pediatric stroke

MOYAMOYA ARTERIOPATHY IN CHILDREN: CLINICAL CHARACTERISTICS AND APPROACH TO CLINICAL EVALUATION

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Introduction

Moyamoya is a chronic, steno-occlusive arteriopathy characterized by progressive stenosis at the terminal portion of the internal carotid artery and its branches and an abnormal vascular collateral network at the base of the brain. Resultant chronic brain ischemia leads to recurrent transient ischemic attacks and strokes, debilitating headaches, and various neurological and cognitive deficits (1, 2). The main pathological changes observed in moyamoya include concentric and eccentric fibrocellular thickening of the intima, attenuation of the media with fragmentation of the inner elastic lamina due to increased proliferation of intimal smooth muscle cells (SMCs) migrating from the media, and endothelial mesenchymal transition, with minimal inflammatory cell infiltration(3). Current treatment options include anti-thrombotic therapy and revascularization surgery which has been shown to reduce the risk of stroke. These modalities, however, have no effect on the progression of arterial stenosis and do not reverse or halt the relentless progression of the primary arteriopathy.

Moyamoya is a complex multifactorial and heterogeneous disorder, comprising diverse genetic diseases and syndromes, genetically predisposing conditions with variable patterns of inheritance, or acquired causes (e.g., cranial radiation, autoimmune diseases). The association with specific ethnic groups and the prevalence of familial cases in up to 12% of the patients, support the role of genetic factors in moyamoya(4). Genetic conditions associated with moyamoya include neurofibromatosis type 1 (NF1), Down syndrome or sickle cell disease, and many more syndromes or genetic disorders. Despite the strong ethnicity-related effect, data from monozygotic twins in East Asia showed discordant phenotypes, supporting the polygenic genetic effect, with both genetic predisposition and environmental triggers implicated. Multiple genetic approaches employed over the years to clarify the genetic background of the disease demonstrate various genetic risk factors for moyamoya. Since the 1990s, several genome-wide linkage analyses and genome-wide association studies (GWAS) have been performed, mostly in East Asian populations to map and identify moyamoya genes. These studies identified multiple associations with various polymorphisms including HLA types, growth factors, and cytokines(5). In 2011, the first susceptibility gene for moyamoya, RNF213, was identified(4, 6). Since then, the list of single-gene disorders associated with moyamoya has been steadily growing. Currently, at least 18 genes have been identified in Mendelian forms of Moyamoya; however, they account for only a small proportion of cases(7, 8). Advances in molecular biology and next-generation sequencing technologies made it possible to study disease mechanisms. This has resulted in the recognition

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of associations between various signaling pathways and moyamoya pathophysiology including the nitric oxide pathway and disorders of the RAS pathway. However, the effect of genetic factors on the occurrence, presentation, and outcomes of moyamoya is not entirely clear, and direct genotype-phenotype correlations to guide management and prognostication are lacking. In this review, we examine moyamoya's most common genetic causes and explore how genetic etiology interacts with clinical care.

From Genotype to Phenotype: Clinical and Radiographic Features of Monogenic Moyamoya

Each monogenic etiology associated with moyamoya exhibits distinct clinical and radiological features (table 1). Comprehensive data on the natural history and progression of moyamoya within each genetic syndrome remain limited. The traditional dichotomy between moyamoya disease (MMD), which may potentially includes patients with RNF213 mutations presening with isolated moyamoya, and moyamoya syndrome (MMS), which encompasses a range of genetic and non-genetic causes (e.g radiation-related arteriopathy), complicates our understanding of clinical behavior across these subtype. Historically, MMD is characterized by earlier onset (50.7 ± 43.4 versus 75.7 ± 47.4 months, $p = 0.0277$), transient ischemic attacks as the initial presentation (as opposed to stroke), and severe, progressive, and bilateral arteriopathy. In contrast MMS has often been described as presenting more asymptomatically(9-11). However, this paradigm may not apply to all monogenic causes. For example, while patients with NF1 often exhibit asymptomatic, and non-progressive disease with low infarct burden, those with Down syndrome or sickle cell anemia more frequently present symptomatically(10, 11). These findings suggest that certain genetic forms classified as MMS may exhibit phenotypes more consistent with classic MMD, challenging the conventional distinction between these categories. In addition, many patients with (idiopathic) MMD are now being diagnosed with mutations in RNF213. However, those harboring homozygous, as well as rare or de novo heterozygous variants in RNF213 have been reported to exhibit multisystem vascular and non-vascular involvement in several cohorts and could therefore be regarded as MMS(12-15).

These contradictions challenge the traditional dichotomization of MMD versus MMS and suggest that a gene/group of genes-related moyamoya classification would be more suitable moving forward.

Notably, the true prevalence of multisystem involvement is likely underestimated, as comprehensive vascular screening is not routinely performed in all MMD patients. The presence of variable penetrance and expressivity further complicates classification, especially since individuals with the same variant may exhibit isolated cerebral arteriopathy or a syndromic phenotype with systemic vascular features. It may be more accurate to view moyamoya as a spectrum disorder, where most individuals—especially those with a monogenic etiology—carry some degree of risk for multisystem involvement, modulated by genetic background, environmental triggers, and potentially epigenetic regulation.

Furthermore, certain monogenic disorders associated with moyamoya exhibit distinct neuroimaging features that differ from the typical presentation seen in idiopathic cases. For instance, abnormalities in the posterior circulation — including stenosis or occlusion of the posterior cerebral arteries can be observed in specific genetic syndromes like NF1, YY1AP1 or ANO1-related moyamoya (5, 8, 16). Notably, posterior circulation involvement may sometimes reflect a developmental or static vascular pattern rather than active arteriopathy.

Therefore, recognizing syndrome-specific imaging patterns is essential to avoid

Genetic Causes of Moyamoya in Childhood

TABLE 1

Syndrome	Affected gene/locus and inheritance pattern (protein name)	Cerebrovascular involvement	Extra-cerebral vascular involvement	Other clinical features
NF-1	*Neurofibromin* *AD*	Moyamoya venous and arterial aneurysms	Coarctation of thoracic and abdominal aorta, venous and arterial aneurysms mid aortic syndrome and reno vascular hypertension	café au lait axillary and inguinal freckling short stature OPG fibromas scoliosis learning disabilities
Down Syndrome	chromosome 21 trisomy	Moyamoya	congenital cardiac defects pulmonary hypertension	typical dysmorphic features duodenal atresia annular pancreas, imperforate anus, Hirschsprung disease hematological abnormalities hypotonia, hyperlaxity GDD and ID early-onset Alzheimer hypothyroidism hearing loss
Moyamoya 6 with achalasia	*GUCY1A3* AR	Moyamoya with posterior circulation involvement	hypertension	Achalasia Low platelets
Sickle cell disease	*HBB* AR	Proximal intracranial stenosis moyamoya cerebral microvascular disease	vaso-occlusive crises, and acute chest syndrome Pulmonary artery hypertension sickle nephropathy	Anemia and aplastic crisis avascular necrosis of bone
	BRCC3/MTCP1 recessive X-linked [117]	Moyamoya	hypertension coronary disease	Facial dysmorphism short stature hypergonadotropic hypogonadism azoospermia dilated cardiomyopathy, premature graying of the hair, cataracts GDD

TABLE 1				
Aicardi Goutières syndrome	*SAMHD1* AR	Intracranial stenoses (including moyamoya) aneurysms intracerebral haemorrhage	peripheral vessel involvement- chilblains and ischaemic ulceration	GDD, ID microcephaly, Encephalopathy and regression, Basal ganglia calcification and leukoencephalopathy, Raynaud syndrome, progressive deforming arthropathy contractures, glaucoma
Schimke immunosseous dysplasia	*SMARCAL1* AR	Moyamoya Arterial stenosis involving anterior and posterior circulation external carotid involvement	pulmonary and coronary involvement systemic hypertension premature myocardial infarctions	spondyloepiphyseal dysplasia short stature nephropathy leading to end-stage renal disease T-cell deficiency characteristic facial features hyperpigmented macules
Moyamoya Disease with diffuse Occlusive vasculopathy	*RNF213* AD or AR	Moyamoya Non- moyamoya intracranial stenosis	Can be associated with systemic vasculopathy including peripheral pulmonary stenosis, pulmonary hypertension with string of beads appearance, coronary, renal and inferior abdominal aorta stenosis hypertension	elevated aminotransferases kidney dysplasia recurrent skin lesions (annular figurate erythema)
Grange syndrome	*YY1AP1* AR	Internal carotid artery stenosis or moyamoya posterior circulation involvement Cerebral aneurysms	Fibromuscular Dysplasia-Like Vascular Disease- Stenosis or occlusion of Renal, coronary abdominal arteries hypertension congenital heart defects	congenital heart defects (patent ductus arteriosus, bicuspid aortic valve, and ventricular septal defect) brachydactyly, syndactyly bone fragility learning disabilities
Microcephalic osteodysplastic primordial dwarfism type II (MOPD2)	*PCNT* (pericentrin) AR	Cerebral aneurysms Moyamoya	Renal, coronary and external carotid artery involvement hypertension myocardial infarctions	growth retardation chronic kidney disease diabetes/insulin resistance and obesity characteristic facial features, skeletal dysplasia abnormal dentition
Alagille syndrome	*Jag1(Jagged-1) Notch 2* AD	Occlusive aneurysmal and tortuous arterial disease mainly in Internal carotid arteries Moyamoya (with posterior	Pulmonary artery stenosis Renovascular stenosis mid aortic syndrome carotid and aortic aneurysm	cholestasis with bile duct paucity Butterfly vertebra posterior embryotoxon characteristic facial features

TABLE 1				
		circulation involvement) Venous anomalies		
Sifrim–Hitz–Weiss syndrome (OMIM 617159)	*CHD4* AD	Moyamoya	Aortic coarctation Ascending thoracic aortic aneurysm/ coronary artery disease Hypertension	developmental delay (+/-) skeletal changes dysmorphic facies congenital heart disease
Williams syndrome	7p deletion (*Elastin*) AD	Moyamoya-rare medium-large vessel stenosis Cervical artery dissection	Cardiovascular disease-Elastin arteriopathy -peripheral pulmonic stenosis. Supravalvular aortic stenosis. coronary artery stenosis/dilatation midaortic syndrome renal and mesenteric arteries stenosis hypertension	'Elfin-facies' hypercalcemia connective tissue abnormalities Intellectual disability unique personality endocrine abnormalities sensorineural hearing loss
CBL syndrome	*CBL* AD	Moyamoya Posterior circulation may be involved		Noonan-like syndrome mild facial dysmorphisms musculoskeletal anomalies cryptorchidism predisposition to JMML
	ANO1 AR/AD	Moyamoya posterior circulation often involved cerebral aneurysms	supravalvular pulmonary stenosis	GDD ID
	CNOT3 AD	Moyamoya		dysmorphic facies GDD ID Autism variable skeletal abnormalities
	SETD5 AD	Moyamoya		GDD ID dysmorphic facies variable skeletal abnormalities
	DIAPH1 AD	Moyamoya		Sensorineural hearing loss thrombocytopenia

AD- autosomal dominant; AR- autosomal recessive; NF-1 – neurofibromatosis type 1, GDD; developmental delay, ID; Intellectual disability.

overestimating disease severity and to tailor management strategies accordingly.

SYNDROME-BASED GENETIC ETIOLOGIES

Neurofibromatosis Type 1 and Other RASopathies-related Moyamoya

The RAS/MAPK pathway is necessary for cellular proliferation, survival, differentiation, metabolism, and angiogenesis(17). RASopathies are disorders caused by germline mutations in genes encoding components of the RAS/MAPK pathway resulting in increased signaling through this pathway. Moyamoya has been reported in several RASopathies, mainly neurofibromatosis type 1 (NF1)(18) as well as reported sporadically in Costello(19), Noonan(20), and Legius syndromes(21). NF1 is the most prevalent RASopathy (approximately 1:3000 live births)(22) and its association with moyamoya has been the best characterized. Endothelial cell (EC) and SMC dysfunction play a role in NF1-moyamoya pathogenesis. Cell-based models suggest that NF1 knock-out induces abnormal EC organization and proliferation(23) and animal models demonstrate that NF1 knock-out mice develop intimal and SMC hyperproliferation after vascular injury(24). The need for a second hit, such as a vessel injury, to induce pathogenesis may explain why only 2.5-7.4% of NF1 subjects(18) develop moyamoya. Other studies suggest that the co-occurrence of mutations in other susceptibility genes, such as RNF213, also impacts moyamoya incidence and severity in patients with NF1. For example, a study comparing NF1 patients with and without moyamoya showed that 18% of subjects with moyamoya had an RNF213 variant compared to none in subjects without vasculopathy(25) while another reported a more severe phenotype in NF1 subjects with an RNF213 variant(26).

RNF213-related Moyamoya

RNF213 is the major susceptibility gene for moyamoya, and the most common non-syndromic monogenic disorder associated with moyamoya. The High familial rate in East Asia (10-15%) and the geographical distribution of the disease are attributed to a founder variant in RNF213 (p.R4810K and p.R4859K). The inheritance pattern is mainly Autosomal dominant with incomplete penetrance; however, autosomal recessive inheritance is also reported, associated with a more severe phenotype. In children with p.R4810K variant, a distinct clinical and angiographic phenotype was reported, characterized by an earlier age at symptom onset, higher frequency of cortical and watershed ischemic strokes involving multiple vascular territories and frequent bilateral posterior circulation involvement, and more anastomosing vessels from PCA to anterior circulation post vascularization, compared to non-RNF213 moyamoya cases (9, 26). A gene dosage effect has been noted for the RNF213 p.R4810K variant in Japanese and Korean moyamoya cases, in which homozygous states highly correlate with early onset and more severe disease and cognitive outcomes(9, 27, 28). Despite these shared phenotypic characteristics, there is significant heterogeneity in RNF213-related moyamoya presentations, with diverse clinical symptoms and involvement of other vascular beds. This heterogeneity, in conjunction with the observed low disease penetrance of RNF213 mutations, suggests that the presence of these mutations may not be sufficient to cause moyamoya, highlighting the potential influence of other genetic or environmental factors. Due to the low disease penetrance, and the lack of data on the natural history and risk for stroke or hemorrhage in asymptomatic patients, family screening is generally not recommended for RNF213-related disease but should be considered in selected cases.

MECHANISTIC AND PATHWAY-BASED ETIOLOGIES

Nitric Oxide Pathway Dysfunction-related Moyamoya

The role of nitric oxide (NO) in SMC function and its impact on moyamoya pathogenesis has been highlighted in recent literature. For instance, mutations in GUCY1A3, which encodes the α1 subunit of soluble guanylate cyclase (sGC), the major receptor for NO, have been reported in three families with moyamoya and achalasia(29). The NO-sGC-cGMP pathway controls vascular smooth-muscle relaxation, and vascular tone and remodeling. This pathway is also affected in Alagille syndrome, another cause of moyamoya, associated with mutations in NOTCH2 or JAG1. These genes were shown to affect the communication between ECs and SMCs thereby impacting angiogenesis and NO availability within SMCs(30, 31).

Inflammatory-Related Pathways and Moyamoya

The role of inflammation in the pathogenesis of moyamoya has been an important question and has been thoroughly reviewed recently(32, 33). However, whether anti-inflammatory medications can alter the progression of arteriopathy remains unknown. An autopsy study in 1993 demonstrated co-localization of inflammatory cells—macrophages and T cells—with proliferating SMCs in the occlusive segments of intracranial arteries(34). Epidemiological studies have suggested a higher than anticipated prevalence of autoimmune diseases (e.g., type 1 diabetes mellitus, Graves' disease, rheumatoid arthritis) in patients with moyamoya (35-37). Although most known monogenic causes of moyamoya are not primary disorders of the immune system, Down syndrome, associated with high autoimmunity, and SAMHD1-related disorder, leading to a lupus-like auto-inflammatory syndrome, are associated with moyamoya(38-40). Additionally, inflammation and/or infection were suggested to be essential in inducing the first step of moyamoya pathophysiology in in-vitro and in-vivo models of RNF213, with pro-inflammatory cytokines activation mediated by RNF213 in endothelial cells and SMCs(41, 42). These associations suggest that moyamoya tends to develop in the context of a double-hit phenomenon through the occurrence of an environmental stressor, such as inflammation, in patients with a susceptibility gene mutation. Whether genetic variation within inflammatory pathways could plausibly modify moyamoya disease onset, progression, susceptibility to infarction, or the downstream inflammatory effects of infarction that impact stroke severity and long-term neurological outcomes is currently unknown. Given the potential therapeutic implications, further research is needed to elucidate the role of immune dysregulation in moyamoya.

Epigenetic Regulation and Chromatin Remodeling in Moyamoya

Epigenetic mechanisms—including DNA methylation, histone modification, and chromatin remodeling—play a critical role in regulating gene expression during vascular development and homeostasis. Chromatin remodeling defects have been directly implicated in rare monogenic syndromes associated with moyamoya. For example, deletions involving the BRCC3 gene, which encodes a chromatin-remodeling protein involved in DNA damage response and transcriptional regulation, have been linked to moyamoya-like vasculopathy. Individuals with BRCC3/MTCP1 deletions often present with arterial hypertension, dilated cardiomyopathy, and other systemic features in addition to cerebrovascular involvement (43). In addition, other moyamoya-associated genes are involved in chromatin remodeling (CHD4, CNOT3, and SETD5)(44). Although the direct contribution of chromatin dysregulation to moyamoya

pathogenesis remains to be fully elucidated, these findings raise the possibility that epigenetic factors may modulate vascular phenotype, influencing interaction with environmental stressors such as inflammation.

Clinical Approach to the Genetic Workup of Moyamoya in Clinical Setup

Evaluation of children with moyamoya should include a detailed family history, a thorough physical examination, and an assessment of neuroimaging patterns. These may direct the clinical suspicion of a Mendelian disorder. Clinical clues for specific genetic syndromes include characteristic dysmorphic features in Down syndrome, Williams or Alagille syndrome, evidence of café au lait in NF1 or other Rasopathies, and microcephaly, developmental delay, or chilblains in SAMHD1-related disorder. Laboratory tests should include a complete blood count including hemoglobin electrophoresis in selected cases and should be performed according to the clinical and radiological phenotype. If a certain monogenic disorder or syndrome is suspected, such as RNF213-related moyamoya in Asians or moyamoya in the context of café-au-lait spots, targeted testing using a single gene panel may be the most efficient and cost-effective approach. In children without clinical or laboratory indications of an associated genetic cause, the decision regarding genetic testing becomes more complex in the current era of genetic discovery and is not uniformly performed. Options include a targeted gene panel covering only known genes associated with moyamoya such as RNF213, or a broader approach such as whole exome or whole genome sequence. However, the diagnostic yield of these broader methods is relatively low and additional data is needed to better assess their utility(7, 45).

Management of Monogenic Moyamoya

Management of these patients should be tailored to cerebrovascular and peripheral vascular system involvement, as well as to the associated comorbidities, which may influence therapeutic decisions, and inform multidisciplinary management. Assessment of other vascular beds should be considered depending on the specific clinical and genetic phenotype (e.g NF1 or RNF213-related disorders)(12).

If a genetic condition, such as RNF213 is detected in a patient with MMD, parental testing may be warranted with subsequent testing of siblings if an affected parent is identified. In

children without an identifiable genetic cause, while the risk of other children in the family being affected by MMD is low, consideration of MRI and MRA screening in selected cases to alleviate familial anxiety and improve quality of life is reasonable(46, 47).

Please see the article on the medical management of moyamoya for an elaborated section on specific management according to a genetic cause of moyamoya).

Does the Genetic Etiology of Moyamoya Affect Surgical Management?

Recent advances in phenotypic and genetic characterization have broadened our understanding of moyamoya, shifting it from isolated intracranial carotid artery stenosis with perforating artery collaterals to a systemic vasculopathy with multi-organ involvement(5). For instance, GUCY1A3-related moyamoya, is associated with arterial hypertension as well as low platelet count, while deletion of BRCC3/MTCP1, may be associated with dilated cardiomyopathy and arterial hypertension (5), all of which should be taken into account prior to

surgery. Still, the impact of genetic background on revascularization risk and outcomes remains incompletely understood. Surgical outcomes in moyamoya are influenced by both the characteristics of the intracranial vasculopathy and inherent patient-specific factors, such as age at onset and systemic comorbidities. Several disease-related features are known to increase perioperative risk, including young age, posterior circulation involvement, and intracranial aneurysms, which may predispose patients to complications such as brainstem infarction or hemorrhage during or after revascularization. In parallel, certain monogenic moyamoya syndromes increase perioperative risk by contributing to systemic manifestations that compromise surgical preparation and recovery. Patients with RNF213 rare variants, for example, may develop renal artery stenosis, cardiomyopathy, mesenteric ischemia, or aortic branch vasculopathy, leading to hypertension or poor general condition at the time of surgery(8, 13). These systemic complications complicate anesthetic management and increase the risk of ischemic or hemorrhagic stroke during revascularization. Notably, posterior circulation moyamoya, more frequently observed with ANO1 variants, is associated with particularly poor neurologic outcomes following surgery (8, 48).

In contrast, some variants inRNF213 (p.R4810K) have been associated with more favorable revascularization outcomes in East Asians populations(49), highlighting the heterogeneity of genetic impact and the importance of individualized risk stratification. Together, these findings emphasize that the genetic etiology of moyamoya can significantly influence surgical management, both through its effect on the nature of the intracranial vasculopathy and through associated systemic disease. Careful genetic evaluation, paired with comprehensive preoperative assessment, is essential for optimizing management and reducing procedural risk.

Knowledge Gaps and Future Research Avenues

Although our understanding of the genetics of moyamoya has advanced over time, there remain several knowledge gaps that would be suitable for future research endeavors. There is a great need to highlight other novel genetic causes of moyamoya as well as to investigate novel variants in known genes implicated in moyamoya angiopathy using modern sequencing technologies, such as short-read and long-read genome sequencing and RNA sequencing. Innovative approaches to collecting and sequencing affected tissue to identify local epigenetic modifications that contribute to disease development and heterogeneity are warranted. A better understanding of the genetic landscape of moyamoya will lead to improved insight into final common pathways that may be disrupted and subsequently, novel treatments targeting these disrupted pathways.

CONCLUSIONS

Moyamoya is one of the most important causes of stroke in childhood with significant disease burden affecting both children and adults. Familial clustering and ethnic predispositions further highlight the genetic basis of moyamoya. However, despite substantial progress, the genetic landscape remains complex, involving multiple genes and inheritance patterns. Ongoing research is essential to better understand the genetic underpinning of moyamoya, which is critical for elucidating its pathogenesis and clinical variability and for developing targeted therapies. facilitating international data sharing in genomic research empowered by joint efforts and by global collaboration to increase the availability of large genomic datasets may yield novel insights into biological mechanisms involved in moyamoya

and open new avenues for biomarker discoveries and therapeutic innovation. Early genetic evaluation, alongside traditional diagnostic methods, is a vital step towards accurate diagnosis, risk stratification, and personalized management, in an attempt to improve patient outcomes.

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