Review Article | Neurointervention

eISSN 2005-8330
https://doi.org/10.3348/kjr.2020.1171
Korean J Radiol 2021;22(8):1379-1396

Korean Journal of Radiology
KJR

Rare Neurovascular Diseases in Korea: Classification and Related Genetic Variants

Yunsun Song[1], Boseong Kwon[1], Abdulrahman Hamed Al-Abdulwahhab[2], Yeo Kyoung Nam[1], Yura Ahn[1], So Yeong Jeong[1], Eul-Ju Seo[3], Jong-Keuk Lee[4], Dae Chul Suh[1]

[1]Division of Neurointervention Clinic, Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [2]Department of Diagnostic and Interventional Radiology, Imam Abdulrahman Bin Faisal University, King Fahd Hospital of the University, Al-Khobar City, Eastern Province, Saudi Arabia; [3]Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [4]Asan Institute of Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Rare neurovascular diseases (RNVDs) have not been well-recognized in Korea. They involve the central nervous system and greatly affect the patients' lives. However, these diseases are difficult to diagnose and treat due to their rarity and incurability. We established a list of RNVDs by referring to the previous literature and databases worldwide to better understand the diseases and their current management status. We categorized 68 RNVDs based on their pathophysiology and clinical manifestations and estimated the prevalence of each disease in Korea. Recent advances in genetic, molecular, and developmental research have enabled further understanding of these RNVDs. Herein, we review each disease, while considering its classification based on updated pathologic mechanisms, and discuss the management status of RNVD in Korea.
Keywords: *Neurovascular; Rare diseases; Genetics; Classification; Diagnosis*

RARE DISEASES IN KOREA

The definitions of rare diseases vary across countries, and most are based on the prevalence, which ranges from 9 to 76 per 100000 individuals (Table 1) [1]. According to Orphanet, a representative portal dealing with rare diseases, 6172 rare disorders had been registered by 2020. In Korea, according to the procedures and standards of the Ministry of Health and Welfare (Rare Disease Management Act of 2015), "rare disease" is defined as a disease in which fewer than 20000 people are affected or which has an unknown prevalence due to diagnostic difficulty. Rare disease (희귀질환, huigwi jilhwan), in addition to cancer, cardiac disease, and stroke, has been supported to receive reduced statutory coinsurance rates (oneself burden rate, legal co-payment rate, 법정본인부담율, beopjeong bonin budamryul) by applying exempted calculation of health insurance (health insurance relieved co-payment policy, 건강보험산정특례, Keongang boheom sanjeong teukrye [kʌngaŋ bohʌm sanzʌŋ tu:ŋne]) in Korea since 2009. The website "Helpline" was established in 2006 to collect and provide general information (epidemiology, diagnosis, treatment, etc.) on 1038 rare diseases in Korea (https://helpline.kdca.go.kr/).

RARE NEUROVASCULAR DISEASES

Rare neurovascular diseases (RNVDs) have some features distinct to other rare diseases. First, RNVD may not be well-recognized as a rare disease unlike other well-known metabolic diseases and syndromic disorders. Second, the mortality and morbidity are relatively severe if RNVD is not properly treated because it affects the central nervous system (CNS) [2]. Third, RNVD is often difficult to treat

Received: September 26, 2020 **Revised:** December 7, 2020
Accepted: January 23, 2021
This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2018R1A2B6003143).
Corresponding author: Dae Chul Suh, MD, PhD, Division of Neurointervention Clinic, Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
• E-mail: dcsuh@amc.seoul.kr

Table 1. Definition of Rare Diseases in Each Country or Continent

Country/ Continent	Years	Definition	Prevalance Per 100000
Korea	2015	"Rare disease" refers to a disease in which fewer than 20000 people are affected or whose prevalence is unknown due to diagnostic difficulty, according to the procedures and standards of the Ministry of Health and Welfare	39.0
Japan	1995	"Rare and intractable diseases" refers to a disease of unknown etiology with no effective treatment that presents a major financial and psychological burden and that is rare, affecting fewer than 50000 patients	39.5
Taiwan	2000	"Rare diseases" refer to diseases with a prevalence lower than the standard proposed by the central government or with special circumstances, and reviewed by the "Review Committee for Rare Diseases and Orphan Drugs" as well as officially announced by the central government. The prevalence rate of rare diseases in the current public notice is lower than 1 in 10000 individuals	10.0
China	2010	Rare diseases are defined as "disorders with a prevalence of less than 1/500000 or with an incidence of less than 1/10000 among newborns"	0.2 (10 in newborn)
EU	1999	Conditions whose prevalence is not more than 50 per 100000 individuals	50.0
USA	1983	Any disease, disorder, illness, or condition affecting fewer than 200000 people in the USA is considered rare	60.4

Prevalence was calculated from the definition in each country based on the current population in 2020.

because medications and surgical treatment are ineffective in most cases. Fourth, recently, rapid advancements in neuroimaging and neurointervention and establishment of genetic and molecular mechanisms have led to a new phase in the diagnosis and treatment of RNVD [3-9].

This review focused on rare diseases that mainly involve the neurovascular, cerebrovascular, head and neck vascular, and spinal vascular systems with related genetic variants. Our goal was to establish a disease panel for RNVDs listed on representative databases worldwide and categorize the diseases based on recent advances in genetics, embryology, and molecular and developmental biology. We also estimated the current prevalence of RNVDs in Korea using the Health Insurance Review and Assessment (HIRA) data.

INCLUSION CRITERIA AND DISEASE SEARCH

In this review, RNVD is defined as any abnormality of the blood vessels within or supplying blood to the brain and spinal cord that does not exceed the global average prevalence threshold of 40 cases per 100000 individuals. In addition, vascular anomalies and hypervascular tumors in the head and neck region that do not belong to the CNS but have close developmental and embryonic relationships are also discussed in this review. We excluded rare systemic diseases causing secondary neurovascular conditions, such as congenital cardiac disease, hereditary thrombophilia, and inflammatory and immunologically mediated conditions (Behçet's disease, sarcoidosis, granulomatosis with polyangiitis, Kawasaki disease, Churg–Strauss syndrome, microscopic polyangiitis, polyarteritis nodosa, Henoch–Schönlein purpura, and cryoglobulinemic vasculitis) and vasculitis associated with infections, drugs, malignancy, radiation, and connective tissue disorders (lupus, Sjögren's syndrome, rheumatoid arthritis, scleroderma, and dermatomyositis).

We searched the electronic database, MEDLINE/PubMed, with terms "rare" paired with "neurovascular," "cerebrovascular," or "vascular." Articles were thoroughly reviewed, and reference lists were scanned for additional studies of potential relevance. We made a list of RNVDs by adding each disease and supplemented it by referring to review articles on these topics. Any case reports on CNS involvement in certain vascular syndromes that involve other systems were thoroughly reviewed for selection.

Rare disease databases of Orphanet (https://www.orpha.net) in Europe, National Organization for Rare Disorders (NORD, http://rarediseases.org) in the United States, and Helpline (https://helpline.kdca.go.kr/) in Korea were reviewed, and lists of neurovascular diseases were obtained and compared among the databases. Diseases were selected using the Korean Standard Classification of Diseases (KCD). We obtained statistical data from the HIRA database using KCD codes to estimate the disease prevalence in Korea.

https://doi.org/10.3348/kjr.2020.1171

Korean Journal of Radiology
KJR

Most genetic variants associated with RNVDs are rare and cause monogenic or Mendelian disorders. These known variants were identified in the Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org) [10]. However, common genetic variants related to neurologic disorders, such as cerebral infarction or hemorrhage, were not included in this review [11].

COMPOSITION OF AN RNVD PANEL AND PREVALENCE OF EACH DISEASE IN KOREA

We organized the RNVD disease panel with a total of 68 diseases (Table 2) and summarized the coverage in each database as a schematic diagram (Fig. 1). The Orphanet, NORD, and Korean Helpline databases contained 62 (91%), 30 (44%), and 22 (32%) diseases, respectively. Among the 68 RNVDs, OMIM included 46 (68%); however, the related genes were identified in only 42 diseases (62%). The number of patients with RNVDs registered in the HIRA database of Korea is summarized in Figure 2. Moyamoya disease was the most prevalent, with 14991 patients, followed by neurofibromatosis, Marfan syndrome, osteogenesis imperfecta, supravalvular aortic stenosis, Ehlers–Danlos syndrome (EDS), and hereditary hemorrhagic telangiectasia (HHT). In the remaining five categories, various diseases were classified together; hence, we could not calculate the number of patients with each disease.

After preparing an included disease pool or panel, we categorized them into vascular anomaly (malformation and tumor), connective tissue disease, small vessel disease (SVD), and others based on the pathophysiologic mechanism and neurological manifestation. The vascular anomaly group was further classified into vascular malformation and vascular tumor according to the International Society for the Study of Vascular Anomalies (ISSVA) classification [12] and included lesions involving the CNS and head and neck region. The connective tissue disease group included inherited diseases related to the synthesis and metabolism of extracellular matrix proteins, mainly collagen and elastin, leading to aneurysm, dissection, or rupture [13]. The SVD group included disorders with various pathophysiologic mechanisms involving the small vessels of the CNS and those that can potentially cause strokes, such as infarction or hemorrhage. Lastly, RNVDs with an uncertain pathology or not fitting any of the above classification were grouped into other diseases, and included vasculitis, which mainly involves the CNS, moyamoya disease, and hypervascular tumor [14].

Vascular Malformation and Tumor

Standardized nomenclature within the widely accepted ISSVA classification system serves as a foundation for the study of vascular anomalies [12]. Unlike vascular masses, vascular malformations are non-neoplastic and represent focal, defective morphogenesis. Vascular malformation is largely divided into simple, combined, malformations of major named vessels, and syndrome-associated malformations [12]. Simple and combined malformations are classified into capillary, lymphatic, venous, and arteriovenous malformation (AVM) according to the constituent malformed vessel type. Simply dividing into “high-flow” and “slow-flow” malformations depending on the presence of arterial components is also useful for diagnosis and treatment [15].

High-flow shunt lesions including AVMs and arteriovenous fistulae (AVFs) are relatively common and clinically important in the CNS. AVMs are characterized by abnormal connections between primitive arteries and veins with an intervening dysplastic microvascular bed, known as the nidus. AVFs present in a similar fashion, but without an intervening nidus.

The exact pathogenesis of the AVM is not yet known. There has been a controversy over whether AVM is a congenital or an acquired lesion that most likely involves an environmental trigger leading to increased angiogenesis compounded by an underlying genetic susceptibility involved in signaling pathways for angiogenesis and inflammation [16,17]. AVMs most commonly occur sporadically, and somatic mutations in *KRAS*, *BRAF* (brain and spine), and *MAP2K1* (head and neck region) genes, associated with the Ras-MAPK pathway, have recently been discovered [18-20]. AVMs can also be associated with inherited genetic disorders such as HHT and capillary malformation–AVM (CM–AVM) [21-23]. All HHT mutations (*ENG*, *ACVRL1*, *SMAD4*, and *GDF2*) appear to cause decreased BMP-Smad signaling that may lead in turn to increased angiogenesis, otherwise CM–AVM has loss-of-function mutations in *RASA1* (CM–AVM1) and *EPHB4* (CM–AVM2) genes, leading to activation of Ras-MAPK pathway [22,24,25]. Cerebral AVMs can also occur as a component of syndrome-associated malformations, such as the Parkes–Weber syndrome, which is characterized by multifocal CMs, high-flow shunt lesion, and limb overgrowth, or congenital lipomatous overgrowth, vascular malformations, epidermal

 https://doi.org/10.3348/kjr.2020.1171

Table 2. Prevalence and Neurovascular Manifestation of Rare Neurovascular Diseases with associated Gene and Pattern of Inheritance

Group	Subgroup	Disease	Gene	OMIM	Inheritance*	Neurovascular Manifestation	Prevalence† (100000)
Vascular malformation	High flow	Arteriovenous malformation	*KRAS/BRAF/MAP2K1*	108010	-	AVM	1–9
		Dural arteriovenous fistula	-	-	-	AVF	-
		Cerebral proliferative angiopathy	-	-	-	AVM	-
		Craniofacial arteriovenous metameric syndrome	-	-	-	Metameric AVM	1–9
		Spinal arteriovenous metameric syndrome	-	-	-	Metameric AVM	< 0.1
		Hereditary Hemorrhagic Telangiectasia	*ENG/ACVRL1/GDF2/ SMAD4*	187300/600376/601101/ 610655/615506	AD	AVM/AVF	10–50
		Capillary malformation-arteriovenous malformation	*RASA1/EPHB4*	608354/618196	AD	CM, AVM	-
		Parkes-Weber syndrome	*RASA1*	608354	AD*	CM, AVF, limb overgrowth	-
		CLOVES syndrome	*PIK3CA*	612918	-	CM, VM, LM, AVM	< 0.1
		Vein of Galen aneurysmal malformation	*RASA1/EPHB4/ ACVRL1*	618196	-	AVF, sinus malformation	-
		Dural sinus malformation	-	-	-	AVF, sinus malformation	-
	Low flow	Internal carotid agenesis	-	-	-	Arterial anomaly	< 0.1
		Familial cerebral cavernous malformation	*KRIT1/MALCAVERNIN/ PDCD10*	116860/603284/603285	AD	VM	10–50
		Sturge-Weber syndrome	*GNAQ*	185300	-	Metameric CM, other anomalies	1–9
		PHACE syndrome	-	606519	-	Arterial, other anomalies	< 0.1
		Craniofacial venous metameric syndrome	-	-	-	Metameric VM	1–9
		Klippel-Trénaunay syndrome	*PIK3CA*	149000	AD*	CM, VM, LM, limb overgrowth	< 0.1
		Mucocutaneous venous malformations	*TEK*	600195	AD	VM	< 0.1
		Blue rubber bleb nevus	*TIE2*	112200	AD*	VM	-
		Sinus pericranii	-	-	-	Venous anomaly	-
Vascular tumors	Benign	Tufted angioma	*GNA14*	607859	-	Vascular tumor	-
		Spindle cell hemangioma	-	-	-	Vascular tumor	-
	Locally aggressive/ borderline	Kaposiform hemangioendothelioma	*GNA14*	141000	-	Vascular tumor	< 0.1
		Hemangioendothelioma	-	-	-	Vascular tumor	-
		Papillary intralymphatic angioendothelioma	-	-	-	Vascular tumor	-
	Malignant	Angiosarcoma	-	-	-	Vascular tumor	0.1
		Epithelioid hemangioendothelioma	-	-	-	Vascular tumor	0.1

https://doi.org/10.3348/kjr.2020.1171

Table 2. Prevalence and Neurovascular Manifestation of Rare Neurovascular Diseases with associated Gene and Pattern of Inheritance (Continued)

Group	Subgroup	Disease	Gene	OMIM	Inheritance*	Neurovascular Manifestation	Prevalence† (100000)
Connective tissue disease	Collagen	Ehlers Danlos Syndrome	*COL3A1*	130050	AD/AR	Aneurysm, dissection	0.5–2
		Autosomal dominant polycystic kidney disease	*PKD1/PKD2/GANAB*	173900/613095/600666	AD	Aneurysm	10–50
		Osteogenesis imperfecta	*COL1A1/COL1A2/ IFITM5/SERPINF1/ CRTAP/P3H1/ PPIB*	166200/166210/166220/ 166230/259420/259440/ 610682	AD/AR	Aneurysm, dissection	10–50
	Elastin	Marfan syndrome	*FBN1*	154700	AD	Aneurysm, dissection	10–50
		Loeys-Dietz syndrome	*TGFBR1/TGFBR2/ SMAD3/TGFB2/TGFB3*	609192/610168/613795/ 614816/615582	AD	Aneurysm, dissection	-
		Pseudoxanthoma elasticum	*ABCC6*	177850	AR	Aneurysm, stenosis	1–9
		Arterial tortuosity syndrome	*SLC2A10*	208050	AR	Aneurysm, stenosis	< 0.1
		Supravalvular aortic stenosis	*ELN*	185500	AD	Steno-occlusion	10–50
		Familial bicuspid aortic valve	*NOTCH1/SMAD6*	109730/614823	AD	Aneurysm, dissection	-
	Generalized connective tissue disease	Neurofibromatosis type 1	*NF1*	162200/162210/613675	AD	Aneurysm, stenosis	10–50
		Spontaneous cervical artery dissection	-	-	-	Dissection	3.5–4.5
		Grange syndrome	*YY1AP1*	602531	AD/AR	Steno-occlusion	< 0.1
		Familial cerebral saccular aneurysm	*ARHGEF17/ANGPTL6/ ADAMTS15/RNF213/ THSD1*	617043/609336/607509/ 613768/105800	AD/AR	Aneurysm	-
		Giant or fusiform aneurysm	-	-	-	Aneurysm	-
Small vessel diseases		COL4A1/2-related small vessel disease	*COL4A1/COL4A2*	175780/614483	AD	Small vessel disease	-
		Hereditary cerebral hemorrhage with amyloidosis	*CST3/APP*	105150/605714	AD	Small vessel disease	< 0.1
		MELAS	*MTTL1/MTND5*	540000	Mitochondrial	Small vessel disease	0.1–0.9
		Fabry disease	*GLA*	301500	XR	Small vessel disease	10–50
		CADASIL	*NOTCH3*	125310	AD	Small vessel disease	0.1–0.9
		CARASIL	*HTRA1*	600142	AR	Small vessel disease	-
		CARASAL	*CTSA*	613111	AD	Small vessel disease	-
		Leukoencephalopathy with calcifications and cysts	*SNORD118*	614561	AR	Small vessel disease	< 0.1
		Retinal vasculopathy with cerebral leukodystrophy	*TREX1*	192315	AD	Small vessel disease	-
		Autosomal recessive leukoencephalopathy-ischemic stroke-retinitis pigmentosa syndrome	-	-	AR	Small vessel disease	< 0.1

https://doi.org/10.3348/kjr.2020.1171

Korean Journal of Radiology KJR

Table 2. Prevalence and Neurovascular Manifestation of Rare Neurovascular Diseases with associated Gene and Pattern of Inheritance (Continued)

Group	Subgroup	Disease	Gene	OMIM	Inheritance*	Neurovascular Manifestation	Prevalence† (100000)
Small vessel diseases		Coats plus syndrome	*CTC1/STN1*	612199/617341	AR	Small vessel disease	< 0.1
		Susac syndrome	-	-	-	Small vessel disease	-
		Hereditary diffuse leukoencephalopathy with spheroids	*CSF1R*	221820	AD	Small vessel disease	< 0.1
Others	Steno-occlusive large vessel diseases	Sneddon syndrome	*ADA2*	182410	AD*	Steno-occlusion	0.4
		Alagille Syndrome	*JAG1/NOTCH2*	118450/610205	AD	Steno-occlusion, aneurysm	1.5
		Aicardi-Goutières syndrome	*SAMHD1*	612952	AD/AR	Steno-occlusion	10–50
		Reversible cerebral vasoconstrictive syndrome	-	-	-	Steno-occlusion	-
		Moyamoya disease	*RNF213/ ACTA2/ GUCY1A3*	252350/607151/608796/ 614042	AD/AR/XR	Steno-occlusion	10–90
		Rare disorder with a moyamoya angiopathy	-	-	-	Steno-occlusion	-
		Multisystemic smooth muscle dysfunction syndrome	*ACTA2*	613834	AD	Steno-occlusion	< 0.1
	Vasculitis	Primary angiitis of the central nervous system	-	-	-	Vasculitis	-
		Giant cell arteritis	-	187360	-	Vasculitis	10–50
		Takayasu arteritis	-	207600	-	Vasculitis	1–9
	Hypervascular tumors	Head and neck paragangliomas	-	-	-	Hypervascular tumor	-
		Juvenile nasopharyngeal angiofibroma	-	-	-	Hypervascular tumor	0.6
		Hemangiopericytoma	-	234820	-	Hypervascular tumor	-
		Von Hippel-Lindau disease	*VHL*	193300	AD	Hypervascular tumor	1–9

*Reported in some cases, †The data of Orphanet were referenced. AD = autosomal dominant, AR = autosomal recessive, AVF = arteriovenous fistula, AVM = arteriovenous malformation, CADASIL = cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy, CARASAL = cathepsin A–related arteriopathy with strokes and leukoencephalopathy, CARASIL = cerebral autosomal recessive arteriopathy with subcortical ischemic strokes and leukoencephalopathy, CLOVES = congenital lipomatous overgrowth, vascular malformations, epidermal nevis, spinal/skeletal anomalies/scoliosis, CM = capillary malformation, LM = lymphatic malformation, MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, OMIM = Online Mendelian Inheritance in Man, PHACE = posterior fossa malformations, large facial hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities syndrome, VM = venous malformation, XR = X-linked recessive

Korean Journal of Radiology
KJR

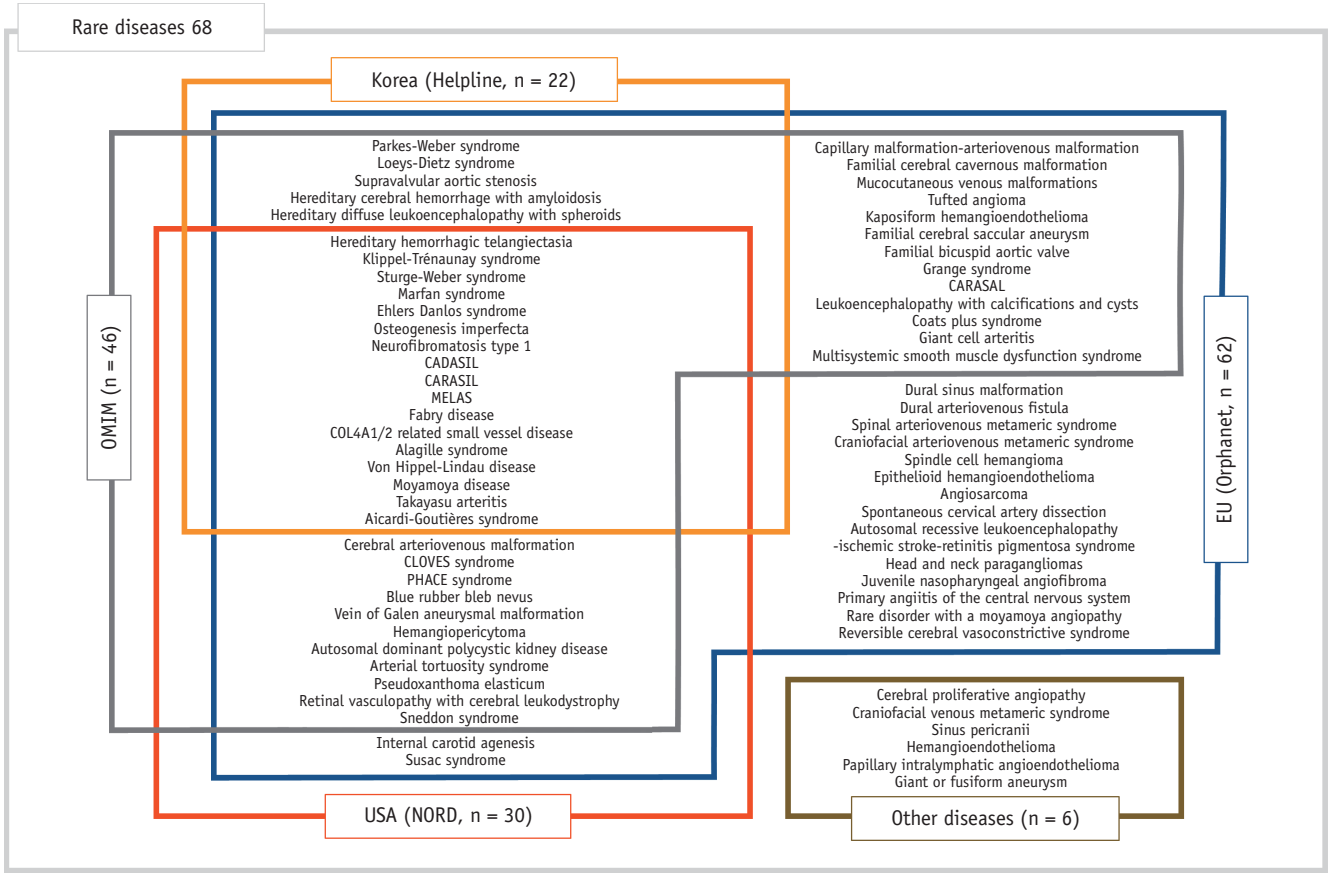

Fig. 1. Schematic representation of rare neurovascular diseases from the rare disease databases worldwide. CADASIL = cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy, CARASAL = cathepsin A–related arteriopathy with strokes and leukoencephalopathy, CARASIL = cerebral autosomal recessive arteriopathy with subcortical ischemic strokes and leukoencephalopathy, CLOVES = congenital lipomatous overgrowth, vascular malformations, epidermal nevis, spinal/skeletal anomalies/scoliosis, MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, NORD = national organization for rare disorders, OMIM = online mendelian inheritance in man, PHACE = posterior fossa malformations, large facial hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities syndrome

nevis, spinal/skeletal anomalies/scoliosis (CLOVES) syndrome [12]. It was once known to be sporadic and non-genetic but found to be associated with *RASA1* mutations in some cases [26]. Cerebral proliferative angiopathy is a rare distinct entity from classical brain AVM characterized by the presence of normal brain tissue intermingled with abnormal vessels and a proliferative nature [27].

Dural AVF is considered to be an acquired disease and may develop by neoangiogenesis due to various etiologies, including venous sinus thrombosis, trauma, and surgery [28]. Dural AVF considering different presentations according to the lesion location and venous drainage pattern may be associated with different orientations in the development of the neural crest and mesoderm [29]. Spinal AVM and/or fistula may have similar aspects but different development compared to the intracranial dura [30]. Vein of Galen aneurysmal malformations (VGAMs) and dural sinus malformations are specific forms of dural AVFs, which are developmental anomalies accompanied by venous sinus malformation that can be found antenatally [6,31,32]. These malformations are largely sporadic, possibly due to an early insult such as somatic mutations [31]. However, recent studies reported that some of the VGAMs were associated with germline mutations in *RASA1* and *EPHB4*, and *ACVRL1* genes [33-35].

Vascular neurocutaneous syndromes are considered to be a predominant disorder of the neurovascular system with secondary neuroectodermal changes [33]. Some of these disorders may show segmental distribution, involve a specific region of the face and brain, the spinal cord, or the cutaneous involvement of the related dermatome [36]. Head and neck endothelial cells (ECs), as elsewhere, derive from mesoderm and the tunica media of these vessels differentiates from neural crest cells [37]. Neural

https://doi.org/10.3348/kjr.2020.1171

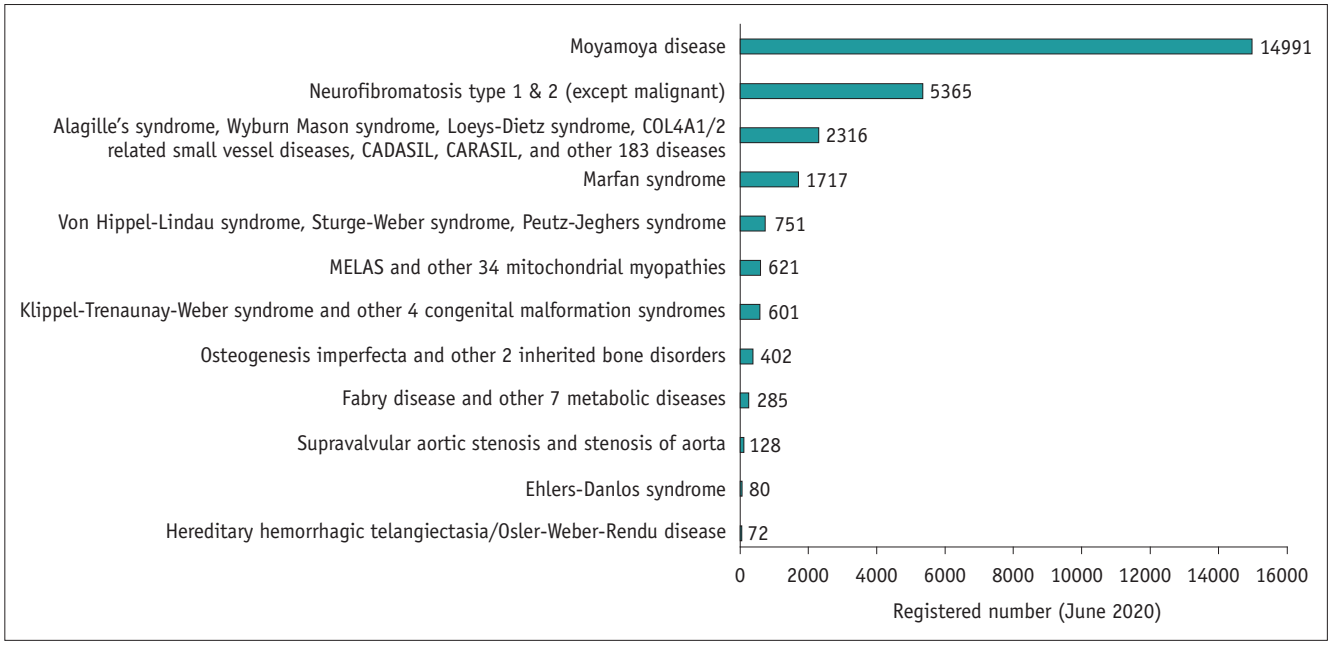

Fig. 2. Registered rare neurovascular diseases in Korea (from the Health Insurance Review and Assessment database). CADASIL = cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy, CARASIL = cerebral autosomal recessive arteriopathy with subcortical ischemic strokes and leukoencephalopathy, MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes

crest and mesodermal cells originating from a given transverse (metameric) level of the embryo finally occupy the same territory in the head [38]. Segmental vascular neurocutaneous disorders include craniofacial arteriovenous metameric syndrome, spinal arteriovenous metameric syndrome, craniofacial venous metameric syndrome, Sturge–Weber syndrome, posterior fossa malformations, large facial hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities (PHACE) syndrome. A somatic mutation developing in the region of the neural crest or adjacent cephalic mesoderm prior to migration could be expected to produce such malformations with a metameric distribution [36].

Slow-flow malformations that can involve the CNS or head and neck region are familial cerebral cavernous malformation (CCM), cutaneomucosal venous malformation (VMCM), blue rubber bleb nevus syndrome (BRBN), and and Klippel–Trénaunay syndrome. Most cases of CCM are sporadic and comprise a single lesion in the brain and spinal tissues, but familial cases of CCM with an autosomal dominant inheritance are rare and associated with multiple lesions [39]. Three genes (*KRIT1*, *CCM2*, and *PDCD10*) are known to cause familial CCM [39]. Venous malformation (VM) is relatively common in head and neck areas, which shows a good response to sclerotherapy [40-42]. Its prevalence or genetic association has not been well-recognized in Korea. Mutations in the *TEK* gene encoding TIE2 have been reported to cause VMs of various clinical spectrums, including inherited VMCM, sporadic unifocal VM, multifocal VM, and BRBN, according to the mode of mutation acquisition [43]. BRBN is a non-inherited disorder characterized by multiple cutaneous and gastrointestinal VMs and rarely accompanying venous anomalies in the brain [44]. Klippel–Trénaunay syndrome is a rare congenital vascular malformation syndrome characterized by a combination of capillary and lymphatic malformations, VMs, and limb overgrowth [45]. Congenital developmental anomalies include ICA agenesis and sinus pericranii, which is a rare venous anomaly abnormally connecting the intracranial dural sinuses with the epicranial veins [46].

Vascular masses included in the 2018 ISSVA classification are subsequently, broadly subdivided by their malignant potential: benign, locally aggressive or borderline, and malignant [12]. Vascular tumors commonly presented in head and neck areas in pediatric ages include tufted angioma, spindle cell hemangioma, pyogenic granuloma, kaposiform hemangioendothelioma, hemangioendothelioma, papillary intralymphatic angioendothelioma, angiosarcoma, and epithelioid hemangioendothelioma, while excluding relatively common infantile hemangioma and congenital

https://doi.org/10.3348/kjr.2020.1171

Korean Journal of Radiology
KJR

hemangioma [12].

Connective Tissue Diseases

The major component of the arterial and venous walls is the extracellular matrix, which contains mainly collagens and elastin [13]. Elastin provides reversible extensibility during cyclic loading of the cardiac cycle, while collagen provides strength and prevents failure at high pressures [47]. Based on the two major constituents of the connective tissue, these disorders can be divided into "collagenopathies" and "elastinopathies" [4].

EDS type IV results from mutations in the *COL3A1* gene, encoding type III procollagen [48]. Involvement of arteries of large and medium diameters, such as cervical artery dissection, intracranial aneurysms, and carotid–cavernous fistula, have been described in EDS type IV [49]. The weak and excessive collagen is suggested to play a central role in the pathogenesis of different manifestations of autosomal dominant polycystic kidney disease (ADPKD) [49]. The most frequent neurovascular complication of ADPKD is intracranial aneurysms, accounting for only 5–9% of cases but occurring three- to five-fold more often than in the general population [50]. Osteogenesis imperfecta is a heterogeneous group of inherited connective tissue disorders characterized by skeletal abnormalities. Although infrequent, ruptured intracranial aneurysm, moyamoya-like disease, carotid–cavernous fistula, and aortic and cervical artery dissections have been reported [51]. This disease is an autosomal dominant disorder caused by mutations in *COL1A1* and *COL1A2*, coding for the α1(I) and α2(I) chains of type I collagen, respectively [52].

There are several genetic diseases with neurovascular manifestation, associated with elastic fiber system. Marfan syndrome is an autosomal dominant disease caused by *FBN1* mutation which encodes the fibrillin-1 protein, an important component of the elastic fiber system [53]. The clinical signs are mainly musculoskeletal, ocular, cardiac with aortic and mitral valve anomalies, and aortic aneurysms and dissections [54]. Although proximal aortic dissection may extend into the cervical arteries, there is no evidence that spontaneous cervical artery dissection (SCAD) is prevalent in Marfan syndrome. Similarly, there is no definite evidence that cerebral aneurysms are more common in Marfan syndrome than in the general population [55]. Loeys–Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder caused by mutations in several genes related to the transforming growth factor-β (TGF-β) signaling pathway. Elastic fiber fragmentation and abnormal collagen deposition were demonstrated in aortic explants from LDS patients [56]. LDS shows facial dysmorphism, aortic aneurysm, and neurovascular involvement such as arterial tortuosity, aneurysm, and dissection [57,58].

Pseudoxanthoma elasticum is a genetic metabolic disease that causes mineralization of elastic fibers of the skin, eyes, and blood vessels [59]. Arterial tortuosity syndrome is an autosomal recessive disorder characteristic by tortuosity, elongation, stenosis, and aneurysm formation in the major arteries secondary to disorganization of elastic fibers in the medial layer of the arterial wall [60]. The syndrome is caused by loss-of-function mutations in the *SLC2A10* gene that is associated with elastin maturation [61].

Supravalvular aortic stenosis caused by mutations in the elastin gene (*ELN*), leads to disorganization of the lamellar architecture of the tunica media, irregular elastic fibers and smooth muscle (SM) cell hypertrophy [62]. Bicuspid aortic valve (BAV) is relatively common and occasionally appears as a familial form or feature of connective tissue disorders [63]. Several genes related to familial BAV have been identified, and the association between familial BAV and intracranial aneurysm has been reported [64].

In addition, although the exact pathology has not been identified, several diseases are probably caused by connective tissue dysfunction. Neurofibromatosis type I (NF1) is characterized by café-au-lait spots and dermal neurofibromas, which result from abnormalities in neural crest-derived cell types [65]. NF1-related vasculopathy may include steno-occlusion of cerebral arteries and aneurysms, resulting in hemorrhage or AVF. It possibly results from loss of neurofibromin function, participating in downregulating the Ras-MAPK pathway, causing alteration of the normal process of vascular maintenance and repair [66].

SCAD is a major cause of stroke in young adults [67]. The exact pathogenesis of SCAD has not been identified. However, the fact that various connective tissue and vascular disorders, such as Marfan syndrome, EDS, and fibromuscular dysplasia (FMD), and familial history are associated with SCAD in some cases, suggests an underlying arteriopathy possibly related to a generalized extracellular matrix defect [68]. Grange syndrome is a rare autosomal recessive syndrome caused by homozygous *YY1AP1* mutations, which is involved in the pathway for DNA repair in vascular SM cells [69]. The syndrome is characterized by arterial stenosis similar to focal FMD, congenital cardiac defects, brachydactyly/syndactyly, fragile bones, and

 https://doi.org/10.3348/kjr.2020.1171

learning disabilities [69]. FMD is not a rare disease, with a prevalence of 3–4% [69]. However, familial FMD was reported in approximately 5% of the population, in which a heterozygous variant of *YY1AP1* is suggested as a cause of the inherited subgroup [70]. FMD mainly causes stenosis and occlusion of renal and cervical arteries and may lead to ischemic stroke [70].

Intracranial aneurysm is a relatively common disease with a prevalence of approximately 3% but rarely occurs as a familial or refractory giant or fusiform subtypes. Recently, five candidate genes (*ARHGEF17*, *ANGPTL6*, *ADAMTS15*, *RNF213*, and *THSD1*) have been identified for familial intracranial aneurysms using next-generation sequencing [71-75]. Giant or fusiform aneurysms are rare and difficult to treat so may be classified as a rare entity distinguished from general aneurysms [76].

Small Vessel Diseases

SVD is defined in various ways [77], but in this review it refers to diseases that mainly involve cerebral small arteries or arterioles. Cerebral SVDs are important causes of stroke (deep infarctions or hemorrhages), cognitive decline, and age-related disability. There are different subtypes according to their pathophysiology. Although arteriolosclerosis is a common cause of SVD, a group of rare hereditary subtypes and associated genetic mutations have been reported recently (Table 2).

COL4A1 and *COL4A2* mutations have been recognized as the cause of type IV collagen-related diseases such as familial porencephaly and hereditary angiopathy with nephropathy, aneurysm, and cramps syndrome [78]. The cerebrovascular manifestations such as leukoencephalopathy, lacunar infarcts, microbleeds, and intracerebral hemorrhages result from increased fragility of small vessels [78-80]. Cerebral amyloid angiopathy is a distinct group of amyloidosis that involves, exclusively or predominantly, the CNS. It may be hereditary or sporadic, and share clinical, pathological and biochemical features with Alzheimer's disease [81]. Inflammatory SVD (vasculitis) is also an important subgroup of cerebral SVD, but it is usually part of a systemic disease [82], and will not be addressed in detail in this review.

Other rare SVDs included mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), Fabry disease, hereditary cerebral hemorrhage with amyloidosis, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), cathepsin-A-related arteriopathy with strokes and leukoencephalopathy (CARASAL), leukoencephalopathy with calcifications and cysts, retinal vasculopathy with cerebral leukodystrophy, autosomal recessive leukoencephalopathy, ischemic stroke, retinitis pigmentosa syndrome, Coats plus syndrome, Susac syndrome, hereditary diffuse leukoencephalopathy with spheroids, and Sneddon syndrome.

Others

Others diseases which seemed to be difficult to categorize into the preceding disease categories were steno-occlusive large vessel diseases, including Alagille syndrome, Aicardi–Goutieres syndrome, reversible cerebral vasoconstriction syndrome, moyamoya disease, rare disorder with moyamoya syndrome (Down syndrome, sickle cell anemia, neurofibromatosis type 1, radiation, connective tissue disorders, or infection), and multisystemic SM dysfunction syndrome, vasculitis, and hypervascular tumors.

EMBRYOLOGICAL CONSIDERATION OF RNVDS

While reviewing the literature, databases and diseases codes, we found out that it would be necessary to make a certain process to be included in RNVDs with several guideline or criteria. Such criteria included vessel wall component from 3 germ layers (endothelium from mesoderm and others from the neural crest), relation with connective tissues (collagen or elastin) and genetics (genetic vs. non-genetic disorder). We applied recent research progress on the dysfunction in endothelium, SM cell, pericyte, neural crest development, and connective tissue components.

Failure of ECs to properly undergo arteriovenous specification may contribute to vascular malformation and dysfunction, such as in HHT and CM–AVM where abnormal vessel structures, such as large shunts lacking clear arteriovenous identity and function, form and compromise peripheral blood flow [83]. Dysregulation of angiogenesis associated with the endothelium has been studied for AVM development or progression [84]. A recent study has revealed that the activation of the ERK1/2 pathway, which is downstream of Ras, was increased in ECs derived from brain AVMs compared to the ECs derived from normal brain vessels [85].

Vascular SM cells (VSMCs), stromal cells of the blood vessels, shows a complex mosaic developmental pattern

https://doi.org/10.3348/kjr.2020.1171

Korean Journal of Radiology
KJR

during embryogenesis with diverse embryonic tissues including the neural crest, the proepicardium, the mesothelium, the secondary heart field, and the somites [86]. Perivascular mural cells (VSMC and pericytes) and ECs may share a common progenitor, namely, Flk1-positive embryonic stem cells [86]. In early development VSMCs in arteries and veins and pericytes in capillaries muscularized primary vessels are formed by ECs. These provide structural stability, and functionality. With the most recent mechanisms, including the role of platelet-derived growth factor-B, Notch, and TGF-β, signaling pathways that regulate SMC and pericyte lineages, embryonic origin may have a role in regulating disease development by building on clinical studies on aneurysms and dissections [87,88].

In addition to most of the skeletal tissues and the connective tissues of the facial area, brain pericytes and meninges of the telencephalon are of neural crest origin except for the blood vessel endothelium which is derived from the mesoderm. Meninges in all the other parts of the CNS are of mesodermal origin [89]. Therefore, neural crest diseases include a variety of developmental neurovascular diseases including Sturge–Weber syndrome, PHACE syndrome, *ACTA2* mutation syndrome, and less frequently in the spontaneous progressive occlusion of the circle of Willis (so-called moyamoya disease) [90]. Cardiovascular lesions in these syndromes include coarctation of the aorta, persistent truncus arteriosus, patent ductus arteriosus, and coronary artery disease, and cerebrovascular lesions include agenesis and stenosis/occlusion of the internal carotid arteries, and moyamoya phenomenon.

GENETICS AND MOLECULAR PATHWAYS OF RNVDS

It is known that 88% of rare diseases can occur in children, and 72% of rare diseases are classified as genetic diseases [91]. In cases of neurovascular disease, many genetic variants associated with relatively common diseases such as atherosclerosis, ischemic or hemorrhagic strokes, have been identified so far [11]. These common variants with modest effects contribute in a multifactorial manner to confer susceptibility. Meanwhile, some rare, high-effects variants mainly contribute to the development of RNVDs, but also play a part in relatively common diseases such as familial intracranial aneurysms [71-74]. In addition, diseases previously thought to be simple aneurysms, AVMs, and strokes are increasingly being diagnosed as part of genetic disorders or syndromes owing to advancement of our understanding of RNVDs and genetic analysis [33,70,72,92-96]. With changes in diagnostic workflow

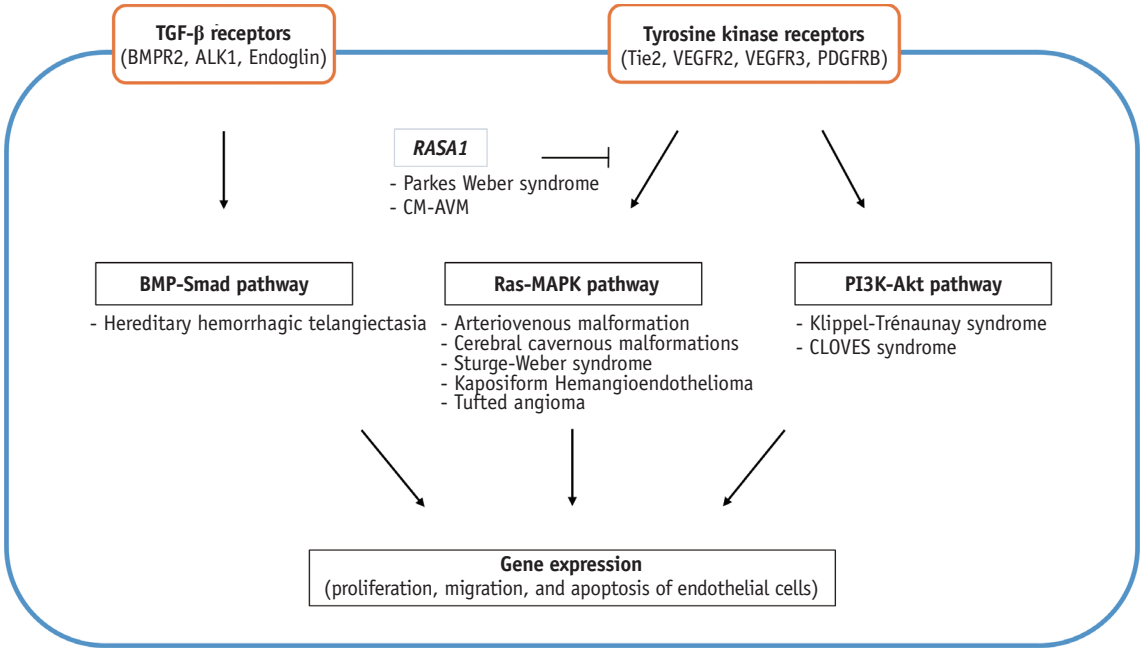

Fig. 3. Main signaling pathways involved in rare neurovascular diseases. ALK = Activin-Like Kinase Receptor, BMP = bone morphogenetic protein, BMPR = BMP receptor, CM-AVM = capillary malformation-arteriovenous malformation, CLOVES = congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi and spinal/skeletal anomalies and/or scoliosis, MARK = mitogen-activated protein kinases, PDGFR = platelet-derived growth factor receptor, PI3K = phosphoinositide 3-kinase, RASA1 = Ras p21 protein activator 1, TGF-β = transforming growth factor beta, VEGFR = vascular endothelial growth factor receptors

https://doi.org/10.3348/kjr.2020.1171

using next generation sequencing, it is expected that more undiagnosed rare Mendelian diseases will be revealed in the future, and this can be used to guide the development of diagnostic and therapeutic options [97-100].

In addition to the germline mutation, more somatic mutation will be identified by virtue of recent development of less expensive and less time-consuming gene study like next generation sequencing. Vascular malformations generally develop as a result of somatic mosaic mutations. Somatic mutations occur during or after embryonic development and are not inherited as part of the germline DNA [101]. It has been commonly mentioned that congenital disease is present at birth and acquired disease develops after birth. However, such definition of congenital vs. acquired is not applicable in the era of genetic molecular diagnosis because phenotypic manifestation of genetic defect varies according to the age and/or triggers after birth [102].

Determining the molecular basis of vascular anomaly has also facilitated the identification of lesions with an equivocal diagnosis with similar clinical manifestation, as well as development of therapeutic agents that act on the molecular pathway [103]. The Ras-MAPK pathway is typically involved in fast-flow AVMs and some vascular tumors, whereas the PI3K-Akt pathway is typically mutated in slow-flow components (Fig. 3) [101].

NEUROIMAGING IN RNVDS

Since RNVD is rare, obtaining the diagnosis based on imaging studies can often be difficult, and knowing which diseases can involve the neurovascular system can be of great help in the diagnosis. Advanced neuroimaging techniques, which are useful in diagnosing various neurologic diseases, are also expected to play an essential role in the evaluation of RNVDs [104-106]. For example, four-dimensional magnetic resonance angiography and arterial spin labeling are useful non-invasive imaging modalities in the detection, evaluation, and follow-up of intracranial shunt diseases (Figs. 4, 5) [107-109]. Vessel

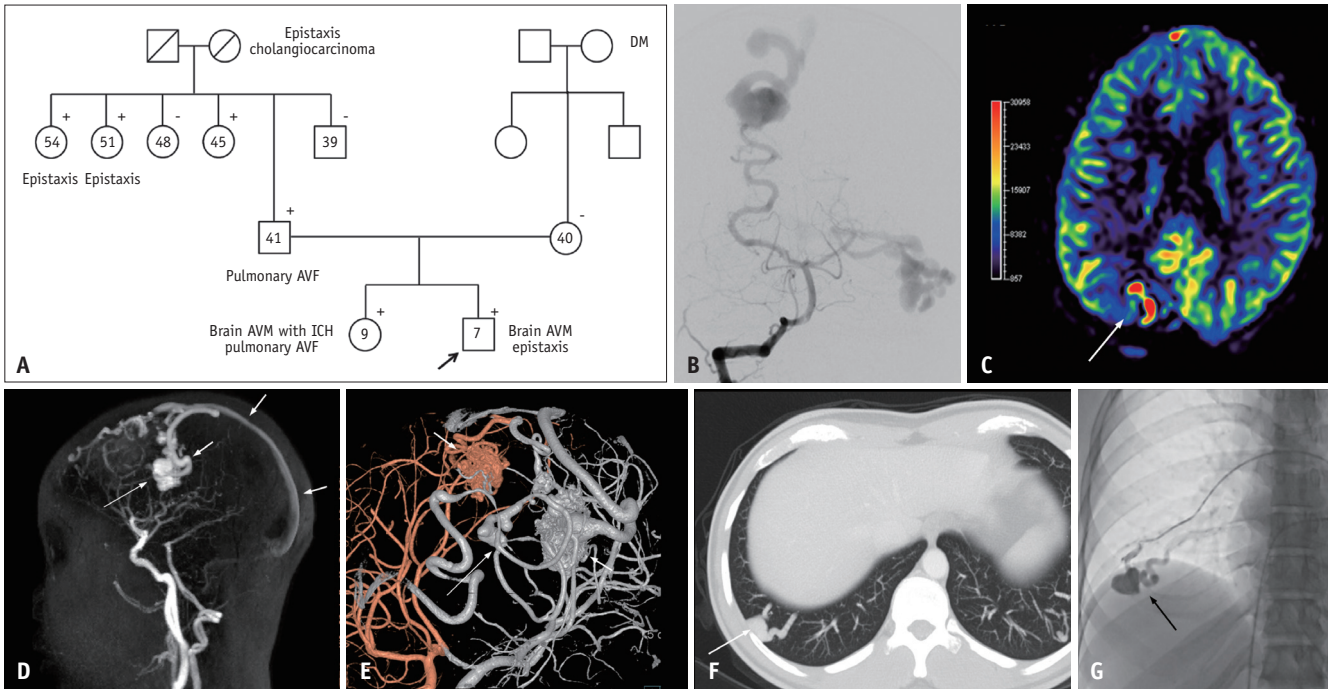

Fig. 4. Imaging evaluation of the family with hereditary hemorrhagic telangiectasia.
A. A pedigree chart for the family. Clinical manifestation and genetic variation status are marked. Positive sign (+) indicates the presence of the ENG c.808C>T hetero variant; negative sign (-) indicates its absence; An arrow in the pedigree chart indicates a proband. **B.** Two pial arteriovenous fistulas were visualized on the right vertebral arteriography in the proband. **C.** Arterial spin labeling perfusion imaging represents arteriovenous shunting (arrow) as red color in the right parieto-occipital lesion. **D.** Four-dimensional MRA showed early filing of the nidus (long arrow) and draining veins (short arrows) on arterial phase in the proband's sister. **E.** A fusion image of three-dimensional rotational angiography in both internal carotid arteries demonstrated multiple arteriovenous malformations (short arrows) and fistula (long arrow). **F, G.** A pulmonary arteriovenous fistula (arrows) was demonstrated on the chest CT **(F)** and confirmed on the pulmonary arteriography **(G)** in the proband's father. The pedigree **(A)** is adapted from Kim et al. Neurointervention 2019;14:91-98 [25]. AVF = arteriovenous fistula, AVM = arteriovenous malformation, DM = diabetes mellitus, ICH = intracranial hemorrhage

https://doi.org/10.3348/kjr.2020.1171

Korean Journal of Radiology
KJR

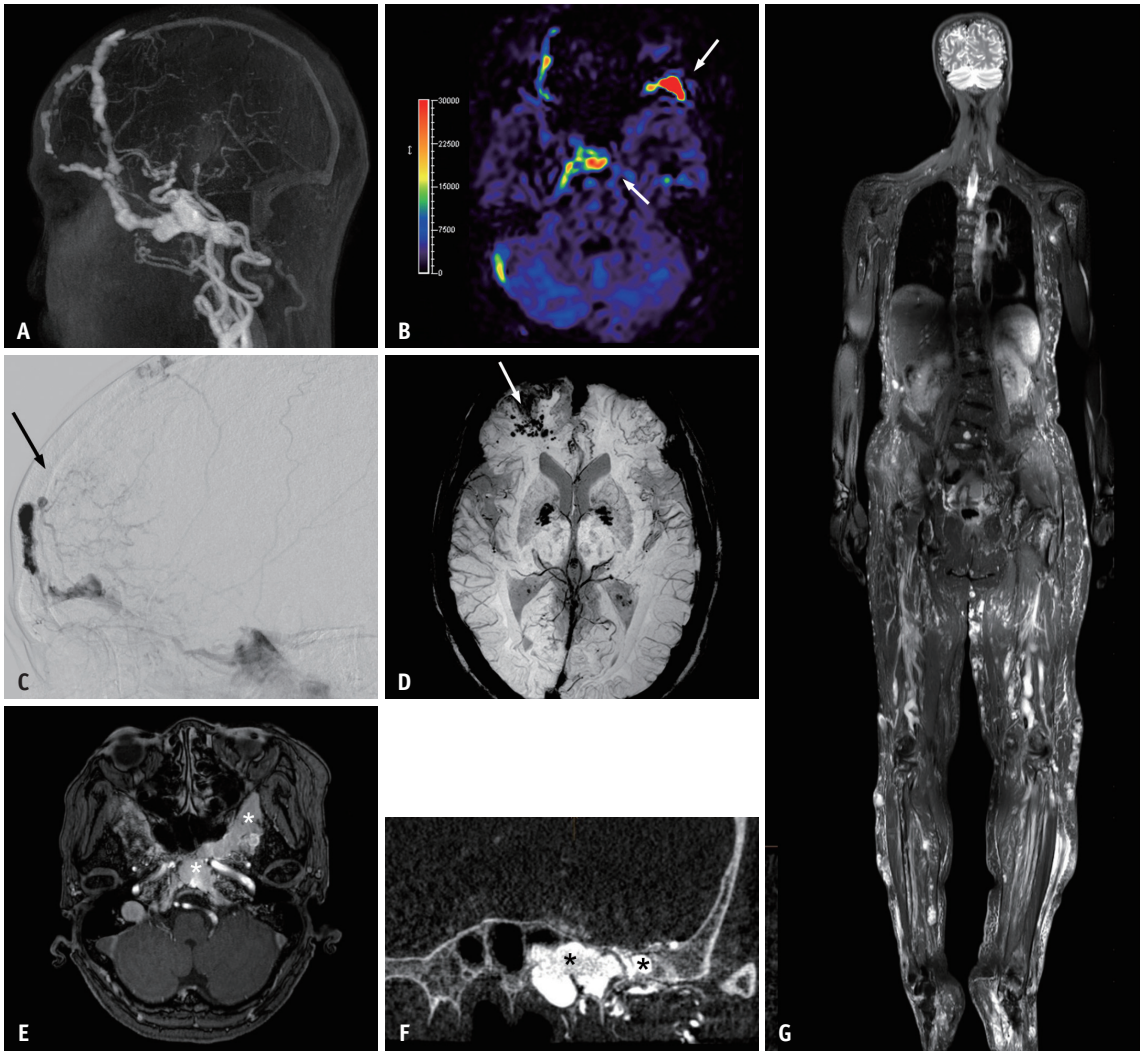

Fig. 5. A patient diagnosed with Klippel-Trénaunay syndrome by advanced MR imaging and genetic test (*PIK3CA* positive).
A. Four-dimensional MR angiography showed arteriovenous shunt in the skull base draining to the frontal diploic veins and superior sagittal sinus. **B.** Arterial spin labeling imaging demonstrated shunted blood within the sphenoid body and the left greater wing (arrows). **C-F.** In digital subtraction angiography **(C)** and susceptibility-weighted imaging **(D)**, cortical venous reflux (black arrow) and consequent hemosiderin deposition (white arrow) were observed in the right frontal lobe. Extensive skull base involvement of the vascular lesion (asterisks) is well visualized on the enhanced time-of-flight images **(E)** and three-dimensional rotational angiography **(F)**. **G.** Whole body MRI with T2-weighted short-tau inversion recovery imaging showed asymmetric soft tissue hypertrophy of the left lower extremity. Multiple subcutaneous high signal intensity lesions in both legs suggest varicose veins and venous malformations.

wall imaging, diffusion tensor imaging, perfusion imaging, and quantitative MRA are also helpful in understanding the pathophysiology of RNVD by evaluating the anatomical structure, microstructural integrity, and vascular malfunction [110].

RARE DISEASE MANAGEMENT SYSTEM IN KOREA

Helpline is the database and portal on rare diseases operated by the Division of Rare Disease Management of the Korea Disease Control and Prevention Agency to improve the diagnosis, care, and treatment of rare diseases. Through this online platform, detailed information on rare diseases is provided to the public. In addition, various projects, such as financial support for medical expenses, genetic testing for confirmation of rare diseases, and registration statistics are implemented.

The number of diseases currently designated as rare diseases in Helpline is 1078 (October 2020), less than 1280 of NORD and 6172 of Orphanet. Moreover, the Helpline database contains only 22 (32%) of our 68 RNVDs. This relatively small coverage can be explained by the facts that

https://doi.org/10.3348/kjr.2020.1171

the prevalence, clarity of the diagnosis, severity of the disease, and expected medical expenses are all considered in designating rare diseases in Korea. Unlike other rare disease databases, there should be a limitation on the number of rare diseases in Helpline, which has to provide financial support to those with designated rare diseases. However, applications for the designation of new rare diseases are received and deliberated periodically, thereby gradually expanding the disease coverage.

In Korea, a specific code starting with 'V' is assigned to all rare diseases for exempted calculation of health insurance. This code allows us to estimate the number of patients with a particular rare disease registered in HIRA. However, when we investigated the prevalence of RNVDs in Korea, we encountered some difficulties. First, several diseases of the same or similar category belong to a single V code (Fig. 2). HHT, Marfan, and moyamoya diseases, which have relatively high prevalence, are the only RNVDs with a disease-specific V code. The prevalence for other diseases cannot be estimated, except for those which have a disease-specific KCD code instead, such as EDS. Second, there are duplicate V code numbers for a single disease. For example, HHT, also known as Osler–Weber–Rendu syndrome, has code numbers V297 and V235 assigned to each disease name. Third, some RNVDs do not have both V and KCD codes. These RNVDs have not been recognized as rare diseases in Korea but may be designated as rare diseases through a review at some point. However, if there is no KCD code, there will be limitations on patient tracking for the review. Furthermore, an acquired cerebral AVF shares the same I67.1 KCD code number as an unruptured cerebral aneurysm, a relatively common and completely different disease. This situation can be confusing to patients as well as to analyze epidemiological data. Therefore, the current rare diseases classification system should be reorganized through the updated definition and classification of rare diseases.

LIMITATIONS

There were several limitations in our study. First, the definition of RNVDs in Korea remains unclear. We had to design a process of classifying RNVDs into rare diseases by combining the prevalence criteria of each country and converging to a prevalence threshold of 40 cases/100000 people. Second, some disease codes were not separated probably due to their unknown prevalence. In addition, it was difficult to proceed with the categorization because some diseases were interchangeably confined to a single disease code. Third, we could not reflect upon all the aspects of neurovascular and/or cerebrovascular disease classification, although we tried to include rapidly evolving disease concepts with the help of recent advances in relevant research. Some diseases may belong to multiple categories due to the mixed and complex pathogenesis of the diseases. RNVD classification is warranted for the inclusion of unidentified diseases based on new diagnostic criteria.

CONCLUSION

RNVDs have not been well defined and categorized into the rare disease classification in Korea. In this review, we established a disease panel of 68 RNVDs by analyzing and comparing four databases (Orphanet, NORD, OMIM and Helpline), performing a literature review, and evaluating the disease codes listed in the HIRA. To categorize vascular malformation/tumor, connective tissue diseases, SVDs and other diseases, we focused on how these diseases can be classified based on the concepts of embryology, development associated with the vessel wall component, and association with genetic disorders. Although RNVDs listed in this study could not reflect all the facets of recent development in genetic and developmental biology, they can be further defined and categorized by the virtue of genetic biology and with advances in research such as next-generation sequencing for germline and somatic mutations, and in developmental biology regarding the neural crest. Patients with RNVD may experience socioeconomic problems as well as high risks of multimodal treatment and may thus require more judicious care leading to complete cure.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Dae Chul Suh, Yunsun Song. Data curation: Yunsun Song, Yeo Kyoung Nam, Yura Ahn, So Yeong Jeong. Formal analysis: Yunsun Song, Boseong Kwon. Funding acquisition: Dae Chul Suh. Investigation: Yunsun Song, Boseong Kwon, Abdulrahman Hamed Al-Abdulwahhab. Methodology: Eul-Ju Seo, Jong-Keuk Lee. Project administration: Dae Chul Suh. Supervision: Dae Chul Suh. Writing—original draft: Yunsun Song. Writing—review

https://doi.org/10.3348/kjr.2020.1171

Korean Journal of Radiology
KJR

& editing: Eul-Ju Seo, Jong-Keuk Lee, Dae Chul Suh.

ORCID iDs
Yunsun Song
https://orcid.org/0000-0003-4738-0533
Boseong Kwon
https://orcid.org/0000-0002-6113-9730
Abdulrahman Hamed Al-Abdulwahhab
https://orcid.org/0000-0003-4398-7864
Yeo Kyoung Nam
https://orcid.org/0000-0002-9754-8149
Yura Ahn
https://orcid.org/0000-0002-9188-1186
So Yeong Jeong
https://orcid.org/0000-0003-4705-0008
Eul-Ju Seo
https://orcid.org/0000-0002-8247-3746
Jong-Keuk Lee
https://orcid.org/0000-0003-1125-4017
Dae Chul Suh
https://orcid.org/0000-0003-1561-5596

REFERENCES

1. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare disease terminology and definitions—a systematic global review: report of the ISPOR rare disease special interest group. *Value Health* 2015;18:906-914
2. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390:1151-1210
3. Krings T, Geibprasert S. Spinal dural arteriovenous fistulas. *AJNR Am J Neuroradiol* 2009;30:639-648
4. Vanakker OM, Hemelsoet D, De Paepe A. Hereditary connective tissue diseases in young adult stroke: a comprehensive synthesis. *Stroke Res Treat* 2011;2011:712903
5. Vanaman MJ, Hervey-Jumper SL, Maher CO. Pediatric and inherited neurovascular diseases. *Neurosurg Clin N Am* 2010;21:427-441
6. Barbosa M, Mahadevan J, Weon YC, Yoshida Y, Ozanne A, Rodesch G, et al. Dural sinus malformations (DSM) with giant lakes, in neonates and infants: review of 30 consecutive cases. *Interv Neuroradiol* 2003;9:407-424
7. Lasjaunias P, Rodesch G, Pruvost P, Laroche FG, Landrieu P. Treatment of vein of Galen aneurysmal malformation. *J Neurosurg* 1989;70:746-750
8. Guerrero BP, Pacheco CD, Saied A, Joshi K, Rodríguez C, Martínez-Galdámez M, et al. First human evaluation of endothelial healing after a pipeline flex embolization device with shield technology implanted in posterior circulation using optical coherence tomography. *Neurointervention* 2018;13:129-132
9. Liang B, Lesley WS, Robinson TM, Chen W, Benardete EA, Huang JH. Off-label application of Pipeline Embolization Device for intracranial aneurysms. *Neurointervention* 2019;14:116-124
10. McKusick VA. Mendelian inheritance in man and its online version, OMIM. *Am J Hum Genet* 2007;80:588-604
11. Griessenauer CJ, Farrell S, Sarkar A, Zand R, Abedi V, Holland N, et al. Genetic susceptibility to cerebrovascular disease: a systematic review. *J Cereb Blood Flow Metab* 2018;38:1853-1871
12. ISSVA. ISSVA classification for vascular anomalies. Issva.org Web site. https://www.issva.org/classification. Accessed July 1, 2020
13. Xu J, Shi GP. Vascular wall extracellular matrix proteins and vascular diseases. *Biochim Biophys Acta* 2014;1842:2106-2119
14. Soun JE, Song JW, Romero JM, Schaefer PW. Central nervous system vasculopathies. *Radiol Clin North Am* 2019;57:1117-1131
15. Jackson IT, Carreño R, Potparic Z, Hussain K. Hemangiomas, vascular malformations, and lymphovenous malformations: classification and methods of treatment. *Plast Reconstr Surg* 1993;91:1216-1230
16. Morales-Valero SF, Bortolotti C, Sturiale C, Lanzino G. Are parenchymal AVMs congenital lesions? *Neurosurg Focus* 2014;37:E2
17. Kim H, Marchuk DA, Pawlikowska L, Chen Y, Su H, Yang GY, et al. Genetic considerations relevant to intracranial hemorrhage and brain arteriovenous malformations. *Acta Neurochir Suppl* 2008;105:199-206
18. Goss JA, Huang AY, Smith E, Konczyk DJ, Smits PJ, Sudduth CL, et al. Somatic mutations in intracranial arteriovenous malformations. *PLoS One* 2020;14:e0226852
19. Hong T, Yan Y, Li J, Radovanovic I, Ma X, Shao YW, et al. High prevalence of KRAS/BRAF somatic mutations in brain and spinal cord arteriovenous malformations. *Brain* 2018;142:23-34
20. Couto JA, Huang AY, Konczyk DJ, Goss JA, Fishman SJ, Mulliken JB, et al. Somatic MAP2K1 mutations are associated with extracranial arteriovenous malformation. *Am J Hum Genet* 2017;100:546-554
21. Komiyama M. Pathogenesis of brain arteriovenous malformations. *Neurol Med Chir (Tokyo)* 2016;56:317-325
22. Amyere M, Revencu N, Helaers R, Pairet E, Baselga E, Cordisco M, et al. Germline loss-of-function mutations in EPHB4 cause a second form of capillary malformation-arteriovenous malformation (CM-AVM2) deregulating RAS-MAPK signaling. *Circulation* 2017;136:1037-1048
23. Wooderchak-Donahue WL, Akay G, Whitehead K, Briggs E, Stevenson DA, O'Fallon B, et al. Phenotype of CM-AVM2

 https://doi.org/10.3348/kjr.2020.1171

caused by variants in EPHB4: how much overlap with hereditary hemorrhagic telangiectasia (HHT)? *Genet Med* 2019;21:2007-2014
24. Robert F, Desroches-Castan A, Bailly S, Dupuis-Girod S, Feige JJ. Future treatments for hereditary hemorrhagic telangiectasia. *Orphanet J Rare Dis* 2020;15:4
25. Kim D, Seo EJ, Song YS, Suh CH, Kim JW, Kim DJ, et al. Current status of clinical diagnosis and genetic analysis of hereditary hemorrhagic telangiectasia in South Korea: multicenter case series and a systematic review. *Neurointervention* 2019;14:91-98
26. Revencu N, Boon LM, Mulliken JB, Enjolras O, Cordisco MR, Burrows PE, et al. Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. *Hum Mutat* 2008;29:959-965
27. Lasjaunias PL, Landrieu P, Rodesch G, Alvarez H, Ozanne A, Holmin S, et al. Cerebral proliferative angiopathy: clinical and angiographic description of an entity different from cerebral AVMs. *Stroke* 2008;39:878-885
28. Gupta A, Periakaruppan A. Intracranial dural arteriovenous fistulas: a review. *Indian J Radiol Imaging* 2009;19:43-48
29. Suh DC. Where did the dura mater come from? *Neurointervention* 2020;15:2-3
30. Tanaka M. Embryological consideration of dural AVFs in relation to the neural crest and the mesoderm. *Neurointervention* 2019;14:9-16
31. Bhattacharya JJ, Thammaroj J. Vein of galen malformations. *J Neurol Neurosurg Psychiatry* 2003;74 Suppl 1:i42-i44
32. Kim DJ, Suh DC, Kim BM, Kim DI. Adjuvant coil assisted glue embolization of vein of Galen aneurysmal malformation in pediatric patients. *Neurointervention* 2018;13:41-47
33. Vivanti A, Ozanne A, Grondin C, Saliou G, Quevarec L, Maurey H, et al. Loss of function mutations in EPHB4 are responsible for vein of Galen aneurysmal malformation. *Brain* 2018;141:979-988
34. Duran D, Karschnia P, Gaillard JR, Karimy JK, Youngblood MW, DiLuna ML, et al. Human genetics and molecular mechanisms of vein of Galen malformation. *J Neurosurg Pediatr* 2018;21:367-374
35. De Luca C, Bevilacqua E, Badr DA, Cannie MM, Sanchez TC, Segers V, et al. An ACVRL1 gene mutation presenting as vein of Galen malformation at prenatal diagnosis. *Am J Med Genet A* 2020;182:1255-1258
36. Bhattacharya JJ, Luo CB, Suh DC, Alvarez H, Rodesch G, Lasjaunias P. Wyburn-Mason or Bonnet-Dechaume-Blanc as cerebrofacial arteriovenous metameric syndromes (CAMS) a new concept and a new classification. *Interv Neuroradiol* 2001;7:5-17
37. Couly G, Coltey P, Eichmann A, Le Douarin NM. The angiogenic potentials of the cephalic mesoderm and the origin of brain and head blood vessels. *Mech Dev* 1995;53:97-112
38. Bergwerff M, Verberne ME, DeRuiter MC, Poelmann RE, Gittenberger-de Groot AC. Neural crest cell contribution to the developing circulatory system: implications for vascular morphology? *Circ Res* 1998;82:221-231
39. Zafar A, Quadri SA, Farooqui M, Ikram A, Robinson M, Hart BL, et al. Familial cerebral cavernous malformations. *Stroke* 2019;50:1294-1301
40. Ahmad S. Efficacy of percutaneous sclerotherapy in low flow venous malformations-a single center series. *Neurointervention* 2019;14:53-60
41. De Maria L, De Sanctis P, Balakrishnan K, Tollefson M, Brinjikji W. Sclerotherapy for venous malformations of head and neck: systematic review and meta-analysis. *Neurointervention* 2020;15:4-17
42. Wouters V, Limaye N, Uebelhoer M, Irrthum A, Boon LM, Mulliken JB, et al. Hereditary cutaneomucosal venous malformations are caused by TIE2 mutations with widely variable hyper-phosphorylating effects. *Eur J Hum Genet* 2010;18:414-420
43. Soblet J, Kangas J, Nätynki M, Mendola A, Helaers R, Uebelhoer M, et al. Blue rubber bleb nevus (BRBN) syndrome is caused by somatic TEK (TIE2) mutations. *J Invest Dermatol* 2017;137:207-216
44. Chung JI, Alvarez H, Lasjaunias P. Multifocal cerebral venous malformations and associated developmental venous anomalies in a case of blue rubber bleb nevus syndrome. *Interv Neuroradiol* 2003;9:169-176
45. Vahidnezhad H, Youssefian L, Uitto J. Klippel-Trenaunay syndrome belongs to the PIK3CA-related overgrowth spectrum (PROS). *Exp Dermatol* 2016;25:17-19
46. Pavanello M, Melloni I, Antichi E, Severino M, Ravegnani M, Piatelli G, et al. Sinus pericranii: diagnosis and management in 21 pediatric patients. *J Neurosurg Pediatr* 2015;15:60-70
47. Wagenseil JE, Mecham RP. Elastin in large artery stiffness and hypertension. *J Cardiovasc Transl Res* 2012;5:264-273
48. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000;342:673-680
49. Ul Haque A, Moatasim A. Adult polycystic kidney disease: a disorder of connective tissue? *Int J Clin Exp Pathol* 2008;1:84-90
50. Kuo IY, Chapman A. Intracranial aneurysms in ADPKD: how far have we come? *Clin J Am Soc Nephrol* 2019;14:1119-1121
51. Gaberel T, Rochey A, di Palma C, Lucas F, Touze E, Emery E. Ruptured intracranial aneurysm in patients with osteogenesis imperfecta: 2 familial cases and a systematic review of the literature. *Neurochirurgie* 2016;62:317-320
52. Forlino A, Marini JC. Osteogenesis imperfecta. *Lancet* 2016;387:1657-1671
53. Robinson PN, Godfrey M. The molecular genetics of Marfan syndrome and related microfibrillopathies. *J Med Genet* 2000;37:9-25
54. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996;62:417-426

https://doi.org/10.3348/kjr.2020.1171

55. Wityk RJ, Zanferrari C, Oppenheimer S. Neurovascular complications of marfan syndrome: a retrospective, hospital-based study. *Stroke* 2002;33:680-684
56. Maleszewski JJ, Miller DV, Lu J, Dietz HC, Halushka MK. Histopathologic findings in ascending aortas from individuals with Loeys-Dietz syndrome (LDS). *Am J Surg Pathol* 2009;33:194-201
57. MacCarrick G, Black JH 3rd, Bowdin S, El-Hamamsy I, Frischmeyer-Guerrerio PA, Guerrerio AL, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med* 2014;16:576-587
58. Rodrigues VJ, Elsayed S, Loeys BL, Dietz HC, Yousem DM. Neuroradiologic manifestations of Loeys-Dietz syndrome type 1. *AJNR Am J Neuroradiol* 2009;30:1614-1619
59. Germain DP. Pseudoxanthoma elasticum. *Orphanet J Rare Dis* 2017;12:85
60. Beyens A, Albuisson J, Boel A, Al-Essa M, Al-Manea W, Bonnet D, et al. Arterial tortuosity syndrome: 40 new families and literature review. *Genet Med* 2018;20:1236-1245
61. Lee YC, Huang HY, Chang CJ, Cheng CH, Chen YT. Mitochondrial GLUT10 facilitates dehydroascorbic acid import and protects cells against oxidative stress: mechanistic insight into arterial tortuosity syndrome. *Hum Mol Genet* 2010;19:3721-3733
62. Morris CA. Genetic aspects of supravalvular aortic stenosis. *Curr Opin Cardiol* 1998;13:214-219
63. Freeze SL, Landis BJ, Ware SM, Helm BM. Bicuspid aortic valve: a review with recommendations for genetic counseling. *J Genet Couns* 2016;25:1171-1178
64. Schievink WI, Raissi SS, Maya MM, Velebir A. Screening for intracranial aneurysms in patients with bicuspid aortic valve. *Neurology* 2010;74:1430-1433
65. Cichowski K, Jacks T. NF1 tumor suppressor gene function: narrowing the GAP. *Cell* 2001;104:593-604
66. Hamilton SJ, Friedman JM. Insights into the pathogenesis of neurofibromatosis 1 vasculopathy. *Clin Genet* 2000;58:341-344
67. Bae HJ, Debette S. Commentary on the cervical artery dissection in stroke study trial. *Stroke* 2016;47:1413-1415
68. Debette S, Markus HS. The genetics of cervical artery dissection: a systematic review. *Stroke* 2009;40:e459-e466
69. Guo DC, Duan XY, Regalado ES, Mellor-Crummey L, Kwartler CS, Kim D, et al. Loss-of-function mutations in YY1AP1 lead to grange syndrome and a fibromuscular dysplasia-like vascular disease. *Am J Hum Genet* 2017;100:21-30
70. Shivapour DM, Erwin P, Kim ESh. Epidemiology of fibromuscular dysplasia: a review of the literature. *Vasc Med* 2016;21:376-381
71. Yang X, Li J, Fang Y, Zhang Z, Jin D, Chen X, et al. Rho guanine nucleotide exchange factor ARHGEF17 is a risk gene for intracranial aneurysms. *Circ Genom Precis Med* 2018;11:e002099
72. Bourcier R, Le Scouarnec S, Bonnaud S, Karakachoff M, Bourcereau E, Heurtebise-Chrétien S, et al. Rare coding variants in ANGPTL6 are associated with familial forms of intracranial aneurysm. *Am J Hum Genet* 2018;102:133-141
73. Zhou S, Ambalavanan A, Rochefort D, Xie P, Bourassa CV, Hince P, et al. RNF213 is associated with intracranial aneurysms in the French-Canadian population. *Am J Hum Genet* 2016;99:1072-1085
74. Santiago-Sim T, Fang X, Hennessy ML, Nalbach SV, DePalma SR, Lee MS, et al. THSD1 (Thrombospondin Type 1 Domain Containing Protein 1) mutation in the pathogenesis of intracranial aneurysm and subarachnoid hemorrhage. *Stroke* 2016;47:3005-3013
75. Yan J, Hitomi T, Takenaka K, Kato M, Kobayashi H, Okuda H, et al. Genetic study of intracranial aneurysms. *Stroke* 2015;46:620-626
76. Biondi A, Jean B, Vivas E, Le Jean L, Boch AL, Chiras J, et al. Giant and large peripheral cerebral aneurysms: etiopathologic considerations, endovascular treatment, and long-term follow-up. *AJNR Am J Neuroradiol* 2006;27:1685-1692
77. Pantoni L, Sarti C, Alafuzoff I, Jellinger K, Munoz DG, Ogata J, et al. Postmortem examination of vascular lesions in cognitive impairment: a survey among neuropathological services. *Stroke* 2006;37:1005-1009
78. Steffensen LB, Rasmussen LM. A role for collagen type IV in cardiovascular disease? *Am J Physiol Heart Circ Physiol* 2018;315:H610-H625
79. Alamowitch S, Plaisier E, Favrole P, Prost C, Chen Z, Van Agtmael T, et al. Cerebrovascular disease related to COL4A1 mutations in HANAC syndrome. *Neurology* 2009;73:1873-1882
80. Lanfranconi S, Markus HS. COL4A1 mutations as a monogenic cause of cerebral small vessel disease: a systematic review. *Stroke* 2010;41:e513-e518
81. Coria F, Rubio I. Cerebral amyloid angiopathies. *Neuropathol Appl Neurobiol* 1996;22:216-227
82. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;337:1512-1523
83. Fang J, Hirschi K. Molecular regulation of arteriovenous endothelial cell specification. *F1000Res* 2019;8:1208
84. Sammons V, Davidson A, Tu J, Stoodley MA. Endothelial cells in the context of brain arteriovenous malformations. *J Clin Neurosci* 2011;18:165-170
85. Barbosa Do Prado L, Han C, Oh SP, Su H. Recent advances in basic research for brain arteriovenous malformation. *Int J Mol Sci* 2019;20:5324
86. Frismantiene A, Philippova M, Erne P, Resink TJ. Smooth muscle cell-driven vascular diseases and molecular mechanisms of VSMC plasticity. *Cell Signal* 2018;52:48-64
87. Bochaton-Piallat ML, Bäck M. Novel concepts for the role of smooth muscle cells in vascular disease: towards a new smooth muscle cell classification. *Cardiovasc Res* 2018;114:477-480
88. Sinha S, Santoro MM. New models to study vascular mural cell embryonic origin: implications in vascular diseases.

https://doi.org/10.3348/kjr.2020.1171

Cardiovasc Res 2018;114:481-491
89. Le Douarin NM, Dupin E. The "beginnings" of the neural crest. *Dev Biol* 2018;444 Suppl 1:S3-S13
90. Komiyama M. Cardio-cephalic neural crest syndrome: a novel hypothesis of vascular neurocristopathy. *Interv Neuroradiol* 2017;23:572-576
91. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet* 2020;28:165-173
92. Thomas JM, Surendran S, Abraham M, Rajavelu A, Kartha CC. Genetic and epigenetic mechanisms in the development of arteriovenous malformations in the brain. *Clin Epigenetics* 2016;8:78
93. Di Monaco S, Georges A, Lengelé JP, Vikkula M, Persu A. Genomics of fibromuscular dysplasia. *Int J Mol Sci* 2018;19:1526
94. Wooderchak-Donahue WL, Johnson P, McDonald J, Blei F, Berenstein A, Sorscher M, et al. Expanding the clinical and molecular findings in RASA1 capillary malformation-arteriovenous malformation. *Eur J Hum Genet* 2018;26:1521-1536
95. Giau VV, Bagyinszky E, Youn YC, An SSA, Kim SY. Genetic factors of cerebral small vessel disease and their potential clinical outcome. *Int J Mol Sci* 2019;20:4298
96. Brinjikji W, Mark IT, Silvera VM, Guerin JB. Cervicofacial venous malformations are associated with intracranial developmental venous anomalies and dural venous sinus abnormalities. *AJNR Am J Neuroradiol* 2020;41:1209-1214
97. Posey JE. Genome sequencing and implications for rare disorders. *Orphanet J Rare Dis* 2019;14:153
98. Posey JE, O'Donnell-Luria AH, Chong JX, Harel T, Jhangiani SN, Coban Akdemir ZH, et al. Insights into genetics, human biology and disease gleaned from family based genomic studies. *Genet Med* 2019;21:798-812
99. Vahidnezhad H, Youssefian L, Saeidian AH, Touati A, Pajouhanfar S, Baghdadi T, et al. Mutations in PLOD3, encoding lysyl hydroxylase 3, cause a complex connective tissue disorder including recessive dystrophic epidermolysis bullosa-like blistering phenotype with abnormal anchoring fibrils and type VII collagen deficiency. *Matrix Biol* 2019;81:91-106
100. Fernandez-Marmiesse A, Gouveia S, Couce ML. NGS technologies as a turning point in rare disease research, diagnosis and treatment. *Curr Med Chem* 2018;25:404-432
101. Fereydooni A, Dardik A, Nassiri N. Molecular changes associated with vascular malformations. *J Vasc Surg* 2019;70:314-326.e1
102. Krings T, Geibprasert S, Terbrugge K. Classification and endovascular management of pediatric cerebral vascular malformations. *Neurosurg Clin N Am* 2010;21:463-482
103. Greene AK, Goss JA. Vascular anomalies: from a clinicohistologic to a genetic framework. *Plast Reconstr Surg* 2018;141:709e-717e
104. Lee YJ. Advanced neuroimaging techniques for evaluating pediatric epilepsy. *Clin Exp Pediatr* 2020;63:88-95
105. Griauzde J, Srinivasan A. Advanced neuroimaging techniques: basic principles and clinical applications. *J Neuroophthalmol* 2018;38:101-114
106. Suh CH, Jung SC, Kim B, Cho SJ, Woo DC, Oh WY, et al. Neuroimaging in randomized, multi-center clinical trials of endovascular treatment for acute ischemic stroke: a systematic review. *Korean J Radiol* 2020;21:42-57
107. Hodel J, Leclerc X, Kalsoum E, Zuber M, Tamazyan R, Benadjaoud MA, et al. Intracranial arteriovenous shunting: detection with arterial spin-labeling and susceptibility-weighted imaging combined. *AJNR Am J Neuroradiol* 2017;38:71-76
108. Arai N, Akiyama T, Fujiwara K, Koike K, Takahashi S, Horiguchi T, et al. Silent MRA: arterial spin labeling magnetic resonant angiography with ultra-short time echo assessing cerebral arteriovenous malformation. *Neuroradiology* 2020;62:455-461
109. Grossberg JA, Howard BM, Saindane AM. The use of contrast-enhanced, time-resolved magnetic resonance angiography in cerebrovascular pathology. *Neurosurg Focus* 2019;47:E3
110. Blair GW, Hernandez MV, Thrippleton MJ, Doubal FN, Wardlaw JM. Advanced neuroimaging of cerebral small vessel disease. *Curr Treat Options Cardiovasc Med* 2017;19:56

https://doi.org/10.3348/kjr.2020.1171