atami Hospital, Atami, Kanagawa, Japan; 3Department of Neurosurgery, Kumamoto University, Kumamoto, Kumamoto, Japan; 4Department of Neurosurgery, Saitama Medical University, Saitama, Japan; 5Department of Neurosurgery, Nagoya University, Nagoya, Aichi, Japan; 6Department of Neurosurgery, Hokkaido University, Sapporo, Hokkaido, Japan; 7Department of Urology, Yokohama City University, Yokohama, Kanagawa, Japan; 8Department of Urology, Hokkaido University, Sapporo, Hokkaido, Japan; 9Department of Urology, Kochi University, Nankoku, Kochi, Japan

Abstract

von Hippel-Lindau (VHL) disease is a hereditary tumor disease in which tumors develop in multiple organs, not only as hemangioblastomas (HBs) in the central nervous system, but also as kidney tumors, pheochromocytomas, and so on. Much about the epidemiology of VHL disease remained unknown until fairly recently in Japan, leading to calls for the establishment of a VHL disease epidemiological database in Japan. To elucidate its epidemiology in Japan, the Japanese Ministry of Health, Labour and Welfare created the VHL Disease Study Group, which was put in charge of carrying out a nationwide epidemiological survey. The survey found close to 400 Japanese VHL disease patients throughout the country. Based on those results, the VHL Disease Study Group created the VHL Disease Treatment Guideline and also a severity classification. It is thought that the prognosis of VHL disease patients can be improved by performing genetic diagnosis and careful follow-up. Accordingly, the University of Tokyo Hospital put in place an in-hospital system for implementing genomic medicine for VHL disease based on genetic diagnosis. For that system, it was especially important to establish (I) accurate genetic diagnostic techniques, (II) genetic counseling capabilities for the patients and their families, and (III) a system of cooperation among multiple departments, including urology departments, and so on. Further elucidation of the epidemiology and the development of genomic medicine are needed to improve the treatment results of VHL disease in Japan.

Key words: VHL disease, database, genomic medicine

Introduction

von Hippel-Lindau (VHL) disease is a hereditary tumor disease that shows an autosomal dominant pattern of inheritance. VHL disease causes tumors to develop in juveniles in multiple organs, including hemangioblastomas (HBs) in the central nervous system (CNS), retinal HBs, renal cell carcinomas (RCCs), pheochromocytomas (PhCs), and so on.1–6 The causative gene of VHL disease (VHL) was identified on chromosome 3 in 1993 by Latif et al.7 Reports from Europe and the United States indicated that VHL disease occurs in 1/36,000 live births, with 44–72% of cases having HBs in the cerebellum and 25–60% having RCCs.1,8 However, in Japan, until recently, there was little epidemiological information available regarding the number of patients, what types of tumors are most common, and so on. As such, some pointed out the need for the establishment of an epidemiological database of Japanese VHL disease patients. To elucidate the epidemiology and establish a medical care system for VHL disease in
Japan, a VHL Disease Study Group headed by Prof. Taro Shuin of Kochi University’s Urology Department was created. Thereafter, Japan’s first epidemiological survey of VHL disease was carried out. Based on those results, the VHL Disease Study Group then created a VHL Disease Treatment Guideline as well as a severity classification.9)

In addition, it is thought that the prognosis of VHL disease patients would not differ greatly from that of healthy people if the patients were diagnosed by genetic testing early and given careful follow-up and treatments. Accordingly, the University of Tokyo Hospital established a system for implementing genomic medicine for VHL disease based on genetic diagnosis.

Here, we will describe the work of the VHL Disease Study Group to date and the genomic medical system that is being implemented in our hospital.

Work of the VHL Disease Study Group

Nationwide epidemiological survey: In 2009–2010, the Study group surveyed Japanese VHL disease patients by the following method. As the primary survey, the Study group asked via direct mailing, neurological surgery departments (at 1,020 institutions) and urology departments (at 1,200 institutions), which were approved as training facilities for neurological surgery and urology in Japan, whether there were experiences of medical care for the VHL disease patients. As the secondary survey, the Study Group sent questionnaires including several questions about the VHL disease patients to 240 facilities which had experiences of medical care for the VHL disease patients. Among these facilities, 146 facilities replied (response rate: 70.4%). A total of 409 patients with VHL disease were identified, and the prevalence of the VHL disease in Japan was estimated 0.455/100,000 by using the response rate of the secondary survey and the population of Japan in 2009 (n = 127,310,000). The results of the survey are described below, with a focus on three journal manuscripts in which the results were reported.10–12)

i. CNS HBs

A total of 409 patients with VHL disease were reported, and 200 patients had HBs (48.9%).10) Detailed clinical data were obtained for 111 of those patients and were subjected to further analysis. The patients’ performance status was evaluated using the Eastern Cooperative Oncology Group (ECOG) criteria.

Among the 111 patients bearing CNS HBs, 92 (82.9%) had HBs in the cerebellum, 22 (20.7%) had HBs in the brain stem, and 43 (38.7%) had HBs in the spinal cord (Fig. 1A). Of the total 63 spinal cord HB lesions, 50.6% were in the cervical region, 37.0% were in the thoracic region, and 12.3% were in the lumbar region. The mean age at onset for the total patients was 29.1 years, but the mean age for patients with multiple HB lesions (25.7 years) was significantly younger than that for patients with a single lesion (34.4 years).

The number of times that resection of an HB was performed ranged from 1–9. The performance status tended to worsen as the number of surgeries increased (Fig. 1B). The patients who had undergone many surgeries showed a significantly younger age at onset (Fig. 1C).

ii. RCCs

RCC was diagnosed in 206 (50.3%) of 409 patients with VHL disease.11) Their mean age at onset was

![Fig. 1](image.png)

(A) Distribution of CNS HBs in 111 VHL disease patients. (B) Relationship between the number of operations and ECOG performance status (PS) score. The ECOG PS score was significantly and positively correlated with the number of operations. (C) The relationship between the number of operations and onset age (years) of CNS HB is inversely correlated with the number of operations. **P < 0.01, *P < 0.05 (Kanno, 2009).10)
37.8 years, with a broad range of 15–75 years, and most occurred between the ages of 20 and 50 years. The percentage of patients with metastases to other organs was 11.1%, which was concluded to be lower than the incidence of metastases in non-VHL RCC.

The treatment details were known for 203 patients. The most common treatments for RCC were partial nephrectomy (46%), nephrectomy (31%), and radiofrequency ablation (14%). Two or more operations were performed in 44% of the 203 patients, with the largest number of operations being six. The estimated glomerular filtration rate tended to decrease as the number of treatments increased (Fig. 2A).

Regarding prognosis, the 10-year disease-specific survival rate was 95%, which was better than that for non-VHL RCC (Fig. 2B).

iii. PhCs

PhC was diagnosed in 62 (15.2%) of 409 patients reported to have VHL disease. Their mean age at onset was 29.7 years, with a broad range of 10–75 years and bimodal peaks at 15–20 years and 35–40 years (Fig. 3A). Bilateral disease occurred in 26 (41.9%) patients, extra-adrenal onset was diagnosed in eight patients (12.9%), and malignancy with confirmed metastasis was seen in four (6.5%) patients. Two or more treatments were performed for 19.3% of the patients (Fig. 3B). These results do not generally differ from those reported from Europe and the United States.

Treatment guideline and severity classification: The Japanese VHL Study Group prepared a VHL Treatment Guideline in 2012 based on the survey results and previous studies, and so on. Here, we describe the clinical diagnostic criteria for VHL disease, and the follow-up observations and treatment strategies for each of the organ-specific VHL lesion types. The treatment strategies for HB are as follows.

• For the high-risk group (patients diagnosed with VHL disease by genetic testing; patients with a family history of VHL disease; and patients diagnosed with VHL disease due to the onset of lesions in other organs), Gd-enhanced magnetic resonance...
imaging should be performed every 2 years from the age of 11 years.

- Even in cases with asymptomatic cerebellar lesions of ≤2 cm or spinal lesions of ≤1 cm, if it is accompanied by a cyst or surrounded by edema, there may be rapid enlargement, and observation of the course should be performed once every 6 months or 1 year.
- HBs of the CNS should be surgically resected if they are symptomatic, with the exception of brain stem intramedullary tumors.
- In principle, surgical resection is recommended for symptomatic tumors, but it should be performed even for asymptomatic tumors if it is a brain stem tumor that is ≥1 cm or if it shows a tendency to grow.\(^{13-18}\)
- Stereotactic radiotherapy should be considered for the treatment of tumors that are difficult to resect surgically.\(^{19-27}\)
- Tumor control effects of radiotherapy are expected for CNS HBs, including those of the spinal cord and brain stem.
- Prophylactic irradiation for asymptomatic lesions is not recommended.
- The 5-year tumor control rate of radiotherapy is approximately 80%.\(^ {28-31}\)
- Radiotherapy is not recommended for expanding cystic lesions.

It is difficult to carry out a large-scale clinical trial because of the small number of VHL disease patients. For that reason, the VHL treatment guideline was not created entirely based on strong evidence, and it will be necessary to revise the guideline as appropriate in the future. However, even in its present level of refinement, it can be surmised that the guideline will be of great help to healthcare givers when providing medical care to VHL disease patients.

In addition, in 2014, the VHL Disease Study Group established a VHL disease severity classification for each organ. The classification deals mainly with the degree of interference with everyday social life. The severity classification for HB is as follows.

- **N0**: No imaging findings of a CNS HB.
- **N1**: Despite imaging findings of a CNS HB, there are no neurological symptoms.
- **N2**: There are mild neurological symptoms, but no problems with regard to daily and social life.
- **N3**: There are neurological symptoms, but with no problems with regard to daily and social life.
- **N4**: There are neurological symptoms and strong interference with daily and social life.

**Cooperation and partnership with a patients’ association:** A VHL disease patients’ association, named “Hotto Chain”, was established in Japan in 2003 (http://www.vhl-japan.org/). The VHL Disease Study Group requested the cooperation of this patients’ group and was able to carry out a status survey of VHL disease patients. In addition, study sessions have been held on a regular basis to raise the awareness of patients and their families with regard to VHL disease treatments. In this way, the VHL Disease Study Group has worked to promote cooperation and collaboration with the VHL disease patients’ group.

**Implementation of genomic medicine**

VHL disease is undeniably a disease in which tumors form in multiple organs. Nevertheless, it is clear that it is not an unmanageable disease, provided that regular follow-up is performed, tumors are discovered early after their onset, and treatment is started quickly thereafter. With such management, the prognosis of VHL disease patients is not all that much different from that of healthy people. Accordingly, for VHL disease, it can be said that it is necessary to provide genomic medicine based on genetic diagnosis. In fact, the American Society of Clinical Oncology (ASCO) recommends performing genetic diagnosis for VHL disease patients.\(^ {32}\) In 2012, the University of Tokyo Hospital established a VHL disease specialist outpatient clinic in its Neurosurgery Department to enable the implementation of genomic medicine for VHL disease. The clinic is characterized by providing not only multidisciplinary treatment of HB, but also (I) genetic diagnosis, (II) genetic counseling, and (III) medical collaboration for the treatment of multiple organ involvement (Fig. 4). These three characteristics are explained in more detail below.

**Genetic diagnosis:** The most important aspect of implementing genomic medicine is the accurate diagnosis of VHL disease. However, several papers have reported that 4–14% of those who had only a single HB and were not diagnosed with VHL disease clinically had germline mutations in the VHL gene.\(^ {33,34}\) We must avoid a scenario in which VHL disease goes untreated because it could not be diagnosed. As such, all patients with HBs should undergo genetic testing for VHL disease.\(^ {35}\) Genetic diagnosis of VHL disease is carried out by analyzing for the presence or absence of an abnormality in the VHL gene. Today, we can ask a gene-testing laboratory to perform direct sequencing to analyze for an abnormality in the VHL gene at the base sequence level. However, in around 10% of patients with VHL disease, there is no abnormality in the base sequence of the VHL gene, and the disease is due to a large deletion in chromosome 3, which is where the VHL gene is located. This deletion cannot be detected by direct sequencing. Therefore,
to be able to diagnose those cases as well, in our hospital, we also perform genetic diagnosis using the multiplex ligation-dependent probe amplification (MLPA) method.\textsuperscript{36–38} The MLPA technique is a method based on polymerase chain reaction (PCR), and it is possible to detect abnormalities in the copy number of up to 50 genomic DNA sequences in a single procedure. For this reason, unlike with the aforementioned direct sequencing method, with the MLPA method, we are able to detect deletions from the exonic level of genes to the chromosomal level. In fact, the VHL Disease Treatment guideline states that a high degree of genetic diagnosis of VHL disease can be achieved by the combined use of the direct sequencing and MLPA methods.

Genetic counseling: The National Society of Genetic Counselors defined genetic counseling as the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.

(National Society of Genetic Counselors (2005), http://nsgc.org/p/cm/ld/fid=386)

Patients diagnosed with VHL disease should be regularly followed-up, and their families need to recognize their own risk of VHL disease onset. Therefore, they need to have a good understanding of the genetics involved in VHL disease. Genetic counseling aims to meet this need.\textsuperscript{40} In fact, Rantana et al. reported that patients’ accuracy in risk perception was poor before genetic counseling.\textsuperscript{40} Our hospital has a clinical geneticist who performs genetic counseling on an outpatient basis. In addition, through cooperation with the Department of Clinical Genomics, which is a specialized department for genetic counseling, we are able to provide genetic counseling to all VHL disease patients in our care, as well as their families. Many of the patients who come to our specialist outpatient clinic have never received genetic counseling in the past.

Fig. 4 For providing genomic medicine to VHL disease patients, it is especially important to establish (I) accurate genetic diagnostic techniques, (II) genetic counseling capabilities, and (III) medical collaboration, including with urology departments, etc.
After undergoing counseling in our clinic, most patients gain—for the first time—a good understanding of VHL disease and are better equipped to cope with it going forward.

Medical collaboration for the treatment of multiple organ involvement: As described above, because VHL disease entails not only HBs, but also tumors in multiple organs, it can be surmised that proper and effective treatment requires the involvement of various departments in addition to the neurological surgery department. However, conventionally, each department involved in treating VHL disease patients has dealt only with lesions in the organ(s) of their specialty, and it cannot be said that there has been a system for applying a holistic approach. In our hospital, we have placed a VHL disease specialist in each department, and we have constructed a system in the specialist outpatient clinic of the Neurosurgery Department to promote medical collaboration for the treatment of multiple organ involvement. As a result, we are now able to provide holistic medical care to VHL disease patients.

Conclusion

The VHL Disease Study Group carried out a nationwide epidemiological survey of VHL disease in Japan with the objective of creating a database for VHL disease in Japanese. Based on that database, the Study Group drew up a VHL Disease Treatment Guideline and a severity classification. The authors’ hospital is now implementing genomic medicine for VHL disease. Going forward, further elucidation of the epidemiology of VHL disease and the development of genomic medicine are needed so that an even better medical care system can be constructed for VHL disease patients in Japan.

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Conflicts of Interest Disclosure

The authors declare no conflict of interest (COI). All authors who are members of the Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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**Address reprint requests to:** Shunsaku Takayanagi, MD, PhD, Department of Neurosurgery, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. e-mail: takayanagi-nsu@umin.ac.jp