Brain Vascular Malformation Consortium: Overview, Progress, and Future Directions

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ABSTRACT

Brain vascular malformations are resource-intensive to manage effectively, are associated with serious neurologic morbidity, lack specific medical therapies, and have no validated biomarkers for disease severity and progression. Investigators have tended to work in "research silos" with suboptimal cross-communication. We present here a paradigm for interdisciplinary collaboration to facilitate rare disease research. The Brain Vascular Malformation Consortium (BVMC) is a multidisciplinary, interinstitutional group of investigators, 1 of 17 consortia in the Office of Rare Diseases Research of the Rare Diseases Clinical Research Network (RDCRN). The diseases under study are: familial cerebral cavernous malformations type 1, common Hispanic mutation (CCM1-CHM); Sturge-Weber syndrome (SWS); and brain arteriovenous malformation in hereditary hemorrhagic telangiectasia (HHT). Each of the 3 study projects is developing biomarkers for disease progression and severity, and has established scalable relational databases for observational and longitudinal studies that are stored centrally by the RDCRN Data Management and Coordinating Center. Patient support organizations (PSOs) are a key RDCRN component in the recruitment and support of participants. The BVMC PSOs include the Angioma Alliance, Sturge-Weber Foundation, and HHT Foundation International. Our networks of clinical centers of excellence in SWS and HHT, as well as our PSOs, have enhanced BVMC patient recruitment. The BVMC provides unique and valuable resources to the clinical neurovascular community, and recently reported findings are reviewed. Future planned studies will apply successful approaches and insights across the 3 projects to leverage the combined resources of the BVMC and RDCRN in advancing new biomarkers and treatment strategies for patients with vascular malformations.

Approximately 25 million people in the United States are affected by an estimated 7000 rare diseases or conditions leading to significant morbidity and mortality. An operational definition of "rare disease" was proposed in an amendment[1] to the Orphan Drug Act of 1983:[2] "any condition affecting fewer than 200,000 Americans or a disease with a greater prevalence but for which no reasonable expectation exists that the costs of developing or distributing a drug can be recovered from the sale of the drug in the United States." In addition to the unmet health care needs, many rare diseases result from unique single or multiple gene defects that offer insight into normal biological function. Understanding the pathogenesis of rare diseases may advance our understanding of other more common medical disorders.

The longitudinal natural history has not been sufficiently characterized for many rare diseases, including the neurovascular disorders we are studying: (1) cerebral cavernous malformations type 1, common Hispanic mutation (CCM1-CHM); (2) Sturge-Weber syndrome (SWS); and (3) brain arteriovenous malformation (bAVM) in hereditary hemorrhagic telangiectasia (HHT). Treatment can be equally challenging, with many unanswered questions and a lack of evidence-based guidelines concerning clinical management. Patients with rare diseases comprise small populations, in most instances

dispersed over wide geographic areas. There are significant logistic challenges to the systematic study of rare diseases,[3] which requires collaboration of scientists from multiple disciplines sharing what are typically scarce research resources and patient samples. The Brain Vascular Malformation Consortium (BVMC), part of the Rare Diseases Clinical Research Network (RDCRN),[4] addresses these challenges.

History and Organization of the Rare Diseases Clinical Research Network

A National Institutes of Health (NIH) Office of Rare Diseases Research (ORDR) Special Emphasis Panel made recommendations on the special research and health care issues posed by rare diseases,[5] followed by passage of the Rare Diseases Act of 2002 directing the ORDR to support regional centers of excellence for clinical research into, training in, and demonstration of diagnostic, prevention, control, and treatment methods for rare diseases. The ORDR responded with the creation of the RDCRN utilizing a U54 (NIH cooperative agreement award) mechanism. The first request for application for funding was issued in 2003 and represented a collaboration between ORDR and several NIH institutes/centers, including the National Center for Research Resources (NCRR), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Child Health and Human Development (NICHD), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and National Heart Lung and Blood Institute (NHLBI). A similar request for application for funding was then issued by ORDR in 2008, in collaboration with NINDS, NICHD, NIAMS, NIDDK, NHLBI, the National Institute of Alcohol Abuse and Alcoholism, National Cancer Institute, and National Institute of Dental and Craniofacial Research, to which the BVMC projects responded. The BVMC is currently in year 4 of the 5-year funding cycle.

The RDCRN is a cooperative network composed of 17 Rare Diseases Clinical Research Consortia (RDCRC) and a single Data Management and Coordinating Center (DMCC) to facilitate clinical research in rare diseases undertaken by the RDCRC. A steering committee is composed of the principal investigators (program directors) of each RDCRC, the principal investigator (director) of the DMCC, the RDCRN program director from the ORDR of the National Center for Advancing Translational Sciences, and program scientists from the NIH. Each RDCRC generally includes a consortium of clinical investigators, institutions, Clinical and Translational Science Award units (or their equivalent), and relevant organizations, including patient support organizations (PSOs), for the study of a group of at least 3 rare diseases that are relevant to the NIH. The DMCC provides RDCRN coordination, data management infrastructure, and other administrative support.

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Having the BVMC function within the larger context of the RDCRN has created the opportunity to collaborate with other consortia with varying degrees of common interests, and importantly, the opportunity to interact with more than 95 PSOs, representing more than 200 rare disorders. The RDCRN has allowed an economy of scale in terms of providing assistance with the standardization of data collection, both conceptually and in terms of data collection instruments. The DMCC also provides the center's support in protocol and amendments for submission to the NIH, preparation for audits, and assistance in obtaining institutional review board approval for their protocols. Biannual RDCRN in-person steering committee meetings and every-other-year conferences provide a venue for interactions and discussions that directly benefit development of the BVMC. If the individual projects existed in isolation from the BVMC and RDCRN context, these opportunities would be missed, including the ability to learn from what has worked—and not worked—for other rare disease consortia.

Brain Vascular Malformation Consortium

The 3 projects correspond to the 3 rare neurovascular disorders (**Figure 1**). These projects are supported by an administrative unit and a genetics and statistical analysis core (GSAC). Two additional components are a training module that provides partial support for 1 rare disease research trainee per year and a pilot/demonstration project program that supports 1 pilot project per year (**Table 1**).

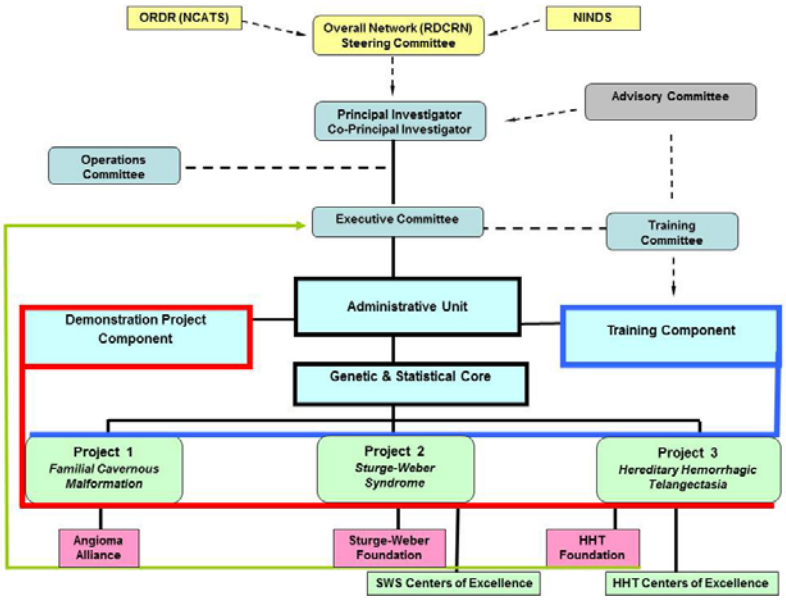
In many respects, both basic and clinical researchers in the area of cerebrovascular malformations have tended to

Table 1. Brain Vascular Malformation Consortium Rare Disease Research Trainees and Pilot Projects

Year	Training Period	Institution	Project No.	Trainee
1	9/1/09-6/30/10	University of New Mexico	1	Yasir Khan
2	7/1/10-6/30/11	University of Toronto and Yale University	3	Takeo Nishida
3	7/1/11-6/30/12	Kennedy Krieger	2	Eboni Lance
4	7/1/12-6/30/13	University of California, San Francisco	1	Hélène Choquet
5	7/1/13-6/30/13	TBD		TBD
Year	**Project Pilot Period**	**Institution**	**Project No.**	**Description**
1	9/1/09-6/30/10	Kennedy Krieger	2	Establish reliability of quantitative EEG, transcranial Doppler, behavioral outcomes, and optical coherence tomography in SWS: a first step toward biomarker development
2	7/1/10-6/30/11	University of New Mexico	1	Permeability in MRI in cerebral cavernous type 1 in New Mexico: effects of statins
3	7/1/11-6/30/12	University of Toronto	3	Topical antiangiogenic therapy of telangiectasia in HHT: proof of concept
4	7/1/12-6/30/13	TBD		
5	7/1/13-6/30/14	TBD		

Abbreviations: EEG, electroencephalogram; HHT, hereditary hemorrhagic telangiectasia; MRI, magnetic resonance imaging; SWS, Sturge-Weber syndrome; TBD, to be determined.

Figure 1. Organizational chart for Rare Diseases Clinical Research Consortium administrative functions (light blue) and experimental service cores serving all projects. NINDS, National Institute of Neurological Disorders and Stroke; ORDR, Office of Rare Diseases Research; NCATS, National Center for Advancing Translational Sciences; RDCRN, Rare Diseases



work in "research silos" with suboptimal cross communication among diseases, even those in the same vascular bed. This "silo problem" was one of the motivations for NINDS to hold a workshop on Biology of Vascular Malformations of the Brain in March 2008,[6] in which most of the BVMC key investigators participated; the workshop was a key event to set the stage for development of the BVMC.

The 3 disorders were chosen for several reasons. Even though causative genetic defects have been identified for 2 of the 3 disorders, they are all poorly understood in terms of biological mechanisms, are resource-intensive to manage effectively, and have high probability of serious neurologic morbidity. Each disease is characterized by the development of a distinct set of vascular malformations and a unique spectrum of clinical and phenotypic outcomes, for which biological risk factors are either poorly understood or completely unknown.

All 3 disorders share a common biological theme: a brain vascular phenotype resulting from failure of the normal physiological mechanisms of blood vessel formation or maintenance. Thus, each of these disease states represents some degree of disordered angiogenesis and vascular remodeling.[6-9] Although they presumably proceed through different final pathways, insights from one disease may help illuminate the biological basis of or treatment strategies for the others as well as related cerebrovascular malformations that are more common.[9] Considerable overlap exists in the neurologic morbidity of these disorders, eg, intracranial hemorrhage (ICH), seizures, and focal deficits. Therefore, therapy aimed at stabilizing the abnormal vessels in one disorder may well be adaptable to more than one disease. Importantly, specific medical therapy is not currently available for any of the 3 disorders. The establishment of clinical research infrastructure and data registries will facilitate multicenter clinical studies of all types.

Central themes of the BVMC are the development of patient registries (both cross-sectional and longitudinal) and biomarkers; the program structure (**Figure 1)** serves these themes. The first aim of each project is development of a deidentified relational database. Each of the diseases has a large number of dedicated clinicians and scientists studying basic and clinical aspects of the disease, while providing the best currently available care. Nonetheless, progress has been hampered, and the pace of discovery held back, by the lack of a central repository for standardized clinical information with common data elements. The extant registries for each disease were either center-specific or, in the case of foundation listings, developed for communication purposes and not designed as research-grade relational databases that utilized common data elements. The BVMC infrastructure and the attendant central support from the DMCC have been a historic opportunity that has brought together investigators in each disease area and created large-scale observational databases of affected individuals. The BVMC structure allows for cross-collaboration of experienced researchers between and within projects that includes sharing of resources and knowledge. Monthly conferences with BVMC key personnel, DMCC representatives, and NIH program staff are highly interactive, and provide continual external input into the ongoing management and development of the BVMC.

Biomarker development is intended not only for use in risk stratification but also for insights into the genetic and molecular underpinnings of these diseases. The methodologic technology for creating and validating biomarkers can be shared across projects, facilitated by the GSAC. Biomarkers for gauging natural history and disease progression risk are particularly important for vascular lesions of the brain: the risk of intervention, eg, surgical or endovascular therapy, may outweigh the risks of the natural history of minimally symptomatic disease. This issue has recently gained attention through an international multicenter randomized controlled trial that is assessing whether patient outcome is less morbid by conservative management than best procedural intervention (endovascular embolization, microsurgical resection or radiotherapy, alone or in combination). This study, A Randomized Trial of Unruptured Brain Arteriovenous Malformations *(*ARUBA*),*[10] has sparked considerable controversy as to whether unruptured bAVMs need to be treated because of their relatively benign course (low spontaneous hemorrhage rate and relatively mild sequelae of ICH) and relatively high risk of causing iatrogenic injury in minimally symptomatic patients.[11-13] Interventionalists argue that intervention results in a better long-term outcome for patients, based on referral-based retrospective case series.[14,15] What is not controversial, however, is the need for better risk markers that can identify patients at highest risk for spontaneous hemorrhage in order to optimally and expeditiously provide treatment.[16] Although ARUBA is concerned with sporadic bAVMs, the issues confronting

invasive treatment of HHT-related bAVMs, and indeed all minimally symptomatic cerebrovascular lesions, are highly relevant to the focus of the BVMC and the clinical neuroscience community.

Patient Support Organizations

A mission-critical aspect of the RDCRN program is the collaborative involvement of PSOs—with their leadership as coinvestigators—to provide patient-oriented input, advice on assessing research priorities, assistance with public awareness of the program, and facilitation of patient recruitment. To our knowledge, this is the first incorporation of PSOs as active collaborators in an ongoing scientific project in cerebrovascular disease.

Commonalities Among the 3 Patient Support Organizations

The PSOs of the BVMC are international voluntary organizations driven by similar missions to inform and support individuals affected by vascular malformations, and to facilitate improved diagnosis and management through education and research. The PSOs work to support the scientific community by funding direct research through pilot grants, and by providing valuable communication and coordination roles, including organizing the annual BVMC executive committee face-to-face meeting. On a rotational basis, the meeting is planned to precede a CCM, HHT, or SWF patient and family conference. This cooperative planning allows for BVMC investigators to both attend the executive meeting and present at the PSO-sponsored family conference in a cost- and time-effective manner.

The PSOs, in addition to scientists, government, industry, and medical professionals, are key stakeholders in the collaborative efforts working to advance pathobiological understanding and clinical care for brain vascular malformations. Each of the PSOs supports independent disease registries and patient databases. These registries are distinct from the aims of the BVMC, as they were designed for communication, to collect unique datasets, and/or to include data and/or participants beyond the scope of the BVMC projects. The purpose of each of these registries was not to be a prospective natural history study; however, the PSO registries provided valuable models for the design and development of BVMC natural history databases.

The PSOs also aim to improve quality of life after diagnosis. To this end, the PSOs sponsor advocacy and provide information and support for patients and their families. Up-to-date disease information is provided through the individual PSO Web sites and newsletters. Each Web site also features a discussion forum, and regional networking is facilitated and encouraged through social media and at patient and family conferences. These activities foster a sense of community and trust between the PSOs and affected individuals. The strength of these community relationships and the tireless efforts of the PSOs offer the BVMC both support from the patient community as well as the vital observational data that helped to originally identify commonalities among CCM, HHT, and SWS, and initiated the genesis of the BVMC.

All 3 PSOs have patient registries, but they primarily are geared toward patient identification, whereas the BVMC databases are more granular, use standardized common data elements, and were specifically designed to address individual project aims, including longitudinal follow-up.

The BVMC PSOs include the following 3 groups:

Angioma Alliance (AA). In addition to the common patient support efforts described above, AA is the host of the CCM Scientific Meeting. Since its inauguration in 2005, this annual meeting has brought together an international group of basic, translational, and clinical researchers, including investigators from all 3 BVMC projects, to share prepublication findings and explore possible collaborations. In an effort to facilitate recruitment for research and clinical studies, AA launched the International Cavernous Angioma (CCM) Patient Registry in 2010. This Web-based communication tool is designed to link the patient and research communities to distribute information about studies to potential participants. Importantly, the AA-managed patient registry is inclusive of all forms of CCM, and is intended to facilitate recruitment for a wide range of CCM research studies. In 2006, to further support the CCM research community, AA established an independent CCM DNA & Tissue Bank, including genetic testing facilities and an extensive clinical database. The data collected include information from medical records, imaging, and patient interviews, with annual follow-up. These data are intended to mirror and expand on those collected by the Scottish Intracranial Vascular Malformation Study (SIVMS),[17,18] and were also used as a model for development of the BVMC CHM-CCM research registry to allow for future international collaboration and use of a comprehensive dataset including all forms of CCM.

Sturge-Weber Foundation (SWF). To speed the pace of discovery in SWS, the SWF funded a translational research summit and subsequently established centers of excellence, to collaborate in gathering clinical and scientific data and establishing standards of diagnosis and care. The SWF has cosponsored 2 NIH workshops on angiogenesis: the biology of vascular malformations[6] and an NIH meeting specifically focused on research priorities for SWS. The SWF has been instrumental in facilitating the collection of the blood, brain, and skin tissue samples for scientific research stored at the National Disease Research Interchange. Additionally, the SWF has collected clinical data in a natural history registry of more than 4300 patients with SWS that includes up to 25 years of follow-up, as well as demographic and at least partial clinical data on both the patients and their family members. Data collection for this database project is ongoing.

HHT Foundation International. The HHT Foundation is engaged in increasing access to expert HHT care throughout North America, overseeing and supporting the establishment of 16 North American HHT Treatment Centers of Excellence to date. The Foundation brought HHT genetic testing to clinical care in North America, advocating for patients and facilitating negotiations among stakeholders. The Foundation's grant program has funded 11 research grants totaling $2.5M since 2004, as well as 12 Young Researcher Grants. Several conferences have been supported by the HHT Foundation, including an NIH HHT Research Conference in June 2006, the conference for development of the first International Guidelines for the Diagnosis and Management of HHT,[19] a National Disease Research Exchange for HHT tissue research, 2 NIH workshops on angiogenesis and neurovascular malformations, and the Genetics and Genomics of Vascular Disease Workshop sponsored by the North American Vascular Malformations Research meeting. Since the first International Scientific Conference in 1996, HHT Foundation International has supported 10 biennial international conferences bringing together basic, translational and clinical researchers. In terms of patient, family, and physician education, the Foundation has sponsored 2 hands-on physician training programs, 16 national conferences, 4 regional conferences in collaboration with HHT Centers of Excellence, and continuing education medical programs for physicians and health care professionals. Furthermore, the HHT Foundation supported the first-ever Centers for Disease Control HHT Conference in March 2008. The Foundation has worked closely with the BVMC investigators, actively participating in participant recruitment through communications with their large patient contact registry and social networks. In addition, the Foundation is currently driving an initiative to develop a prospective North American HHT database, including comprehensive data regarding natural history of all aspects of HHT, which will be complementary to the BVMC HHT bAVM database.

Main Disease Projects

Project 1: Cerebral cavernous malformation (cavernous angioma; cavernoma; cryptic vascular malformation) is a vascular abnormality of the central nervous system (brain and spinal cord) with extra–central nervous system involvement of skin in some patients. The lesions consist of a cluster of abnormal, dilated capillaries invariably containing extravasated blood products of various ages. Lesions are low flow without shunting of blood, and are detected on magnetic resonance imaging (MRI) by the typical patterns of blood breakdown products (**Figure 2**).[20] CCMs are a significant source of neurologic morbidity, including ICH, seizures, and focal neurologic deficits. CCMs can occur in a solitary, sporadic form, or occur in an autosomal dominant condition typically characterized by multiple lesions on brain MRI that appear to increase with age (**Figure 3**).[21]

Figure 2. Magnetic resonance imaging scan of a 78-year-old man with cerebral cavernous malformations type 1, common Hispanic mutation (CCM1-CHM). Axial T2-weighted image (A) shows a posterior right temporal lobe typical CCM with reticulated, mixed signal internally and peripheral hemosiderin rim (arrow), and a few small additional small foci of low signal. The axial susceptibility-weighted image (B) is more sensitive for blood breakdown products and shows numerous areas of low signal intensity (dark areas on the image) within small CCMs.

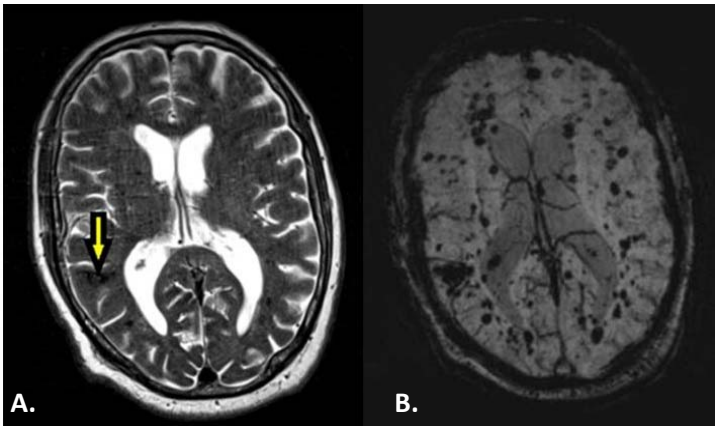
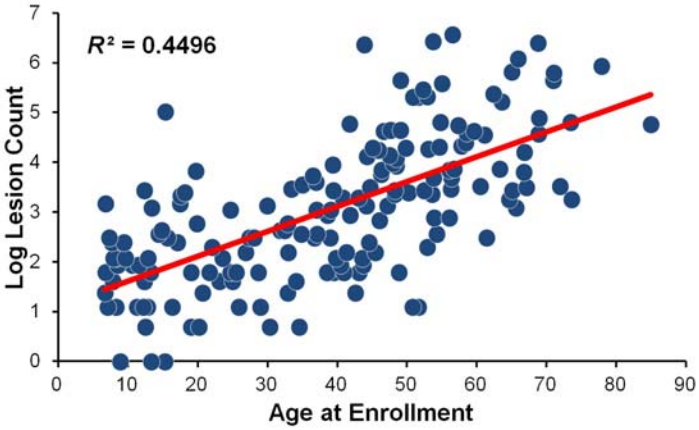


Figure 3. Scatterplot of log-transformed lesion count by age in 176 patients with cerebral cavernous malformations type 1, common Hispanic mutation (CCM1-CHM) showing a significant positive linear relationship (R^2 = 0.4496 , *P*< .001). Linear regression analysis showed a 5% increase in lesion count for every 1-year increase in age (95% CI=1.04-1.06, *P*< .001).



Project 1 studies one of the familial forms of the disease known as CCM1, caused by loss-of-function mutations in the *KRIT1* (Krev interaction trapped 1) gene. In the Hispanic population of New Mexico, virtually all cases are caused by the same *KRIT1* founder mutation (Q248X), termed the common Hispanic mutation (CHM).[22-24] Genealogy studies conducted in New Mexico families with CCM suggest the mutation originated in a common ancestor from Spain who relocated to Mexico in the 1500s, traveled up El Camino Real, and settled in the New Mexico area. Because of this founder mutation, the autosomal dominant transmission of this disease, large Hispanic families, and settling in this geographic area, CCM1-CHM is a huge public health burden in the state of New Mexico. The estimated population prevalence of CCM1-CHM worldwide is less than 1 in 100,000, but in New Mexico the prevalence is much higher at 15 in 100,000.

The natural history of CCM is not clearly established, nor is it known why patients with CCM present with a wide range in symptoms and lesions, even among those with the same gene mutation or age. The overall goal of this project is to identify and understand modifiers of disease severity in familial CCM to improve patient care and prognosis. The project will recruit a relatively large cohort (N = 500) of familial CCM1 cases, all carriers of the CHM (CCM1-CHM) and geographically clustered in New Mexico, to identify clinical characteristics and modifier genes influencing lesion burden, a marker for disease severity. We are also evaluating the association between lesion burden and risk of hemorrhage, seizures, and other neurologic sequelae. Results from this genetically homogenous group are likely to yield important findings that may have relevance to the CCM community at large.

Aim 1 is to establish a database of CCM1-CHM cases recruited through the University of New Mexico in collaboration with the RDCRN DMCC and the AA PSO. Thus far, we have recruited 218 patients toward our goal of 500 patients with familial CCM1-CHM by 2014. We are collecting detailed clinical characteristics, neurologic examinations, imaging features from MRI and susceptibility-weighted imaging, and blood specimens at baseline; we are also performing annual follow-up phone calls to obtain outcome information. We will identify clinical characteristics associated with lesion burden (ie, number of lesions) and define specific clinical and imaging features unique to this large cohort, paying particular attention to how the disease features cluster within families.

Table 2 summarizes characteristics for eligible participants enrolled in our study as of December 2012: 190 individuals from 43 families with ≥2 members and 42 singletons had partial or complete information entered from data collected at baseline visits. At study enrollment, most participants were symptomatic (88%), with a mean (SD) age of 39.1 (19.7) years; the mean age at diagnosis was younger (31.8 [19.3] years). Approximately 24% presented with a hemorrhage, and 26% had surgical resection for a CCM lesion. As expected, lesion count was highly variable and the distribution was right-skewed. The mean number of lesions was 59.5 (114.9) and the median was 18 (interquartile range, 6–50.5). Three persons had no lesions and 5 harbored a single lesion **(Figure 3)**, reflecting our ascertainment strategy of recruiting family members based on CCM1-CHM carrier status and not phenotype. This strategy ensures that we see a broad spectrum of phenotypes associated with the disease. Of interest, 2 of the individuals with a single lesion were in their third decade of life. Participants with CCM1-CHM also had a high prevalence of comorbid conditions. Clinically, most were neurologically normal (93%) and had little to no significant disability (88% had modified Rankin score of <3).

Aim 2 is discovery driven, based on the overarching hypothesis that there is a distinct set of genetic modifiers acting in concert with CCM1-CHM to result in higher lesion burden. We will perform a cross-sectional genome-wide association study (GWAS) to identify modifier genes influencing CCM lesion burden. We have already genotyped 176 CCM1-CHM cases using the Affymetrix Axiom® Genome-Wide LAT 1 (Axiom GW LAT) Human Array at the University of California, San Francisco, and will test for association with lesion burden when we achieve our target enrollment of 500. Our primary GWAS analysis will adjust for potential confounders, including age, gender, Hispanic ancestry, and other important clinical covariates identified in Aim 1, followed by additional fine-mapping and haplotype analysis. Secondary analysis will examine copy number variants.

Table 2. Baseline Demographic and Clinical Characteristics of 190 Patients With Familial CCM1-CHM Enrolled in Project 1.

Baseline Characteristic	Value
Female gender, No. (%)	123 (65)
Age at enrollment, mean (SD), year	39.1 (19.7)
Age at diagnosis, mean (SD), year	31.8 (19.3)
Symptomatic at presentation, No. (%)	122 (64)
Hemorrhage	46 (24)
Seizure	46 (24)
NH-FND	7 (4)
Headache	41 (22)
Ever symptomatic, No. (%)	167 (88)
Hemorrhage	58 (31)
Seizure	63 (33)
NH-FND	9 (5)
Headache	101 (53)
Comorbidities, No. (%)	
Obesity	68 (38)
Hypertension	56 (29)
Hyperlipidemia	98 (52)
Depression/anxiety	34 (18)
Diabetes	22 (12)
Arthritis	21 (11)
Hypothyroidism	13 (7)

Abbreviations: CCM1-CHM, cerebral cavernous malformations type 1, common Hispanic mutation; NH-FND, Nonhemorrhagic Focal Neurological Deficit.

Aim 3 is to perform longitudinal analysis of lesion growth (number and size) over the study observation period. The first 100 participants enrolled in year 1 of the study will be brought back for a follow-up MRI at year 5 to assess change in lesion growth. Exploratory outcomes will include changes in modified Rankin scores and Short Form -36 quality-of-life scores.

Project 1 utilizes a unique patient population and practice setting at the University of New Mexico, along with statistical and genetics expertise at the University of California, San Francisco from the GSAC, to identify biomarkers for CCM disease progression, using both cross-sectional and longitudinal designs. The longitudinal part of the design will be especially valuable, as it will permit estimates for risk of hemorrhage (and clinical sequelae), development of seizures or epilepsy, and headaches over the period of study. Rare disease research is challenging; however, we have benefited greatly from the RDCRN infrastructure, including the RDCRN registry, and AA for helping to support educational family meetings and the recruitment of study participants and for identifying additional participants for the study. Publications for Project 1 include references 9, 25-28.

Project 2: Innovative Approaches to Gauge Progression of Sturge-Weber Syndrome

Sturge-Weber syndrome is a rare congenital vascular disorder characterized by brain, ocular, and cutaneous vascular anomalies. Clinically, SWS is characterized by a facial port-wine birthmark, glaucoma and choroidal angioma, leptomeningeal angioma, epilepsy, stroke-like episodes, headache, and cognitive impairment. The characteristic extracranial manifestations are facial port-wine stain and glaucoma. The population prevalence is estimated to be 5 in 100,000.

The severity of neurologic symptoms varies greatly but can include blindness, paralysis, severe mental retardation, or sudden unexplained death from epilepsy. The cellular and molecular etiology of SWS remains unknown. However, the disease is characterized by variable degrees of vascular overgrowth, and histopathologic studies of SWS lesion tissue show abnormal expression of vascular phenotypes and angiogenic factors. These observations suggest that the primary defect in SWS is abnormal angiogenesis (vascular development). The hypothesis of aberrant angiogenesis forms one arm of our central hypothesis and suggests that longitudinal analysis of angiogenesis biomarkers may

have clinical relevance in the prediction of disease severity and outcome.

The vascular malformation of the brain in SWS consists of enlarged and tortuous leptomeningeal vessels and dilated deep venous vessels, most often involving the occipital cortex. Impaired venous drainage from the involved brain regions results in reduced arterial perfusion to these regions.[29] Single-photon emission computed tomography studies in young infants with SWS have shown that cerebral perfusion goes from being generous in the very young infant to being deficient in the involved cortical region by the end of the first year.[30]

The vessels of leptomeningeal angiomas are thin-walled venous structures, many of which are hugely dilated. The vessels are innervated only by noradrenergic sympathetic nerve fibers[31] and show increased endothelin-1 expression,[32] suggesting there may be increased vasoconstrictive tone in SWS. The impaired venous drainage through these vessels results in reduced microcirculation and hypoxia in the surrounding brain tissue. Microscopically, the cortical tissue underlying the angioma shows neuronal loss, calcium deposition, hypoplastic blood vessels, breakdown of the blood–brain barrier and gliosis, as reviewed in Comati et al.[8] Changes are also seen in the underlying white matter: there is an early phase of hypermyelination, which is then followed by white matter loss.[33]

The brain lesions in SWS are progressive, suggesting there is ongoing angiogenesis in these lesions. Consistent with this idea, increased levels of endothelial proliferation and apoptosis were seen in leptomeningeal vessels from patients with SWS relative to those of controls,[8] as well as overexpression of fibronectin.[34] The vessels also showed increased levels of expression of vascular endothelial growth factor (VEGF), VEGF receptors 1 and 2, neuropilin, Tie-2 receptor tyrosine kinase, and hypoxia-inducible factor (HIF)-1α and HIF-2α.[8] Thus, leptomeningeal angiomas in SWS do not appear to be static lesions, but rather show evidence of ongoing vascular remodeling.

The second arm of our central hypothesis stems from clinical observations and relates to the role of early somatic mosaicism (somatic mutation) in neurocutaneous mosaic phenotypes. Rudolf Happle first proposed the concept of mutation of autosomal lethal genes occurring early in development and surviving only in a mosaic state, to explain the genetic basis of several syndromes characterized by the following characteristics: (almost always) sporadic occurrence, distribution of lesions in a scattered or asymmetrical pattern, variable extent of involvement, lack of diffuse involvement of entire organs, and equal sex ratio.[35] This phenotypic pattern was termed paradominant inheritance. Significantly, SWS was one of the phenotypes Happle used to formulate his theory.

The central hypothesis brings these 2 seminal concepts together and proposes that SWS is caused by an early somatic mutation in a gene involved in angiogenesis. We propose that a somatic mutation occurs in a cell derived from the primordial vascular plexus. As predicted by the paradominant inheritance hypothesis, we propose that this gene is essential to survival because of its critical importance in angiogenesis, such that only somatic mutations in this gene are compatible with life. The extent of the phenotype associated with SWS would depend on the time during development when the somatic mutation occurred. Angiogenesis biomarkers might therefore correlate with disease severity. Our work has investigated this central hypothesis with clinical, biochemical, and molecular analyses organized under the following aims.

Aim 1 creates a standardized SWS registry and clinical database to comprehensively define the phenotype of SWS brain involvement **(Figure 4)** and foster future clinical research. The registry is a resource for future clinical and molecular investigations of SWS. This database is being created through the collaborative efforts of the lead clinical site at the Kennedy Krieger Institute, the DMCC,

Figure 4. Axial magnetic resonance images from the same individual with Sturge-Weber syndrome showing typical imaging findings of loss of signal on susceptibility-weighted imaging in the right parietal-occipital region, indicating calcification (thick arrow, left panel) and leptomeningeal and choroid plexus enhancement (thin arrows, right panel).

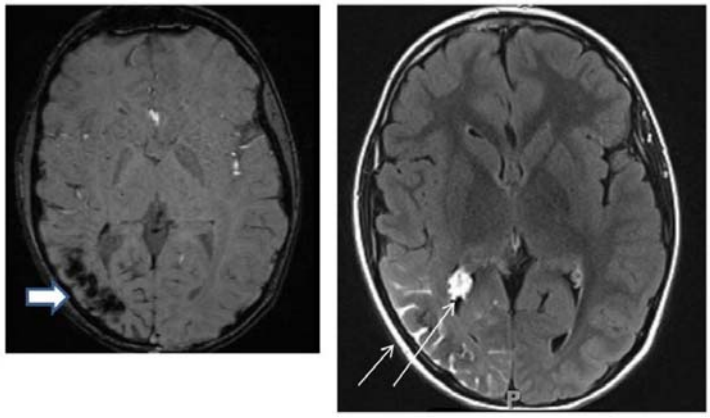


Table 3. Characteristics of Patients With Sturge-Weber Syndrome, Obtained From Deidentified Research Questionnaire

Characteristic	Study Population, No. (%)
Gender (N = 108)	
Male	46 (42.6)
Female	62 (57.4)
Brain involvement (N = 108)	
Unilateral	94 (87.0)
Bilateral	14 (13.0)
Skin involvement (N = 108)	
Unilateral	55 (50.9)
Bilateral	41 (38.0)
None	12 (11.1)
Eye involvement (N = 108)	
Unilateral	43 (39.8)
Bilateral	10 (9.3)
None	53 (49.1)
Unknown	2 (1.9)
Epilepsy (N = 108)	
Yes	97 (89.8)
No	8 (7.4)
Unknown/unattainable	3 (2.8)
Age at diagnosis (N = 101)	Mean = 19.8 mo Range = 0-624 mo

the SWF, and the other recruiting SWF centers of excellence. It has also utilized the statistical resources of the BVMC. The contributing centers are currently working together to analyze the current database **(Table 3)** and are being solicited for ideas for future research utilizing it.

Aim 2 evaluates the hypothesis that use of urine levels of angiogenesis biomarkers will correlate with and predict the severity of neurologic progression in SWS. The study protocol collects data at baseline and then at 1 and 2 years' follow-up. Neurologic status is estimated using the Sturge-Weber neurologic clinical score.[36] This biomarker study is a collaboration between the lead clinical site and the laboratory of Dr. Marsha Moses at Boston Children's Hospital.

Aim 3 is the search for somatic mutations causing SWS. In collaboration with the University of Maryland Brain Bank, the National Disease Research Interchange, and the SWF, we have banked autopsy or biopsy vascular tissue and matched control tissue from patients with SWS. We will use a variety of whole genome approaches to search for somatic mutations in affected SWS tissue. Aim 3 is a collaborative effort between laboratories at the Kennedy Krieger Institute (Pevsner and Comi) and the Marchuk laboratory at Duke University, with the support of the SWF aiding in the donation of tissue to brain and tissue banks. Identifying a causative somatic mutation(s) in SWS will uncover the underlying disease mechanism, and this could, in turn, lead to a definitive biomarker for SWS and the development of novel therapeutic strategies.

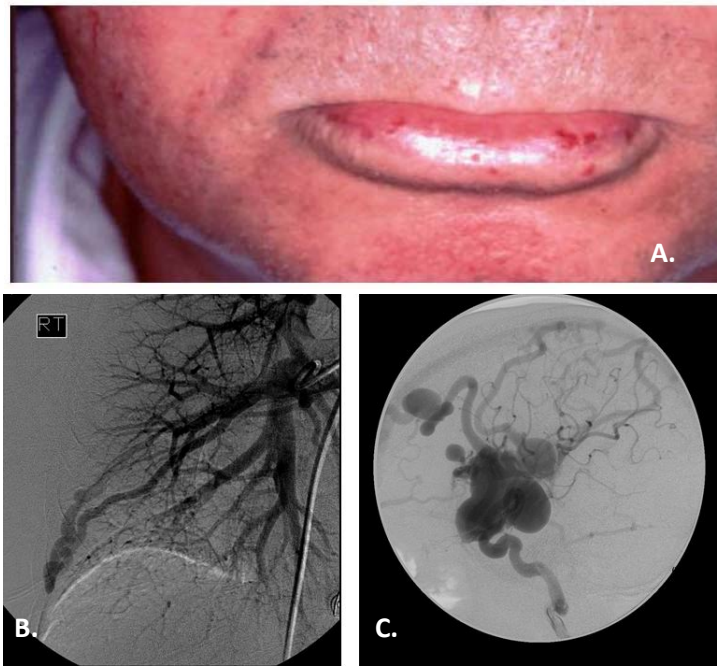
This work has resulted in 2 original clinical research manuscripts,[37,38] a case report,[39] and a review of SWS.[40] A trainee project with funding from the BVMC summarized the results of treating children with SWS with low-dose aspirin, describing the low rate of complications, and quantifying outcomes through the use of the SWS neurologic clinical score applied prospectively.[37] This article adds significantly to the growing literature suggesting that low-dose aspirin is safe, reduces stroke-like episodes, helps to control seizures, and may improve outcome in SWS. Our work has also clarified the approach to the diagnosis and treatment of central hypothyroidism in patients with SWS.[38] Pilot funding from the BVMC has aided the development of additional biomarkers relevant to SWS, including quantitative electroencephalogram, medical rehabilitation scales, transcranial Doppler, and optical coherence tomography; this has resulted in a submitted manuscript and additional in-progress manuscripts. Significant progress has been made on all 3 of the main aims mentioned previously such that other manuscripts directly relating to the aims are currently in submission or progress. The collaborative efforts of the BVMC have provided essential resources and a framework by which the work described herein was made possible.

Project 3: Cerebral Hemorrhage Risk in Hereditary Hemorrhagic Telangiectasia.

Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) is a disorder of mucocutaneous fragility and vascular dysplasia. The most common presentation is epistaxis, followed by gastrointestinal bleeding. Furthermore, patients harbor AVMs in the pulmonary, hepatic, and cerebral circulations; the latter is associated with ICH and attendant risk of neurologic morbidity. HHT is an autosomal dominant disorder with a prevalence of at least 10 in 100,000. The prevalence of bAVMs in the general population is approximately 1 in 100,000, of which less than 5% are due to HHT.

The disease is an autosomal dominant condition characterized by vascular malformations, specifically developing mucocutaneous telangiectasia and solid-organ AVMs (primarily brain, lung, and liver) **(Figure 5).** Because of the relative rarity of bAVM lesions in HHT (pulmonary AVMs are much more common in HHT), the systematic study of their epidemiology is difficult. Risk factors for spontaneous ICH are a major management consideration. However, while the clinical behavior of sporadic bAVMs has been studied in some depth, comparable studies for HHT are limited to small series of 20 to 30 cases each. Our project represents the first large-scale collaboration of a number of HHT centers of excellence in North America to perform a study of ICH in patients with HHT harboring bAVMs **(Table 4).** Aim 1 is the construction of an HHT clinical research database. Data include demographics, symptomatology, cerebral angioarchitecture, and information about other organ involvement. Approximately half of the HHT cases have mutational analysis (causative gene) information available.

Figure 5. Hereditary hemorrhagic telangiectasia is characterized by the presence of (A) mucocutaneous telangiectasia and (B and C) organ arteriovenous malformations (AVMs): (B) lung AVMs demonstrated on pulmonary angiogram, and (C) 2 brain AVMs on catheter angiogram in a 4-year-old boy.



The database has been successfully created with comprehensive data collected for 551 recruited patients with HHT to date, 129 of whom have bAVMs. The population characteristics are reported in **Table 5** and are similar to those reported in the literature, suggesting that this is a representative population of patients with HHT.

Table 4. Hereditary Hemorrhagic Telangiectasia Centers of Excellence Across North America Recruiting for Brain Vascular Malformation Consortium Study Project 3.

Participating Site Name	Principal Investigator
Georgia Regents University	James R. Gossage
Johns Hopkins University School of Medicine	Doris Lin
Mayo Clinic	Karen Swanson
University of California, Los Angeles	Justin McWilliams
University of California, San Francisco	William L. Young
University of Utah	Jamie McDonald
Washington University School of Medicine	Murali Chakinala Andrew White
Yale University	Robert White Jr.
University of Alberta	Dilini Vethanayagam
University of British Columbia/ St. Paul's Hospital	Pearce Wilcox
University of Toronto/Hospital for Sick Children	Felix Ratjen
University of Toronto/St. Michael's Hospital	Marie Faughnan

The database is used to serve the other aims but will also serve as a platform to foster further HHT research, and the centers of excellence that comprise the network have been solicited to submit projects that will utilize the database.

Aim 2 determines risk factors for hemorrhage in patients with HHT bAVMs. Although well known for sporadic AVMs, the risk factors for ICH in HHT bAVMs are poorly characterized, and it is unknown whether the risk is similar to that of sporadic cases. This information is essential for rationale planning of potentially high-risk interventional

therapy (surgery, embolization, and radiation). At the completion of data collection, we will perform a cross-sectional analysis of ICH risk factors in patients with HHT. We hypothesize that HHT bAVM lesions will have a lower incidence of hemorrhagic presentation and comprise mostly low-risk AVMs (Spetzler-Martin grade 1 or 2).[41] We predict that, although the fraction of HHT bAVM cases with ICH at presentation will be lower than that for sporadic bAVMs, adjusting for the effects of demographic, clinical, and angioarchitectural risk factors will render HHT bAVMs comparable to sporadic cases. Second, we will compare new ICH rate between patients with HHT bAVMs to an already collected cohort of sporadic bAVMs after diagnosis but before any intervention (natural history). We will compare ICH rate in this HHT cohort to that in a combined database of sporadic bAVMs that has been created using both University of California, San Francisco and University of Toronto cases. This will be a longitudinal study, analogous to the various analyses that have been undertaken for sporadic AVMs.[42-45]

While recruitment and data collection for this aim continue in 12 centers across North America, we have capitalized on our collaborative network and published new clinically relevant observations for HHT bAVMs. We quantified the association between bAVM multiplicity and HHT, compared with sporadic bAVMs, demonstrating that the presence of bAVM multiplicity is highly predictive of the diagnosis of HHT.[46] In addition, we reported gene-phenotype correlations among patients with HHT bAVMs, the first and largest series of its kind with 161 patients, from BVMC participants and patients from collaborating centers.[47] The clinically relevant observations were that bAVMs can occur in patients of all HHT genotypes and that ICH can occur in all HHT genotypes and at any age, from infancy onward. Presently, we are combining data from the BVMC with databases from BVMC centers to study hemorrhage-free survival in patients with HHT bAVMs versus sporadic bAVMs.

Aim 3 is an exploratory investigation to identify common genetic markers for increased ICH risk utilizing a candidate gene approach. Polymorphic variation in several genes, eg, single nucleotide polymorphisms (SNPs), mostly inflammatory, is associated with ICH in patients with sporadic bAVMs.[48-53] Although probably not causal, certain alleles are associated with increased risk of ICH at presentation or new ICH after diagnosis but before any intervention. Therefore, such SNPs could be developed as biomarkers for clinical management and risk stratification. The primary analysis will be cross-sectional, using genotype as the predictor and the outcome as ICH presentation versus other presentations, but genotype associations with longitudinal risk of ICH will also be assessed.

In summary, the combined Project 3 aims will provide much-needed information about the natural history of bAVMs in HHT, quantifying the risk of ICH and describing risk factors for this morbid outcome. Publications for Project 3 include references 46 and 47.

Table 5. Recruited Hereditary Hemorrhagic Telangiectasia Population for Project 3.

Characteristic	Study Population, No. (%)[a] (N = 551)	Published Adult/Mixed Series,[19] %[b]
Female	338 (61)	60
Age, mean (range), year	46.1 (1-89)[c]	40-45
Epistaxis	437 (79)	50-96
Telangiectasia	421 (76)	80-90
Brain AVM	129 (23)[d]	5-23
Pulmonary AVM	235 (43)	15-50
HHT GI bleeding	75 (14)	25-30
Symptomatic Liver VM	22 (4)	8
Anemia	213 (39)	NA

Abbreviations: AVM, arteriovenous malformation; GI, gastrointestinal; NA, not available; VM, venous malformation.

[a] All values are shown as number (%) except for age.
[b] All values are shown as percentages except for age.
[c] Twenty-four children (aged <18 years) at registration.
[d] Targeted recruitment proportion of 25%.

SUMMARY AND FUTURE DIRECTIONS

The BVMC has provided critical infrastructure and research project funding for 3 important rare neurovascular disorders. The cohesiveness within and among research groups in the BVMC is a model for interdisciplinary and translational collaboration, which will certainly lead to further synergistic and parallel project development and funding. Key advances that have been accomplished or will be accomplished by the BVMC include but are not limited to: (1) understanding genetic modifiers of disease severity for familial CCM (Project 1); (2) the promise of identifying somatic mutations in a gene (or genes) that causes SWS (Project 2); and (3) improved understanding of underlying genotype (mutation)-phenotype correlations for HHT, as well as modifier genes for disease severity (Project 3). Furthermore, for both SWS and HHT, a high-quality relational database drawing from

a novel North American network of centers of clinical excellence has been accomplished. Current cross-project collaborations include evaluating urine angiogenesis biomarkers developed for disease severity and progression in SWS (Project 1) as markers for disease severity in CCM1-CHM and HHT. Moreover, SNPs associated with ICH in sporadic bAVMs being tested for HHT are being evaluated for their association with disease severity and progression in CCM1-CHM and SWS. The ORDR initiative to fund the RDCRC has been a historic and highly successful experiment to form a productive, effective, and durable alliance among a dedicated cadre of rare disease investigators, with the strongest possible support from 3 well-recognized and proactive PSOs.

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Appendix

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