FACULTY OF MEDICINE AND HEALTH SCIENCES

Genetics and pathophysiology of Moyamoya, a rare cerebrovascular disease

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Contents

Abstract

Moyamoya disease (MMD) is a cerebrovascular disease characterized by progressive stenosis at the terminal portion of the internal carotid artery and an abnormal, fragile vascular network at the base of the brain. MMD is more common in people living in East Asian countries such as Korea and Japan in comparison to those living in the Western Hemisphere. The onset of symptoms shows a bimodal peak in age: one around 10 years and one at 30-40 years. The peak appears to occur slightly later in women than men. The predominant presentation in children is ischemic symptoms such as TIA or cerebral infarct. In contrast, adult patients are more likely to present with intracranial hemorrhages. Other possible manifestations are headache, epilepsy and involuntary movements. The gold standard for diagnosing MMD is cerebral angiography although magnetic resonance angiography and computed tomographic angiography are also used. To date, the underlying mechanisms of MMD pathogenesis have yet to be fully elucidated, but certain studies have indicated that genetic factors play an important role in its development. *RNF213* in the 17q25-ter region has been identified as an important susceptibility gene of MMD among East Asian populations. The *RNF213* p.R4810K polymorphism was identified in 95% of familial MMD patients and in 79% of sporadic cases. Patients carrying this *RNF213* p.R4810K polymorphism exhibited significantly earlier disease onset and a more-severe form of MMD. This master thesis encapsulates current advances of MMD regarding epidemiology, clinical features, diagnosis and etiopathogenesis.

Abstract (Dutch)

Moyamoya ziekte (MMZ) is een occlusieve cerebrovasculaire ziekte die gekenmerkt wordt door een progressieve stenose ter hoogte van het uiteinde van de interne halsslagader en de ontwikkeling van een abnormaal, fragiel vaatnetwerk aan de basis van de hersenen. MMZ komt vaker voor bij mensen die in Oost-Aziatische landen wonen zoals Japan en Korea. De ontwikkeling van de eerste symptomen vertoont een bimodale leeftijdspiek: één rond de leeftijd van 10 jaar en één rond 30-40 jaar. De piek lijkt bij vrouwen iets later op te treden dan bij mannen. De voornaamste presentaties bij kinderen zijn ischemische symptomen zoals TIA of cerebraal infarct. Volwassen patiënten daarentegen hebben meer kans op een intracraniële bloeding. Andere mogelijke symptomen zijn hoofdpijn, epilepsie en onwillekeurige bewegingen. Voor het diagnosticeren van MMZ is cerebrale angiografie de meest aangewezen beeldvorming, hoewel magnetische resonantie-angiografie en computer tomografische angiografie ook mogelijk zijn. Tot op heden

moeten de onderliggende mechanismen van de pathogenese van MMZ nog worden opgehelderd, maar onderzoeken hebben aangetoond dat genetische factoren een belangrijke rol spelen bij de ontwikkeling ervan. *RNF213* in de 17q25-ter-regio werd geïdentificeerd als een belangrijk gen dat de gevoeligheid voor het ontwikkelen van MMZ in Oost-Aziatische populaties zeer sterk verhoogt. Het *RNF213* p.R4810K-polymorfisme werd gevonden bij 95% van de familiale MMD-patiënten en in 79% van de sporadische gevallen. Patiënten met dit polymorfisme vertoonden een significant vroeger begin van de ziekte en een ernstigere vorm van MMZ. Deze masterproef omvat de huidige vorderingen van MMD op vlak van epidemiologie, symptomen, diagnose en etiopathogenese.

Introduction

Moyamoya disease (MMD) is a rare[1] and idiopathic[2, 3] condition in which a progressive stenosis or occlusion of the terminal internal carotid artery (ICA) and its proximal branches, namely the anterior and/or middle cerebral arteries, occurs.[3, 4, 5] This stenosis of the ICA can occur unilaterally or bilaterally and in a subgroup of MMD patients, the posterior cerebral arteries will also be occluded.[3,6] The stenosis results in a progressive hypoperfusion of the cerebral parenchyma distal to these narrowed vessels, especially in the frontal lobe.[6, 7] As a compensation for this ischemia[8], the thalamoperforating and lenticulostriate perforating vessels, the pial collateral arteries from the posterior circulation and eventually the transdural collateral arteries from the external carotid arteries will dilate and function as an important collateral circulation.[6, 9, 10, 11] These vessels at the base of the brain are fragile and abundant.[11, 12] Angiographically, these collateral vessels have a smog-like structure[13] and are termed the ‘moyamoya’ vessels. ‘Moyamoya’ is a Japanese expression meaning “something hazy, like a puff of cigarette smoke drifting in the air”. [7, 9, 12] An example of these typical angiographic findings in MMD can be found in figure 1.

Takeuchi and Shimizu described this pathological manifestation of MMD in 1957 for the first time as ‘hypoplasia of bilateral internal carotid arteries’ and it was officially named Moyamoya disease in 1969.[2, 14, 15, 16] Synonyms of MMD are ‘bilateral hypoplasia of the ICAs’, ‘cerebral juxta-basal telangiectasia’, ‘cerebral arterial rete’, ‘cerebral basal rete mirabile’ and more commonly ‘spontaneous occlusion of the circle of Willis’.[17, 18, 19] The histological characteristics of MMD are progressive stenosis of the arterial lumen because of intima hyperplasia, medial thinness and elastic lamina fluctuation.[20, 28] There are typically no indications of atherosclerosis.[16, 20]

This disease was first described in Japan, but since then MMD cases have been reported all over the world.[16] The incidence of MMD is highest in East Asian populations and lower in North American

and European populations.[14] MMD can occur both in children and in adulthood. Most of the MMD patients present with bilateral involvement; only 18% of MMD patients have a unilateral involvement.[7] A unilateral MMD case is also called 'probable Moyamoya disease' and 30-40% of these individuals will eventually progress to bilateral MMD.[9, 10] In children, unilateral involvement typically progresses to bilateral involvement within 1–2 years.[7]

MMD can result in both cerebral ischemia or cerebral hemorrhage. Cerebral ischemia can occur due to the ICA occlusion and cerebral hemorrhage can arise because of development of abundant fragile vessels at the base of the brain.[14] Yet, not all MMD patients show clinical symptoms. MMD cases are considered asymptomatic if they meet the angiographical criteria but have not suffered from these ischemic or hemorrhagic manifestations.[19] Often, the angiographic characteristics of asymptomatic MMD are found incidentally. About 20% of asymptomatic MMD hemispheres has had a silent cerebral infarction and about 40% showed disturbed cerebral hemodynamics.[19] The annual risk of infarction in asymptomatic MMD patients is estimated at 3.2%.[19] Thus, asymptomatic MMD is not a benign disorder because it can readily progress to cause ischemic and hemorrhagic stroke[6] and it can be seen as an early stage or a less severe form of MMD.[19]

When this Moyamoya vasculopathy is associated with an underlying acquired or inherited disease, it is called Moyamoya syndrome (MMS), quasi-moyamoya or akinmoyamoya.[2, 10, 12] Examples of underlying disease include autoimmune diseases such as systemic lupus erythematosus or Grave's disease [3, 21], brain tumors, Down syndrome, neurofibromatosis type 1 and inflammatory diseases such as meningitis.[22] MMS can also arise when Moyamoya vasculopathy is caused by cranial irradiation.[21, 22] Despite the distinctions between MMD and MMS, angiographic findings and clinical courses are nearly identical.[7] In this review, MMD will be the main topic.

Because MMD is a rare disorder, it generally takes some time to correctly diagnose patients often presenting with non-specific symptoms such as hemorrhages or infarction.[23] In a study by Graf and Schwitalla an initial misdiagnosis was identified in 119 patients out of 192 Caucasian patients.[23] The most prevalent misdiagnoses were cerebral vasculitis (31%), etiological ill-defined stroke diagnoses (30.2%) and MS (3.6%).[23] Several patients received more than one misdiagnosis.[23] Thus, MMD patients are at high risk to being falsely diagnosed and treated.[23]

MMD is an irreversible cerebral disease and female gender is a risk factor for MMD progression.[25] The mean interval between onset and disease progression visible on MRI in unilateral MMD was circa 60 months and 28.4 months in bilateral MMD.[25] This proves that the course of MMD is rather slow despite the acute clinical symptoms. Because of this progressive nature, correct diagnosis

and appropriate management are crucial to improve prognosis of the patients.[15] Untreated MMD contributes to a lifelong risk of stroke, hemorrhages and devastating, permanent neurological demise.[7, 9]

Large amounts of research on MMD have been performed and some studies suggest the involvement of genetic factors but the pathogenetic mechanisms are not yet fully understood. This article provides a review of the international literature for the following MMD aspects: epidemiology, clinical features, diagnosis and etiopathogenesis.

Methodology

For this literature review, the online database 'Pubmed' was utilised for a systematic search in the English language literature. The review is based on data published after the discovery of *RNF-213*, the first Moyamoya disease gene, in 2010.[26] When using secondary literature, there was no time limit. In the first stage of this research, the keyword "Moyamoya disease review" was used. Out of the 658 results, 59 articles were included based on their titles and abstracts. To preserve the boundaries of the topic of this review, namely epidemiology, symptoms, diagnosis and etiopathogenesis of MMD, the following exclusion factors were established: no case reports were used, no articles where only treatment was discussed were included and also the articles in which MMD and pregnancy were examined, were excluded. Based on these reviews, the major subtitles were chosen and these formed the body of this literature review. The term 'Moyamoya disease' was than combined with each subtitle separately and used as a new keyword in 'Pubmed'. Again, articles were selected based on their title and abstract. Additional exclusion factors were: articles dealing with quasi-moyamoya and articles with a content of other subtitles or other cerebral diseases. When an article was already selected in the previous search, it was not included again. A clear overview of this systematic search and the exclusion factors for each keyword can be found in figure 2.

Epidemiology

MMD cases appear all over the world, but the incidence exhibits regional differences. MMD incidence shows a peak in East Asian populations[14, 27], mainly in countries such as Japan, Korea and China[12, 29], followed by Black, Caucasian and Hispanic people.[17, 18, 30] The annual incidence rate and prevalence of MMD in different countries is summarized in table 1. Despite the fact that very few studies have been conducted on Western MMD epidemiology, it is generally accepted that the Western incidence of MMD is about one-tenth of the incidence in East Asian countries.[4, 7,

[36] An American study by Uchino and Johnston in 2005 showed that the annual incidence of MMD in Asian-Americans was 4.6 times higher than in White Americans, which suggests that ethnic differences in incidence appear to remain after migration.[17, 31, 33] The racial discrepancy could be explained by genetic variations among these different populations.[17, 31]

Table 1: incidence rate and prevalence of MMD

COUNTRY	1994		2006		2013	
	Incidence (/ 100 000)	Prevalence (/ 100 000)	Incidence (/ 100 000)	Prevalence (/ 100 000)	Incidence (/ 100 000)	Prevalence (/ 100 000)
Japan[14, 19, 29, 31]	0.35	3.16	0.94	10.5		
South-Korea[14, 29]			1.7	8.2	4.3	18.1
China[14, 17, 29, 32]			0.43	3.92		

According to epidemiological data about MMD, there is a clear increasing trend in the incidence and prevalence of MMD in both Asian and Western countries.[19, 25, 37] This rise may indicate an increase of actual cases of MMD. However, a more conceivable explication would be the advances in non-invasive radiological features such as MRI and MRA [17, 25], an increasing number of survivors due to better management [17, 19] and/or an increase in establishment of registration programs and genetic counselling.[29, 38]

The incidence and prevalence of asymptomatic MMD is still unclear. Previously, asymptomatic patients were rarely reported.[6] Patients can now be incidentally diagnosed on MRI and MRA performed for a brain health check-up or in the context of familial screening.[6] In a study of 11,402 healthy Japanese subjects who underwent a general brain checkup, the percentage of people with asymptomatic MMD was reported to be 0.07%.[27, 39]

The onset of symptoms in Asian MMD patients shows a bimodal peak in age.[14, 27] The major juvenile peak occurs during childhood, commonly before ten years of age. A Japanese survey of 2075 MMD patients mentioned that the age of onset in 47.8% of the patients occurred during this first decade of life.[18, 31] The smaller second peak occurs typically during the fourth decade of life.[12, 14, 16] In general, both of the age peaks seem to occur slightly later in women than men.[17] This typical bimodal incidence is also found in some epidemic cohorts in the US and Europe [17, 34] yet other studies did not detect the childhood age peak [9, 18, 19, 42]

In most studies, there is a consistent female preponderance: The female-to-male ratio in MMD typically ranges from 1.8:1 to 2.2:1 in East Asian populations.[14] Although the female gender generally tends to be neuroprotective for other stroke diseases[40], it seems to be a risk factor for

development of MMD.[41] There is no consensus for female predominance in American or European MMD patients: some articles mention an even more extreme (4.25:1) female preponderance [18, 44, 45], others report a similar female-to-male ratio as in East-Asian MMD population.[17, 34]

Research of the familial occurrence of MMD shows a positive family history in 10-15% of the patients.[12, 27, 46] The mode of inheritance appears to be autosomal dominant with an incomplete penetrance.[27] In comparison with the general population, the risk of having MMD is approximately 30-40 times higher when a first- or second-degree relative is already diagnosed with MMD.[17, 47] The mean age of disease onset is significantly lower in familial cases.[48] Furthermore, the female-to-male ratio rises from about 1.6:1 to 5.0:1 when it comes to a familial form of MMD.[8, 9]

The familial incidence of MMD is almost ten times lower in western countries.[29] The concordance of MMD in monozygotic twins is predicted to be 80%.[18, 49]

Clinical features

There are a wide range of clinical presentations in MMD patients. This can be explained by the individual variations in the rate and extent of arterial occlusion and the response of the brain cells to the reduction in blood and oxygen supply.[29, 43, 52] In some patients, the occlusions of the main cerebral arteries and formation of fragile collateral vessels remain asymptomatic,[20] but MMD can also lead to permanent and devastating neurological deficits and cognitive impairment.[32]

Table 2 provides an overview of the possible manifestations in MMD.

Ischemic manifestation of MMD

In children with MMD, mainly ischemic injuries occur such as transient ischemic attacks (TIA's) and cerebral infarction.[14, 27, 53] MMD is one of the most important causes of cerebrovascular disease in East-Asian children.[17, 29, 59] It accounts for about 62% of cerebrovascular diseases in children requiring surgery.[40] These ischemic attacks are seen in 70-80% of pediatric MMD cases [7, 21] and are often precipitated by coughing, hyperventilation, crying, fever, even playing a harmonica or flute or during physical exertion.[9, 12, 17, 29] These triggering events ensure a decrease in carbon dioxide which leads to a cerebral vasoconstriction and thus aggravating the cerebral hypoperfusion.[9, 12] The severity of MMD in children is age-related: in younger children, the condition is more severe.[21]

In MMD children, the infarction type is more often observed than the TIA type.[21, 36] A study by Pines et al. on 51 pediatric MMD patients found in 43% of the cases a stroke as initial presentation followed by TIA's in 24% of the MMD children.[54] However, pediatric patients cannot accurately

describe TIA symptoms whereby the diagnosis may often be missed thus the incidence of TIA's in pediatric MMD patients may be much higher.[21, 36] When triggering events as mentioned above stop, TIA symptoms usually resolve.[55]

Infarct topography in MMD patients is significantly different from the classic vascular territory. The distribution of the stroke pattern is different according to the age of onset. Gyral and borderzone patterns tended to develop during childhood MMD whereas in adult MMD the honeycomb type infarction is the most common type.[21, 56]

Signs of anterior circulation ischemia include motor disturbance, aphasia, dysarthria, extremity weakness or paralysis, hemiplegia, hemisensory symptoms, seizures, cognitive impairment and even a vegetative state.[7, 9, 12, 14, 17, 19, 21, 27]

Involvement of PCA in MMD disease occurs in roughly 20-30% of pediatric MMD patients and 18.2% in adult patients.[10, 16, 57] PCA involvement usually leads to more severe clinical manifestations and is one of the factors related to poor prognosis.[17, 29, 58] This can be explained by the task of PCA as the supplier of leptomeningeal feeders to the anterior circulation.[58] Infrequent symptoms of posterior circulation ischemia include visual field hemianopia, visual field defects, decreased visual acuity, transient blindness, scintillating scotomas, diplopia, ataxia, amaurosis fugax and vertigo.[7, 16, 21, 36, 58] However, not all patients with PCA stenosis present with these typical PCA symptoms.[58]

The ischemic events in MMD patients are mostly multiple and recurrent.[29] An American study showed a recurrence rate of 18% in symptomatic MMD patients in the first year after onset, followed by 5% each year. The cumulative 5-year risk is roughly 40%.[60] MMD in a Non-Asian background shows more ischemic stroke types at all ages and they often have a more benign presentation.[14, 19, 43]

Chronic ischemia in patients with MMD may induce decreased axonal and neurite density, simplified network connectivity and thus lead to neurocognitive dysfunction.[70, 71, 72] Deterioration of cognition has a linear relationship with the number of strokes and long-time chronic hypoxemia from progressive stenosis of the cerebral vessels.[9, 12, 21, 73] A study by Karzmark et al. mentioned that cognitive impairment can also occur in patients without the presence of stroke on MRI.[74] Neurocognitive impairment caused by MMD differs between adult and pediatric populations. In children, intelligence is the most affected cognitive parameter, whereas executive function is the most impaired parameter in MMD adults.[75] A study by Kurakawa et al. demonstrated that the

percentage of normal intelligence levels 4 year after MMD onset was 92% in pediatric patients. Sadly, 10-15 year after MMD onset, this percentage was only 33%.[21, 76]

Table 2: overview of possible manifestations in MMD

Ischemic manifestations	Hemorrhagic manifestations	Other symptoms
Cerebral infarction TIA Neurocognitive impairment	Intracranial hemorrhages Intracranial aneurysm Cerebral microbleeds	Epilepsy Syncope Fever Involuntary movements Nausea, vomiting Headache Livedo racemose Psychiatric manifestations

Cerebral infarction was also identified in asymptomatic patients with MMD, who experienced no cerebrovascular events. A Japanese survey reported that silent cerebral infarction was identified in about 20% of the involved hemispheres.[61] Therefore, the incidence of silent cerebral infarction is much higher in asymptomatic MMD than in normal population.[61] These findings reveal that asymptomatic MMD is not a benign disorder. It is therefore very important that these asymptomatic MMD patients are properly followed-up.[61]

Hemorrhagic manifestation of MMD

In adult MMD patients, 40-65% present with intracranial hemorrhages.[7, 24, 27, 32] These hemorrhages mainly result from a rupture of the fragile, maximally dilated, collateral moyamoya vessels[12, 18, 62] and occur mostly in the anterior circulation territory.[17] These lesions are largely seen in the deep areas of the brain, such as the periventricular deep white matter and the basal ganglia.[12] Because of their close proximity to the ventricles, the hemorrhages in the thalamus (15%)[7] and basal ganglia (40%)[7] can lead to a perforation towards the lateral and third ventricles.[17, 63] Typical symptoms of hemorrhagic MMD patients are consciousness disturbance [14, 27], seizures [12] and motor paresis.[19]

The clinical presentation of European MMD patients is comparable to that of American patients yet its clinical features seem to be distinct compared to the Asian population.[59] Asian adult MMD patients have much higher rates of intracerebral hemorrhages than European or American adult MMD patients.[14, 42, 44] Patients with a hemorrhagic MMD often face rebleeding attacks which also

affects the patients' prognosis. The annual rebleeding rate is reported to be 4.3% and the cumulative rebleeding risk was 7.8% at 5 years, 22.6% at 10 years and 35.9% at 15 years.[64]

Intracranial aneurysms have been found in association with MMD and are another possible cause of intracranial bleeding.[19, 36] These aneurysms can be responsible for intracerebral or intraventricular hemorrhages although sometimes spontaneous regression occurs.[66] The reported prevalence of artery aneurysms, which occur principally in the posterior circulation[64] because of increased hemodynamic stress, varied from 3.4% to 14.8% in adult MMD patients.[67, 68] This percentage interval is significantly higher than that of aneurysms in a non-MMD population.[66] The presence of aneurysms in MMD patients increases the risk of hemorrhages. [67]

Cerebral microbleeds (cMBs) are a radiological construct which describes the small foci of blood degradation products containing hemosiderin after leakage of blood cells out of the dilated, fragile vessels.[17, 42] cMBs are present in 28-46% of the MMD patients [6, 17] The incidence of cMBs is significantly higher in MMD patients in comparison to healthy controls and they are located mainly in the periventricular white matter.[17, 42] The occurrence of cMBs as an initial symptomatic event is much more common in Asian moyamoya patients in comparison to European patients. cMBs lead to a higher risk of intracerebral hemorrhages which are also more frequent in Asian MMD patients as mentioned before.[6, 42, 69]

Other more rare symptoms of MMD

Another possible symptom of MMD is epilepsy[14] which is more common in children younger than 10 years of age.[1, 14, 19] Further, syncope[9] and nausea/vomiting may occur.[17] Data obtained from a study of 23 pediatric MMD patients also found the presence of fever in 30% of the patients. The hypothesis is that fever might trigger symptoms because hyperthermia induces vasoconstriction of the carotid artery. This leads to a compromise of blood flow in an already ischemic brain which thus induces symptoms.[16]

Involuntary movements like chorea, dyskinesia, periodic tremor, choreoathetosis, dystonia, epilepsia-partialis continua and limb-shaking are rare symptoms of MMD which are also more common in childhood MMD.[14, 16, 27, 77]

A questionnaire about self-reported quality of life in pediatric MMD patients showed scores which were comparable with non-MMD patients in the social, school and physical domains but within the psychosocial health and emotional health, the MMD patients reported significantly lower scores.[78] The parents of these MMD patients reported significantly lower scores for their children in all

domains compared to healthy controls.[78] Children with MMD clearly mention a lower quality of life than healthy controls; they would benefit from mental health support beyond what a mild physical presentation may indicate.[78]

Twenty percent of MMD patients complain of headache as a symptom[9, 14, 27] which is the most non-specific symptom.[21, 36] This headache exhibits in the majority of the cases a migrainous-like feature which can cause impairment of everyday life and is often refractory to medical therapies.[79, 80] A less frequent type is a tension-type headache.[79] Data from a study by Kim et al. in 2013 observed that 23% of the pediatric MMD population complained of headache prior to the main symptom-onset and 14% of all patients mentioned severe headaches.[81] The reason why these headaches develop is still unclear.

Another symptom, earlier not realized to be associated with MMA, is the involvement of the skin with livedo racemosa.[44] Livedo racemosa differs from livedo reticularis, by being generalized and persisting in warmth.[44] This symptom has rarely been described in MMA patients before. Yet, a recent study by Kraemer et al. found a presence of livedo racemosa in 24 out of 188 MMA patients (= 12.8%). This finding could indicate a global vasomotor dysfunction arguing that MMA might be a more generalized disease than previously thought.[44]

Exclusively psychiatric manifestations of MMD are extremely rare in literature.[82] Depression and anxiety are the most common psychiatric sequelae of illness. [82] The patients with MMD also scored higher for obsessive-compulsive and phobic anxiety symptoms.[83] In children and young adults, the most frequent psychiatric manifestation is psychosis.[82] Thus, although it is uncommon, MMD carries a possible risk for misdiagnosis as a psychotic disorder.

Further, MMD should be considered in the differential diagnosis of MS, as both affect young adults, cause intermittent neurological symptoms, and show multifocal abnormalities on brain imaging.[84]

In conclusion, the clinical diagnosis of MMD requires a strong suspicion when treating hemorrhagic or ischemic CVA in young females or children without other risk factors for stroke such as hypertension, diabetes mellitus, smoking history, dyslipidemia or history of heart diseases. [24, 85]

Diagnosis

Diagnostic criteria

Up to now, MMD lacks specific molecular markers for diagnosing the disease. Instead, the identification of MMD depends especially on morphological characteristics made visible by imaging techniques.[14, 96] These techniques focus on identification of acute or chronic ischemic/hemorrhagic lesions and presence of the typical arteriopathy seen in MMD.[9] MMD and MMS have largely comparable angiographic phenotypes.[97] Imaging techniques have a key role in management of MMD, as they are necessary for diagnosis, choice of treatment and follow-up.[98]

Previously, the guidelines for diagnosing childhood and adult MMD were as follows: (1) occlusion or stenosis at the terminal portion of the ICA and/or at the proximal portion of the ACA and/or MCA, (2) presence of an abnormal vascular network in the proximity of these occlusive/stenotic lesion and (3) these lesions should be evident bilaterally. These guidelines were adjusted in 1997 and the new criteria also include unilateral terminal ICA steno-occlusions in definitive diagnosing MMD.[14, 17, 27, 99] Furthermore, these new guidelines also mention that conventional cerebral angiography may not be mandatory when brain MRI and MRA can clearly demonstrate all MMD diagnostic criteria.[100]

According to angiographic findings, MMD can be classified into 6 categories according to Suzuki's grading system. Stage 1: occurrence of narrowing of the carotid fork. Stage 2: initiation of the moyamoya arteries and dilatation of the main intracranial vessels. Stage 3: intensification of the moyamoya arteries and defects of the ACA and MCA. Stage 4: minimization of the moyamoya arteries and defects of the PCA. Stage 5: reduction of the moyamoya arteries and development of external carotid artery (ECA) collaterals and stage 6: disappearance of the moyamoya arteries and circulation only via vertebral artery (VA) and ECA.[7, 9, 10, 14, 27] As seen in the progression of these categories, the intracranial ischemia shall eventually be compensated by transdural anastomosis from the extracranial arterial system in the more severe stages of MMD.[13, 14] Figure 3 provides angiographic images during these different stages in MMD. A disadvantage of this Suzuki's grading system is that it cannot really represent the hemodynamic status of the patient's brain parenchyma thus the cerebral hemodynamic status has no correlation with these angiographic stages.[15] In addition, only a limited number of MMD patients shows this step-by-step disease progression.[17] Even asymptomatic patients show radiographic progression which confirms that MMD is a progressive disorder.[101] The PCA can also be involved in MMD. Just as the Suzuki grade describes

the progression of stenosis in the ICA, ACA and MCA, the stenosis of the PCA also varies in degree of severity: (1) normal, (2) slightly involved: only a small stenotic lesion is present and there is still a normal filling of most of the PCA branches, (3) moderately involved: only a few of the PCA branches are visualized and (4) severely involved: there is a progression of the occlusion into the vertebral arteries or into the trunk of the basilar artery.[58]

Histopathologic characteristics of MMD

The histopathological changes that occur in MMD arteries consist of an intimal hyperplasia and an atrophy of the medial layer.[13, 85, 86] The typical occlusion and direct narrowing of the arterial lumen seen in MMD is caused by excessive fibrocellular thickening of the intima.[28, 87, 88] The same intimal hyperplasia is seen in atherosclerosis however in MMD, no infiltration of macrophages and no lipid deposits are observed.[13, 89] Examination of autopsy samples of the MCA from patients of MMD found fewer than normal smooth muscle cells (SMC) in the media which might cause the medial thinness. [13, 28, 88] A study by Fukui et al. also found proliferated SMC in the intima which were considered to have migrated from the media.[90] The attenuation of the media causes narrowing of the outer diameter of involved vessels [85, 88, 91] which is not observed in intracranial arterial stenosis caused by atherosclerosis. [92] The involved arteries decrease their outer diameter serially in parallel with progressive luminal stenosis during disease progression in MMD.[93] Mural thrombi are frequently observed. [92, 94] Finally, the internal elastic lamina of MMD arteries was found to be abnormal.[28] The common irregularities of this elastic lamina were fragmentation, elongation and disappearance.[87] Ikeda et al. confirmed that all these histological changes are not limited to the internal carotid artery; aberrant extracranial vasculature such as renal, pulmonary and pancreatic arteries, have been documented in MMD patients.[36, 95]

Imaging techniques

1. *Cerebral angiography*

Cerebral angiography or digital subtraction angiography (DSA) is the gold standard in diagnosing MMD and it can also be used in assessing disease progression or postoperative changes.[9, 11, 14, 27, 102] In angiography, there is a visible occlusion or stenosis of the unilateral / bilateral terminal portion of the ICAs as well as a transient dense angiographic blush which is the cause of the typical ‘puff of smoke’ in MMD.[19] This collateral vascular system is an important component of cerebral blood flow in MMD patients and varies from patient to patient.[103] It grants a more dynamic and

consequently functional assessment than CTA or MRA.[9] The spatial resolution of conventional DSA is as high as 0.1 mm.[104]

2. CT-ANGIOGRAPHY

Recently, CTA has been widely accepted as a diagnostic tool for MMD and MMS in both adults and sometimes children.[15, 21] This 3D-imaging technique is helpful in the emergency department after the manifestation of specific cerebrovascular symtoms.[11, 15, 21] It allows visualization of possible extracranial collateral networks.[7] It is less time-consuming[21] than DSA but it is still accompanied with radiation exposure.[15] This technique has the highest specificity and provides valid information about the anatomic state of the vessels, the affected area in the brain parenchyma and the degree of narrowing.[9, 12, 17, 21] A disadvantage of this imaging tool besides the exposure to radiation, is the need for a contrast medium with possible risks of acute kidney injury or adverse reactions.[9, 105]

3. MR-ANGIOGRAPHY

MRA too is accepted for diagnosis of MMD or MMS.[15, 21, 43] It is able to display the possible vessel abnormalities consistent with cerebral angiography such as the degree of stenosis and the development of collaterals.[12, 14, 17, 106] For this technique too, a MRA score system is written based on the severity of ICA, ACA, MCA and/or PCA involvement. This score system correlates well with Suzuki's grading system.[12, 14, 27, 35] The specificity and sensitivity of MRA for artery stenosis are high, 93% and 100% respectivitely.[7, 16, 21, 107] The advantages of this technique are not requiring any contrast injection and the absence of ionizing radiation, thus this is the imaging tool of choice for long-term follow-up [9, 21] and it can be used in the diagnosis of MMD in children.[21] Yet, MRA is limited in critically ill patients and it is relatively time-consuming.[15]

4. ELECTROENCEPHALOGRAM

For patients presenting with seizures, an electroencephalogram (EEG) should be done. About 50% of the pediatric MMD patients present with a distinctive EEG feature, known as a ‘rebuild-up phenomenon’. Normally, there is an appearance of a slow wave induced by hyperventilation which is characterized by a build-up and termination at the end of this hyperventilation.[21] However, this ‘rebuild-up phenomenon’ typical for MMD is a reappearance of slow waves within 20-60 seconds after termination of hyperventilation and it is resolved in roughly 10 minutes. The cause of this reappearance of slow waves in pediatric MMD patients is said to be because of the increased arterial CO_2 tension after the cessation of hyperventilation. This causes vasodilatation of the previously vasoconstricted cerebral vessels which might lead to a steal phenomenon as blood is

diverted from the dilated cortical vessels to the moyamoya-associated collaterals.[7, 12, 21, 24, 36] This is not seen in any other pathology.[12] The weakness of EEG as a diagnostic tool is that it is unable to quantify the indices of CVR.[21]

Hemodynamic changes in MMD

The progressive nature of MMD leads to an increasing stenosis and thus a reduction of cerebral perfusion pressure (CPP). This reduction in CPP causes a reduction of cerebral blood flow (CBF). Initially, this reduction of CBF can be compensated for by autoregulation: vasodilatation of the resistance arterioles helps to maintain CBF. This process is called the cerebrovascular reserve (CVR) and is an important indicator of ensuing ischemic stroke or TIA.[35, 108, 109] To determine this parameter, respectively the resting CBF and activated CBF should be measured. This activation can be provoked by administration of acetazolamide or CO_2, which are vasodilators. However acetazolamide loading has been reported to result in serious potential side effects such as acute heart failure and pulmonary edema. Therefore, it should not be routinely performed for every MMD patient during screening.[110, 111] Because of this autoregulation, CBV, which comprises arterial, venous, capillary, parenchyma and pial components, may increase when CPP decreases. Yet, it can be overruled due to the progressive stenosis and reduction in CPP and eventually CBF will decrease as well. Another compensatory mechanism to maintain normal oxygen metabolism is the increase in oxygen extraction fraction (OEF). This also works temporarily and when the decrease in CPP is beyond the limit of this compensatory mechanism, ischemic symptoms can occur.[6, 10, 15, 112] In conclusion, MMD patients tend to be in a state of chronic vasodilatation[35] and the cerebral hemodynamics are altered: there is an increase in OEF, a reduction of CBF, a proportional increase in posterior cerebral flow[21] and an impaired cerebrovascular reactivity to acetazolamide and CO_2 which suggests a low CVR.[12, 19] It was found out that in children with MMD the decrease in CBF, the increase in CBF and OEF are much more pronounced than in adult MMD populations. These differences may explain higher incidence of ischemic lesions in pediatric MMD patients as opposed to intracranial hemorrhages, which are more common in adults.[113]

About 40% of the asymptomatic MMD patients show disturbed cerebral hemodynamics.[6] Often, there is a discrepancy between the angiographic findings and the clinical severity of disease.[35, 114] Measuring these parameters could give us a better idea of the hemodynamic status of the patients' brain[15] and it could provide a more objective indicator for the selection and efficacy assessment of surgical procedures.[27] There are various possible imaging tools to assess these hemodynamic characteristics.[15]

1. Positron emission tomography and single-photon emission CT

Positron emission tomography (PET) is one of the most reliable hemodynamic assessment tools for MMD and MMS. In this technique, tracers such as H_2 ^{15}O, $C_{15}O^2$, and $^{15}O_2$ are often used. This functional assessment measures CBF, CBV and OEF.[15, 115] Yet, PET is not always available, it is an expensive evaluation tool and it exposes the patients to radiation.[15]

Single-photon emission CT (SPECT) uses blood tracers like 133Xe, 99mTc-ECD, 99mTcHMPAO or 123I-IMP, which cross the blood-brain barrier[19], to measure patients' CBF and CVR.[15, 116] By the additional use of a vasodilator such as acetazolamide or CO_2, the cerebral blood flow increases. However, in areas of reduced cerebral perfusion pressure, the degree of cerebral vessel dilatation is lower because the cerebral vessels are already dilated. A visible discrepancy is then created between areas of adequate vascular reserve and the regions of inadequate reserve.[35] Thus, SPECT is a useful technique for measuring cerebrovascular reserve and it might help to predict the possible further disease progression.[7] SPECT has a good quantitative accuracy but it is expensive and shows risks of radiation damage.[15]

2. Fluid-attenuated inversion recovery MRI

In fluid-attenuated inversion recovery (FLAIR) MRI sequences, 50% of the MMD patients and 33% of the asymptomatic patients show a specific linear hyperintensity following the cortical sulci of the brain. This is called 'the ivy sign' and it is associated with the slow flow of developed leptomeningeal collateral vessels and dilated pial vessels in MMD patients.[9, 11, 12, 15, 117] This ivy sign can be an early indicator of MMD even in the absence of typical moyamoya collaterals [9, 10] or symptoms.[118] The degree of the ivy sign shows a positive correlation with ischemic symptoms but a negative relationship with CBF and an even more negative relationship with CVR.[9, 15, 119] Thus this ivy sign can be used to evaluate the hemodynamic status of the leptomeningeal collateral passages in MMD.[15]

3. Arterial spin labelling MRI

Arterial spin labelling MRI (ASL-MRI) is widely used for the evaluation of MMD. This non-invasive tool is repeatable, has no need for contrast injection and the patient is not exposed to radiation.[15, 120] It can be performed alongside an acetazolamide challenge to judge CVR.[35] It works with endogenous water as a tracer and it uses an inversion pulse to magnetically label upstream intravascular water protons to the region of interest.[19] Nevertheless, presence of extensive collaterals in MMD can prolong the arterial transit delays which results in an inaccurate estimation of perfusion, often a underestimation.[121, 122, 123, 124] This imaging technique has some potential to

monitor the clinical course of MMD, including surgical treatment responses instead of DSA.[125] Ultimately, the feasibility and repeatability of ASL-MRI may improve our understanding of cerebral hemodynamics in MMD.[125]

4. Blood Oxygenation Level Dependent (BOLD) MRI

CO_2-triggered breath-hold BOLD MRI seems to be a promising tool for the evaluation of the CVR in MMD patients. Using the breath-hold technique to trigger hypercapnia results in cerebral vasodilatation and therefore enables the evaluation of the CVR. This technique represents a less expensive and more widely available method for the evaluation of hemodynamics in patients with moyamoya disease.[126] Nevertheless, this technique relies on the cooperation of patients and on individual physiological factors (for example individual lung size and metabolism) which induces some interindividual variation.[127]

Diagnostic biomarkers

A possible future diagnostic tool is the use of biomarkers, which is a non-invasive screening test to detect MMD.[117] Biomarkers are biologically derived agents that can recognize the presence of a disease, may assist in deciding the treatment and/or may help to predict its course.[117] As mentioned above, MMD lacks reliable specific biomarkers. Measurement of proteins in blood, urine or CSF would be useful for this goal. Patients with MMD have increased expression of angiogenic factors and pro-inflammatory molecules. For example, increased levels of bFGF found in CSF of MMD patients or increased levels of hepatocyte growth factor in CSF could be potential biomarkers.[19] Possibly, biomarkers will one day be an intervention point for the treatment of this disease.[117]

Etiopathogenesis of MMD

The exact etiology of MMD is not yet known. There are various factors that might contribute to the pathology of MMD including genetic influences, inflammatory, angiogenic, lipid and environmental factors.[20, 92] These factors will be discussed below. Because of familial aggregation in 10-15% of the patients, MMD is probably a polygenic genetic disease. As mentioned before, the mode of inheritance tends to be autosomal dominant with incomplete penetrance.[9, 31, 129] Several risk factors for development of MMD are identified, such as female sex, family history and East Asian ethnicity.[128]

Genetic factors

1. Initial genetic studies

There is a high suspicion of a genetic contribution in the pathogenesis of MMD because of the incidence of familial MMD cases, the monozygotic concordance of 80%[130], the association of MMD with many genetically transmitted disorders (such as neurofibromatosis, Down syndrome etc.) and the occurrence of a strong ethnicity preference.[185] In Japanese patients, initial studies revealed linkage between MMD and several loci. In 1999, Ikeda at al. found a linkage between the disease and markers located at chromosome 3. Using genomic DNA of both affected and non-affected individuals from different families, they genotyped for 371 highly polymorphic microsatellite markers spanning the 22 autosomes. Analysis revealed strong evidence of linkage of the microsatellite polymorphism D3S3050 which is mapped to chromosome 3p26-p24.2 with a logarithm of odds (LOD) score of 3.18.[132] In genetics, the LOD score is a statistical estimate whether a gene and a disease are linked to one another and a LOD score of 3 means the odds are a thousand to one that this gene is indeed linked to this disease.[133] 3p26-p24.2 was the first genetic locus found to be involved in MMD pathogenesis.[132] Inoue et al. conducted a linkage study of MMD using 15 microsatellite markers on chromosome 6 in 20 affected sibling pairs. They concluded that marker D6S441 on chromosome 6q25.2 might be linked to MMD.[9, 134] A genetic study by Sakurai et al. performed a genome-wide scan of 12 families with moyamoya affected sibling pairs who had not been used for other genome-wide linkage analysis previously.[135] This genome-wide scan with 391 markers revealed markers on chromosome 8q and 12q. Then, 17 additional microsatellite markers were used to analyse linkage on chromosome 8 and another 20 markers to analyse linkage on chromosome 12. [135] They discovered that the region near D8S546 on 8q23.1 yielded significant linkage with an LOD score of 3.6 and that marker D12S1690 on 12p12 reached a suggestive linkage level with an LOD score of 2.3. [135]

An overview of the known associations between MMD and genetic loci can be found in table 3.

2. Discovery of the *RNF213* gene as a genetic susceptibility factor

In 2011, a whole genome-wide association study of 72 Japanese MMD patients and 45 controls was conducted by Kamada et al.[130] Single-marker allelic tests comparing the MMD cases and controls were performed for 785 720 single nucleotide peptides (SNPs). These tests revealed a single locus with a strong association with MMD on chromosome 17q25.[130] To confirm these results, Kamada et al. conducted a locus-specific association study in which 384 SNP markers were selected within the chromosome 17q25-ter region. The SNP markers showing a high

association with MMD were all clustered in a 151-kb region which lies entirely within the ring finger protein 213 (*RNF213)* locus.[130] Kamada et al. identified the *RNF213* gene on chromosome 17q25.3[1] as the first susceptibility gene for MMD in East Asian adults and children with an odds ratio of 190.8. [130, 136] *RNF213* (MIM: 607151), also known as mysterin (moyamoya steno-occlusive disease-associated AAA+ and RING finger protein),[137, 138] encodes an intracellular 591 kDa protein and includes two AAA-type ATPases, an alpha-2-macroglobulin and RING finger domains from its amino to carboxyl termini.[91, 139]

RNF213 mutations in MMD patients tend to cluster around the RING finger domain and C-terminal portion of *RNF213* rather than in its AAA+ domain and N-terminal region.[91]
The *RNF213* p.R4810K genetic variant (c.14429G>A, formerly described as c.14576G>A, rs112735431, ss179362673) is currently the only known founder mutation[91] and its heterozygous presence dramatically increases the susceptibility to MMD in the East Asian population with an odds ratio of 190.8.[91] Analysis of MMD patients and healthy controls revealed that *RNF213* p.R4810K significantly increased familial MMD risk in Japanese, Chinese and Korean population, with a 5 to 36 times larger effect sizes than that in sporadic cases.[140] Homozygous MMD patients with the R4810K variant are rare (10%).[145] They had a younger age at onset of symptoms, their symptoms were more severe, the disease mainly manifested as cerebral infarction, there was more PCA involvement at the initial onset, there was more cognitive dysfunction and they had a worse prognosis.[141, 142, 143, 144] This suggests that the homozygous *RNF213* p.R4810K might be a good biomarker for predicting an early-onset and severe form of MMD.[145]

A study by An et al. investigated the relation between the vascular tortuosity of the internal carotid artery and *RNF213* p.R4810K variant in MMD patients.[147] Data in the study suggested that the tortuosity of ICAs was significantly lower in the mutant group compared to the wild-type group and the healthy control subjects showed the highest tortuosity.[147] Lower tortuosity of the ICA seems to affect wall shear stress around the bifurcation of the ICA. Vascular tortuosity influences hemodynamics and possible relationships between hemodynamics and vascular remodeling have been proposed.[147]

It is striking that this *RNF213* variant has been shown to be associated not only with MMD, but also with intracranial artery steno-occlusive stenosis / occlusion (ICASO) of the non-MMD type among East Asian populations, including Chinese, Japanese, and Korean people.[91, 148, 149, 150] ICASO is an important cause of stroke and can occur by various causes such as atherosclerosis, dissection,

cardio embolism or vasculitis. In particular, atherosclerosis is known to be a main cause of ICASO and can be caused by numerous risk factors: hypertension, hyperlipidemia, diabetes and smoking.[151, 152] Miyawaki et al. found that 23.8% of the patients with non-MMD ICASO had the p.R4810K variant in *RNF213*.[146] Another ICASO sample found a similar rate of 21.9%.[152] These findings strongly indicate that some cases of ICASO attributed to unknown etiology or atherosclerosis might be part of the MMD spectrum caused by the p.R4810K variant in *RNF213*.[152] Among the ICASO patients, *RNF213* variant carriers were younger and more likely to have a family history of MMD than non-carriers were.[153] A study by Park et al. also found an association between *RNF213* p.R4810K and systolic blood pressure: hypertension was more frequent in MMD patients with the p.R4810K polymorphism of the *RNF213* gene than in MMD patients with wild type gene.[149] This finding is also confirmed by Koizumi et al.[154]

The polymorphism in p.R4810K was identified in 95% of familial MMD and in 79% of sporadic Asian MMD cases.[91, 131, 139, 155] The total incidence of *RNF213* p.R4810K variant carriers is estimated to be 16.16 million people (0.5-2.0%) in East Asian countries.[2, 156, 157, 158] The allele frequency of p.R4810K was 0.43% in the Chinese population, which is only one third of the allele frequency in the Japanese or Korean populations.[22] Yet, the incidence of MMD in the East Asian population is much lower, indicating the need of an additional insult in genetically susceptible individuals, such as immune or inflammatory response for the onset of MMD.[2, 13, 65] This is the so-called 'double-hit theory'.[13, 85, 155] In conclusion, the R4810K variant is a founder mutation in East Asian however it is absent from European, African and Hispanic MMD cases.[9, 27, 159, 160] The high prevalence of the p.R4810K founder mutation among East Asians may account for the higher prevalence of MMD than in Caucasians.[32] Furthermore, no patients with MMS have been reported to carry the *RNF213* p.R4810K variant.[150] An analysis of Moteki et al. revealed that about 20% of Japanese MMD patients did not harbor susceptibility variants of *RNF213*, indicating the presence of other susceptibility genes for MMD.[161]

Other non-p.R4810K *RNF213* variants were identified in East Asian patients. A Korean genetic study found that the variant *RNF213* p.E4950D was more frequent in MMD patients and they mentioned that it was particularly relevant to the occurrence of moyamoya in the adult group.[162] In a Chinese study, two other rare variants of the *RNF213* gene, p.E4950D and p.A5021V, were found to be significantly associated with MMD.[140] A study by Jang et al. confirmed this latter variant as a possible variant in MMD.[163] More rare non-p.R4810K variants of *RNF213* in East-Asian MMD patients were identified such as p.D4863N, p.D5160E and p.D5176G.[91] All identified *RNF213*

variants in East-Asian MMD patients are listed in figure 4. It is suspected that many variants in *RNF213* can cause MMD.[140]

Up to now, no susceptibility gene has been conclusively detected in non-Asian patients.[91] In the European MMD population, two novel missense variants of the *RNF213* gene were found; namely p.(Lys4185Glu) and p.(Ala4188Thr).[164] Another study of 5 European multigenerational families found a rare variant of *RNF213* in all affected members of 2 of these 5 families; missense p.A3927T and p.P4033L variants detected in these 2 families are now included in the mutational European hotspot, highly suggesting that they might be causative variants.[165] A study of Slovakian and Czech MMD patients noted p.R4019C, p.E4042K, p.V4146A, and p.W4677L as rare variants of the *RNF213* gene.[166] Other known rare variants of *RNF213* in Caucasian patients are p.N3962D, p.R4062Q, p.D4013N and p.P4608S.[91, 167] Two *de novo* variants, p.H4014N and p.C4017S affect histidine or cysteine residues of the RING-finger domain in *RNF213* that are directly involved in zinc coordination.[167] All identified *RNF213* variants in Caucasian MMD patients are listed in figure 4. These variants are all predicted to alter the *RNF213* structure or impair its binding to partners.[167] These studies add weight to a growing amount of evidence that variation in the *RNF213* gene also has an important role in disease susceptibility in European populations.[164, 165]

Mysterin is the only known protein that exerts both AAA+ ATPase and E3 ubiquitin ligase activities.[91, 137, 168] Multiple studies have explored the physiological role of mysterin but a precise and unified understanding has not been established.[91]
A study with *RNF213* mutant zebrafish was done to figure out the function of *RNF213*.[151, 169] These *RNF213* mutant zebrafish showed abnormal angiogenesis in intersegmental vessels and cranial secondary vessels. [151, 169] Angiogenesis and vasculogenesis are two different stages of normal vascular development: Vasculogenesis is the preceding process in which hemangioblasts differentiate into vascular endothelial cells and form the primitive vascular plexus. [91] Angiogenesis is the formation of new sprouts from existing vessels, which is thus a secondary process to vasculogenesis.[169] This study suggests that *RNF213* is involved in intracranial angiogenesis primarily in the embryonic and postnatal period[170] and not in vasculogenesis.[13, 85, 155]

Despite this obvious phenotype in zebrafish, a study with *RNF213* deficient mice showed some controversial findings. First of all, all the homozygous mutants (*RNF213*-/-) were born normally and grew normally.[155] There was no significant difference in the structure of the major arteries at the base of the brain, no difference in MRA findings of intracranial arteries, no steno-occlusive

histological changes (no intimal hyperplasia or medial layer thinness) around the terminal portions of the internal carotid artery and no abnormal vascular network developed at the base of the brain.[85, 155] After common carotid artery (CCA) ligation, initially only the wildtype mice showed temporary hyperplasia of the intima and medial layers. Yet, 14 days after the CCA ligation, the intima and medial layers of *RNF213*-/- mice were significantly thinner than in wild-type mice.[155] This finding matched one typical histological characteristic of MMD.[155] Another study on *RNF213* mRNA expression in mouse brains was done by Sato-Maeda et al. [171] They subjected the mouse brain to 60 minutes of transient middle cerebral artery occlusion. They found an upregulated *RNF213* gene in the ischemic brain as early as 6 hours after occlusion. This indicates the involvement of *RNF213* in cerebral ischemia which is an underlying pathology of MMD.[171] It still remains unclear how mutations in *RNF213* may affect protein function in MMD patients [85, 92, 155] yet *RNF213* deficiency could lead to fragility in the vessels which makes them more vulnerable to hemodynamic stress and secondary insults such as infection, radiation or autoimmune response.[155] This could facilitate the development of MMD.[155] It is however clear that an abnormality in *RNF213* alone, is not sufficient to induce MMD.[155]

3. GENETICS BEYOND *RNF213*

1. *ACTA2*

Actin alpha 2 (*ACTA2*) mutations are responsible for 10 –15% of all familial thoracic aortic aneurysms and dissections and are currently the most commonly identified cause of an inherited predisposition for thoracic aortic disease.[172, 173, 174] Further linkage analysis and association studies in 20 families with *ACTA2* mutations uncovered a predisposition among mutation carriers for occlusive vascular diseases, such as coronary artery disease and MMD. Histopathologic characteristics seen in vessels of patients with *ACTA2* mutations are a significant medial degeneration by focal loss of SMCs and an elastic fiber disruption which are also histological characteristics of MMD.[172, 175]

ACTA is a gene on 10q23.31 that codes for α2-smooth-muscle-actin (α2-SMA) where 70% of the actin is composed.[173, 176] Actin is an important component of muscle cell contraction[175] and the major function of vascular smooth muscle cells is contraction in response to the stretch caused by pulsatile blood flow.[65] Thus, *ACTA* mutations can cause diffuse smooth muscle dysfunction and can induce an arteriopathy. *ACTA2* mutations are seen in MMD patients but this genetic mutation is only present in a small minority of MMD cases.[86, 117]

2. HLA

Human leukocyte antigen (*HLA*) genotyping has been conducted to discover MMD-specific genetic markers.[25] The *HLA* genes are located on chromosome 6.[7, 18] In Korean MMD patients, the HLA-B35 allele was significantly recognized. In MMD pathogenesis, HLA-B35 might have a role in terms of auto-immunity or infection.[25, 177] Familial MMD patients showed significantly increased frequencies of HLA-DRB1*102 and HLA-DQB1*0609 phenotypes in comparison to the healthy control group and the non-familial MMD patients.[21, 25] These HLA-haplotypes could be associated with arterial occlusion and intimal fibrosis.[25]

3. BRCC3

A rare recessive X-linked moyamoya syndrome was recently reported in three families: The disease is caused by an overlapping deletion at Xq28 which leads to complete loss of expression of both *MTCP1* and *BRCC3* genes. All patients showed a maternal inheritance.[91, 178] In nine out of ten mutation carriers, bilateral moyamoya angiopathy was present.[91, 178] BRCA1/BRCA2-containing complex subunit 3 (*BRCC3*) encodes for a nuclear DNA repair complex and a cytoplasmic complex that might have a role in cardiomyocyte protection. Studies of knocked down zebrafish suggest that BRCC3 might also play an important role in angiogenesis and vessel maintenance.[91, 179] It may therefore be involved in the development of moyamoya angiopathy in these patients.[178] Other frequent symptoms in patients with this mutation are short stature, hypergonadotropic hypogonadism, stereotyped facial dysmorphism and heart involvement.[91, 178]

4. SAMHD1 gene

Xin et al. described an autosomal recessive condition characterized with cerebral vasculopathy and early onset of stroke in 14 individuals in Old Order Amish.[180] The phenotype of the disease was highly heterogeneous, ranging from severe developmental disability to normal schooling. Cerebral vasculopathy is a major characteristic of this condition.[180] Neuroimaging findings include chronic ischemic changes, multifocal stenoses of the large intracranial arteries including moyamoya morphology in 50% of the mutation carriers, aneurysms and evidence of previous acute infarction and hemorrhage. [180] These clinical features are caused by a single mutation in the *SAMHD1* gene. Little is known about the function of *SAMHD1*: evidence suggested an immune function as it is upregulated in response to viral infections and it may have a role in mediating TNF-α pro-inflammatory responses. A more recent study suggests that *SAMHD1* may have a protective role in preventing self-activation of innate immunity. [180] Further studies of the role of *SAMHD1* in vessel integrity and homeostasis will be necessary.

5. NF1 gene

The *NF1* gene (MIM: 613113) is a tumor suppressor gene which encodes neurofibromin. Neurofibromin is expressed in both endothelial cells and vascular smooth muscle cells (VSMCs).[91] Heterozygous loss-of-function mutations in the *NF1* gene causes neurofibromatosis Type 1 (NF1) (MIM: 162200), an autosomal dominant disorder affecting approximately 1/3000 newborns. This disease is associated with café au lait maculae, neurofibromas, cutaneous freckling, iris hamartomas and a predisposition to various malignant tumors.[91, 181] Furthermore, in NF1 vascular lesions are often present which show an intima hyperplasia and leads to stenosis. In 1 - 4% of the NF1 cases a moyamoya angiopathy is present. This leads to a hypothesis that the *NF1* gene might play a role in MMD pathogenesis. [91]

6. GUCYA3

A study of Hervé et al. in 2014 conducted a genetic analysis on three families, including 9 individuals affected by a syndromic condition associating moyamoya with achalasia. Achalasia is a rare disease characterized by failure of the lower esophageal sphincter to relax and aperistalsis of the esophagus. [182] In all three families they identified homozygous *GUCY1A3* (MIM 139396) mutations cosegregating with the affected phenotype.[182] *GUCY1A3* encodes the α1 subunit of soluble guanylate cyclase (sGC), which is the major receptor for nitric oxide (NO).[91] NO is one of the principal molecules in vasoregulation by regulation of smooth cells in vascular and extravascular systems.[91] It is further responsible for endothelium-dependent vasorelaxation, inhibition of leukocyte and platelet adhesion and attenuation of inflammatory mediators.[65] This discovery implicated that alterations of NO-sGC pathway might lead to an abnormal vascular-remodeling process in sensitive vascular areas. It is hypothesized that this concept could be also valid with sporadic, non-syndromic forms of MMD.[182, 183]

Table 3: overview of the known linkages between MMD and genetic loci.[184]

LOCATION	PHENOTYPE	INHERITANCE	PHENOTYPE MIM NUMBER	GENE/LOCUS	GENE/LOCUS MIM NUMBER
3p26-p24.2	Moyamoya disease	AR	252350	*MYMY1*	252350
4q32.1	Moyamoya 6 with achalasia	AR	615750	*GUCY1A3*	139396
8q23	Moyamoya disease 3		608796	*MYMY3*	608796
10q23.31	Moyamoya disease 5		614042	*ACTA2*	102620
17q11.2	Neurofibromatosis type 1	AD	162200	*NF1*	613113
17q25.3	Moyamoya disease 2	AD, AR	607151	*RNF213*	613768
Xq28	Moyamoya disease 4	XLR	300845	*MYMY4*	300845

In conclusion, considerable studies revealed an association between MMD and several loci: 3p24-p26, 4q32.1, 6p25, 8q23, 10q23.31, 12p12, 17q25 and Xq28.[9, 13, 31, 131, 155] This suggests genetic heterogeneity in MMD.[31, 172] Despite the genetic appearance of MMD, sporadically occurring MMD is still the most prevalent form.[19, 167]

Biomarkers

Because of compensatory revascularization, MMD is characterized by increased levels of pro-inflammatory molecules and angiogenic factors in serum and/or CSF.[13, 86, 185] This chapter discusses several biomarkers present in MMD patients. Biomarkers can indirectly say something about etiopathogenesis, but rather points to the various underlying processes in MDD.

1. ANGIOGENIC FACTORS

Immunohistochemical studies have confirmed that many factors related to angiogenesis such as vascular endothelial growth factor (VEGF) receptors and fibroblast growth factor (FGF) receptors are abnormally expressed in vascular endothelial cells (ECs).[86] This finding may explain the pathologic angiogenesis and spontaneous bleedings seen in MMD patients.[13]

A large RNA sequencing study by Peng et al. on differentially expressed genes in peripheral blood of MMD patients in comparison with healthy controls, demonstrated that up-regulated genes in MMD patients were mainly involved in extracellular matrix (ECM) organization. [187] ECM plays very important roles in many biological processes such as cell proliferation, cell migration and cell adhesion. Moreover, ECM proteins and proteoglycans can interact with various growth factors like VEGF and bFGF to regulate many signal transduction pathways. Thus, disruption of ECM organization might somehow trigger abnormal proliferation, differentiation and migration of vascular cells like smooth muscle cells in the blood vessel wall. This subsequently results in the accumulation of fibrous substances, finally leading to the progressive vascular stenosis typical in MMD.[187]

1. MMPs and TIMPs

Matrix metalloproteinases (MMPs) play a role in both anti-angiogenic and pro-angiogenic processes. [5, 92, 187] MMPs can promote blood-brain barrier damage, hemorrhage and oedema[65] but they can also induce angiogenesis as a response to hypoxia.[31] Active MMP-9, also known as gelatinase B,[188] is a proteolytic protein that causes destabilization and leakiness of blood vessels by degradation of the endothelial basal lamina.[92, 189] Increased expression of MMP-9 seen in serum of MMD patients may thus contribute to the spontaneous intracranial hemorrhages typical for MMD.[13, 65, 186, 188] Another function of increased active MMP-9 is formation of extensive collateral vessels, the moyamoya vessels, by remodeling of the ECM.[188] A study by Kang et al. found more than a 30-fold increase in serum MMP-9 of MMD patients.[188] The pro-angiogenic and vascular barrier rearranging action of MMP-9 is strongly dependent on the bioavailability of VEGF.[189] Thus, functional impairments in MMD could be partially abolished by inhibiting the VEGF signaling pathway.[189]

A study by Kang et al. found a decrease in MMP-3 levels in MMD patients. It is known that an overexpression of MMP-3 leads to inhibition of smooth muscle cell migration and neointima formation in a rabbit vein graft model. [190] Thus, this implies that decreased MMP-3 levels, seen in de serum of MMD patients, may result in the facilitation of the smooth muscle cell migration and intimal hyperplasia.[188]

Inhibitors of MMPs are tissue inhibitors of metalloproteinases (TIMPs).[25, 65] The balance between MMP and TIMP is important in blood-brain barrier maintenance and vascular angiogenesis.[65, 92] In MMD there is an decreased expression of TIMP-1 and TIMP-2 which leads to less inhibition of MMPs.[25, 65, 188] The occurrence of single nucleotide polymorphisms in TIMP-2 and TIMP-4 in familial MMD was studied.[25] A G/C heterozygous genotype at position -418 in the promoter region of TIMP-

2 was found to be associated with familial MMD, significantly more than that of healthy control groups or non-familial MMD.[21, 25, 65] For familial MMD, this single nucleotide polymorphism might be a genetic predisposing factor.[25, 31]

In conclusion, MMPs and their tissue inhibitors regulate the interaction between SMC and the ECM.[191] Disturbance of balance between TIMP and MMP is seen in MMD[5] and could lead to spontaneous intracranial hemorrhages, angiogenesis, excessive smooth muscle cell migration and the intimal hyperplasia seen in histopathologic changes in MMD.[25, 65]

2. Vascular endothelial growth factor

VEGF levels are significantly higher both in serum and dura of MMD patients in comparison with healthy controls.[13, 65, 155] A study by Weng in 2017 found a fivefold increase in VEGF serum levels.[192] This increase in VEGF levels may be caused by the upregulated levels of regulatory T-cells (Treg cells) and T-helper 17 (Th17) cells, seen in MMD.[192] Treg cells secrete VEGF-A in response to hypoxia and IL-17 is responsible for upregulating VEGF and promoting VEGF-receptor expression.[192] VEGF binds its receptor tyrosine kinases: VEGF receptor-1 and VEGF receptor-2, also known as kinase insert domain containing receptor (KDR).[65] VEGF promotes angiogenesis in cerebral ischemia and thus might cause the formation of pathological vessels.[65, 188]

3. Monocyte chemoattractant protein-1

Monocyte chemoattractant protein-1 (MCP1) is another molecule that is increased in plasma of MMD patients.[13, 65, 155] A study by Kang et al. found more than a 15-fold increase in serum MCP1 of MMD patients.[188] MCP1 is a pro-arteriogenic molecule and is associated with the recruitment of vascular progenitor cells and thus the subsequent formation of MMD vessels which will be described below.[25, 188]

4. Endothelial colony-forming cells

The combination of increased levels of MMP-9[31], VEGF[193] and MCP1 may result in recruitment of endothelial colony-forming cells (ECFCs), previously termed “endothelial progenitor cells” from the bone marrow.[5, 92] Normally, ECFCs stay in a homeostatic bone marrow microenvironment, but stimulating factors such as inflammation, trauma or ischemia can mobilize these ECFCs and they leave the bone marrow.[86] These cells play a role in repairing the endothelium by first adhering to the endothelial cells in the target tissue and then differentiate into new endothelial cells.[86, 194] They have been implied to be a pathogenetic marker in MMD.[5] A study by Ah Choi et al. in 2019 investigated the activity of ECFCs of MMD patients versus healthy controls.[195] Chronic cerebral

hypoperfusion was induced in a rat model via ligation of the bilateral common carotid arteries. A part of the rats was injected with ECFCs from MMD patients, the other part was injected with ECFCs from healthy controls.[195] The normal ECFC-treated group revealed a greater amount of neovasculogenesis and thus improvement in the restoration of cerebral perfusion in comparison with the MMD ECFC-treated group. This in vivo study suggests an impaired functional role of ECFCs in the pathogenesis of MMD.[195, 196] A microscopic study on the morphology of these dysfunctional ECFCs showed a disrupted mitochondrial morphology, including a shorter and more circular shape.[197] In addition to morphological abnormalities, functional limitations of the mitochondria were also found: a decreased oxygen consumption rate, a reduced basal respiration, a decreased ATP production and an increased intracellular Ca2+ concentration. Furthermore, the ECFCs from MMD patients showed increased reactive oxygen species (ROS) levels.[197] Interestingly, administration of a scavenger that only decreased the ROS levels not only reversed both the mitochondrial morphological and functional abnormalities but also restored the angiogenic activity of the ECFCs.[197] Mitochondria are involved in energy production, signaling cascades, cellular proliferation, senescence and cell death.[197] Mitochondrial dysfunction results in numerous diseases, such as neurodegenerative disorders, metabolic diseases and even cancers.[197] This study indicates that the impaired function of the ECFCs in MMD patients may result from mitochondrial abnormalities which suggests that MMD may be a mitochondria-related disease.[197] To further prove this hypothesis, mutations in the nuclear DNA that encode mitochondrial components or mutations in the mitochondrial DNA should be identified.

A study by Phi et al. found higher expressed levels of CXCL6, IL8, CCL2 and CCL5 in ECFCs derived from MMD patients. Within vitro migration assays, they discovered that CCL5 is the main chemokine mediating smooth muscle progenitor cell (SPCs) recruitment.[198] Although both ECFCs and SPCs showed defective functions in previous studies, these data indicate that mainly ECFCs and not SPCs are the major players in pathogenesis of MMD.[198] They concluded that defective ECFCs in MMD patients direct the aberrant recruitment of SPCs to critical vascular locations through the action of CCL5.[198]

A study by Bao et al. found a correlation between ECFC levels and score on the modified ranking scale (mRS), which is a scale to measure the degree of disability or dependence in the daily activities of people who have suffered stroke or other causes of neurological disability: the higher the ECFC levels, the better the mRS score.[194] This could be interpreted that good angiogenesis leads to less permanent brain damage.

5. Circulating endothelial cells

Another pathogenetic marker that is present in higher levels in multiple vascular diseases are circulating endothelial cells (CECs) which are derived from the vascular wall.[194] MMD has been characterized by prominent vascular changes probably caused by endothelial injury and the level of CECs in MMD patients is significantly higher than in the control group.[194] CECs may serve as an in vivo indicator of vascular injuries.[194]

6. Angiopoietin-2

MMD is characterized by a highly unstable cerebrovascular system which is prone to rupture due to pathological neovascularization.[199] Angiopoietin-2 facilitates vascular responses regulating angiogenesis and EC barrier integrity which makes it a pro-angiogenic and barrier-destabilizing factor.[199] Angiopoietin-2 was significantly upregulated in moyamoya vessels especially in the M3 segment of the MCA, while serum concentrations of soluble angiopoietins were not changed. This important finding suggests a local effect of the angiopoietin-2 up-regulation.[199] After in vitro incubation of cerebral endothelial cells with serum from these MMD patients, an intracellular overexpression and secretion of angiopoietin-2 in an autocrine manner occurred. In addition, increased levels of antiopoietin-2 lowers the transendothelial electrical resistance of brain ECs which induced a downregulation of important cell–cell contacts and thus a reduced ability to form reliable EC–EC interactions. This loss of endothelial integrity was absent in endothelial cells of non-brain origin, again suggesting local brain endothelium specificity.[199] These findings suggest that angiopoietin-2 plays a decisive role in the development of vascular instability and permeability in MMD.[199]

7. Basic fibroblast growth factor

Increased production of basic fibroblast growth factor (bFGF) is seen in CSF of MMD patients [19, 65, 188] and there are also increased levels in the SMCs, intima and endothelial cells of the circle of Willis and the superficial temporal artery.[5, 65, 188, 200] bFGF was not detected in the plasma of MMD patients possibly because of its low permeability through the blood-brain barrier (<1%).[200] This suggests that the production and release of bFGF in MMD patients are a local rather than systemic phenomen.[188, 201] bFGF could induce proliferation and differentiation of smooth muscle cells, vascular endothelial cells and fibroblasts which causes a vascular stenosis and further stimulate the formation of the typical moyamoya collateral blood vessels by promoting vascular endothelial cell movement, proliferation and differentiation.[5, 7, 21, 92, 202] The reason why bFGF results in two

different pathological MMD changes, both stenosis of the internal carotid artery terminal and the formation of abnormal vascular network in the skull base, might be related to different concentration of bFGF in the two positions.[201]

8. Hepatocyte growth factor

A rise in expression of hepatocyte growth factor (HGF) in CSF and in the intracranial artery is seen in MMD patients.[13, 203, 204] HGF was discovered as a growth factor of hepatocytes but it was subsequently shown to have numerous functions in every tissue. HGF is additionally known as a strong inducer of angiogenesis and it might be even more potent than VEGF or bFGF.[202, 204] Via a tyrosine kinase receptor encoded by the c-Met proto oncogene, HGF can mediate its biological responses.[204] HGF and c-Met are both expressed in the brain parenchyma and cerebral ischemia upregulates the pair.[202] Nagayama et al. reported that HGF is expressed in the reactive astrocytes in the peri-infarct region after permanent MCA occlusion.[205] Overexpression of HGF gene stimulates angiogenesis and ameliorates tissue damage due to this MCA occlusion which makes HGF both an angiogenic and a neurotrophic factor.[204] Other studies mention that HGF may also be involved in vascular smooth muscle cell migration.[204, 206] Besides patients with bacterial meningitis and patients with Alzheimer disease, MMD is the third unique disease in which CSF levels of HGF is significantly elevated.[204]

9. Cellular retinoic acid-binding protein-I

In CSF, elevated cellular retinoic acid-binding protein-I (CRABP-I) levels are measured.[65, 200, 207] CRABP-I can be a candidate protein in MMD pathogenesis. It increases retinoic acid production which might lessen the inhibition of retinoid activity on growth factors and cytokines for smooth muscle proliferation and migration.[208] This results in neo-intimal thickening typically seen in MMD. Bilateral MMD cases have significantly higher levels of CRABP-I than unilateral MMD cases.[25, 208]

10. Hypoxia induced factor-1α and transforming growth factor beta 1

Hypoxia induced factor-1α (HIF-1α) and endoglin too has increased levels in the endothelium and intima of the MCA of MMD patients.[19, 209] HIF-1α upregulates transforming growth factor-β (TGF-β) transcription and in the presence of bFGF or HGF, HIF-1α promotes the proliferation of smooth muscle cells.[51]

It is seen that serum TGF-β1 is also increased in MMD patients.[13, 65, 155, 200] TGF- β1 was shown to increase elastin synthesis, which is a potential mechanism for intimal thickening.[19] Furthermore, in normal concentrations, it is involved in regulation of various biological processes (e.g. synthesis of

ECM, wound healing and cell proliferation, differentiation and migration).[210] It thus plays a critical role in formation of an abnormal internal elastic lamina, the fibrotic thickening of the intima and the excessive ECM deposits in MMD vessels.[19, 21, 187, 202] Further, in supraphysiological concentrations, it has an additional pathological angiogenetic function: TGF-β1 produced by Tregs can also induce production of VEGF and thus stimulate subsequent vascular endothelial cell proliferation and formation of abnormal vessels in MMD.[192, 202] In addition to the increased serum levels of TGFB1, it is seen that the cerebrospinal fluid too might contain higher levels of TGFB1[200, 207] although this was not confirmed in every study.[205, 210]

11. Caveolin-1

Caveolin-1 (Cav-1) is a protein component of caveolae plasma membrane domains and plays an important positive role in the regulation of endothelial cell differentiation which is an essential step in the process of angiogenesis.[211] A study by Chung et al. found that the serum level of Cav-1 was positively associated with the distal ICA diameter.[211] In MMD patients, the ICA diameters are significantly smaller than the diameters of ICAs in healthy controls which confirms the lower levels of caveolin-1 found in serum of MMD patients.[212] A study by Bang et al. found even more decreased levels of Cav-1 in *RNF213* variant carriers.[212] An in vitro experiment showed that a decreased Cav-1 level induces reduced capillary formation, vascular cell apoptosis and impaired angiogenesis.[211] Thus a lower serum Cav-1 level is associated with the pathological features of arterial remodeling seen in MMD patients.[211]

12. Connexin 43

Gap junctions are intercellular channels between neighboring cytoplasms. These channels provide the possibility of small molecule diffusion between cells.[214] Consequently, this type of communication is an important mechanism for regulating events between cells. Connexin 43 (Cx43) is an intercellular gap junction protein playing an important role in the normal function of the heart and arteries.[213] Immunofluorescence staining of Cx43 on cerebral artery specimens from patients with MMD showed that abundant fluorescence of Cx43 could be seen in the cytoplasm of the media and the neointima of the cerebral arteries.[213] However, in the control group, no fluorescence or few fluorescence of Cx43 was seen in the cytoplasm at both the media and the intima. As mentioned before, it is considered that SMCs in MMD patients migrate from the media of the vessels to the intima through a fractured internal elastic lamina. This study suggests that Cx43 may play an important role in vascular intimal thickening in MMD.[213]

13. Haptoglobin

A study by Kashiwazaki et al. investigated the cerebrospinal fluid of MMD patients. Data showed an increased level of haptoglobin in CSF.[207] Haptoglobin is a plasma α2-glycoprotein consisting of an alpha and a beta polypeptide chain and it is produced in the liver. Haptoglobin has several biological functions: It is recognized as an acute-phase protein that operates as an antioxidant by binding free hemoglobin. It is also known as an inflammation-sensitive protein and it is induced by proinflammatory cytokines such as IL-6. But most importantly in the pathogenesis of MMD, haptoglobin acts as a pro-angiogenic factor.[207] Chronic elevation of serum haptoglobin in the setting of ischemia and inflammation is considered to stimulate angiogenesis and tissue repair. Hence, haptoglobin might be involved in the development of moyamoya vessels in MMD.[207]

14. α-1-B-glycoprotein

The same study by Kashiwazaki et al. also showed an increased level of α-1-B-glycoprotein.[207] Its function is still unknown. α-1-B-glycoprotein has been reported to be overexpressed in pancreatic and hepatocellular cancers but there is no information on its role in the central nervous system. It has also been reported that a couple of proteins, including A1BG, are upregulated in the plasma of pediatric patients with multiple sclerosis.[207] Future studies are necessary to investigate the significance of α-1-B-glycoprotein overexpression in the CSF of MMD.

15. Cyclooxygenase-2

A study by Yamamoto et al. demonstrated that SMCs in MMD responded to inflammatory stimuli, such as interleukin-1β[214], to produce excessive amounts of prostaglandins E2 through the activation of cyclooxygenase (COX)-2.[215, 216] Zhang et al. found higher levels of COX-2 in all layers of the MCA samples from all 5 hemorrhagic MMD patients, whereas positive but weak expression of COX-2 was observed only in the endothelial layer from most ischemic MMD patients. This increased expression of COX-2 was not detected in the MCA samples from the controls.[214] Increased levels of COX-2 contribute thus to higher levels of prostaglandin E2 which increases vascular permeability and decreases vascular tone.[214] This could explain why COX-2 expression was found to be much higher in hemorrhagic MMD patients than in their ischemic counterparts. This study suggests that selective COX-2 inhibitors might prevent the development of MMD and the occurrence of hemorrhagic stroke.[214, 216]

16. Noncoding RNA's

Noncoding RNA's are microRNA's (miRNAs) or circular RNA's (circRNAs) without protein-coding ability.[217] Several of these RNA's are differently expressed in patients with MMD.[29]

MiRNA's negatively regulate the expression of many proteins by altering their gene expression. This occurs through posttranscriptional repression or mRNA degradation. Serum of MMD patients showed elevated levels of miRNA's associated with *BRCC3* and *RNF213* which leads to altered expression of both genes. Both of these genes were found to be involved in pathogenesis of MMD, as mentioned before.[131] In addition, a specific single nucleotide polymorphism of miRNA-196a was related to MMD. The gene target of microRNA-196a is ANXA1 which is expressed in endothelial and smooth muscle cells. It mediates apoptosis and inhibition of cell proliferation.[131]

A study by Zhao et al. found increased expression of miRNA let-7c in MMD patients.[218] They were the first to confirm that let-7c could bind to *RNF213* using a dual luciferase assay thus this data suggests that increased expression of let-7c could contribute to MMD by targeting *RNF213*. This makes microRNA let-7c a potential biomarker for diagnosing MMD. Further experiments are warranted to examine the association between *RNF213* and let-7c in vitro and in vivo.[218]

MiRNA sequencing in patients after ischemic stroke showed some affected miRNAs. Since one of the major manifestations for MMD patients is cerebral ischemia, the MMD-affected circulating miRNAs might share some commonalities with miRNAs associated with ischemic stroke. Indeed, the miR-27a-3p in cerebral endothelial cells was also found in patients after ischemic stroke and it significantly reduced the phosphodiesterase 3 level (PDE3) which was found to play a role in endothelial function and vascular integrity.[219] Two brain-specific miRNAs, namely miR-9-5p and miR-124-3p are decreased in serum of patients with a history of acute ischemic stroke.[185, 220] On the contrary, CSF from patients with ischemic stroke showed a significant increase in miR-9-5p levels compared to controls. A possible explanation for this opposing direction of concentration change between CSF and serum is the presence of the blood–brain barrier blocking miRNA complexes from entering the bloodstream.[221]

CircRNAs are single-stranded circular molecules that are stably and abundantly expressed in human cells. CircRNAs regulate gene expression at the transcriptional or posttranscriptional level through interaction with miRNAs.[223] A study by Zhao et al. demonstrated for the first time that at least 146 circRNAs are aberrantly expressed in MMD patients. Of these, 29 circRNAs were upregulated and 117 circRNAs were downregulated as compared to healthy controls.[223] Functional annotation of these differentially expressed circRNAs showed that they are primarily involved in

angiogenesis, cellular and metabolic processes and immune responses.[223] The results demonstrate that circRNAs too are associated to the pathogenesis of MMD partly through modulation of the mitogen-activated protein kinase (MAPK) signaling.[223] The MAPK signaling pathway plays important roles in vascular pathological processes and vascular inflammation. Inflammatory responses lead to hyperplasia of intimal VSMCs, which causes lumen stenosis, typically seen in MMD.[217] Many cytokines can induce proliferation of vascular smooth muscle cells via this MAPK pathway, such as platelet-derived growth factor, angiotensin II and tumor necrosis factor-α, all of which are present at elevated concentrations in MMD patients.[217, 223] Thus, the MAPK signaling pathway should be further studied as the major pathway associated with MMD pathogenesis and it could be a possible therapeutic target in the future. [222, 223]

17. Transfer RNA-derived fragments

Transfer RNA-derived fragments (tRFs) were originally viewed as tRNA degradation products, but accumulating evidence suggests that they might serve roles in various biological processes including cell proliferation, regulation of gene expression and tumor suppression.[224] A Chinese study compared the serum tRFs of MMD patients with these of healthy controls and significant differences were found: 38 tRFs were differentially expressed and may thus be linked to the development of MMD.[224] Amongst these differentially expressed tRFs, 5'-tiRNA derived from $tRNA^{Glu}$(TTC) was the most significantly upregulated tRF, while i-tRF from $tRNA^{Gln}$(CTG) and tRF-1 from pre-$tRNA^{Gln}$(CTG) were significantly downregulated. In addition, tRFs from $tRNA^{Gly}$ and $tRNA^{Val}$ were upregulated in patients with MMD.[224] These latter tRFs are known to be upregulated in ischemic tissue which occurs in MMD patients because the stenosis of the intracranial vessels leads to reduced blood supply and cerebral ischemia.[224] These results suggest that the above-mentioned alternate expressed tRFs may have the potential to serve as novel possible biomarkers for MMD. [224]

2. INFLAMMATORY FACTORS

There is a strong epidemiologic association between moyamoya angiopathy and certain diseases with a component of inflammation. This may indicate that pathologic vessel changes typically seen in MMD patients may be sequela of systemic inflammation.[193, 225] Research indicated that interferon gamma, tumor necrosis factor alpha and other proinflammatory cytokines might synergistically activate the transcription of *RNF213*, which is an important susceptibility gene in MMD as mentioned before.[22] Further, MMD patients exhibited a significant increase of naïve CD4 cells and naïve B cells, as well as a significant decrease of resting natural killer cells compared to healthy

controls. The combination of this disturbance in these three leukocyte subtypes and other cell types like ECFCs and smooth muscle cells may contribute to the vascular occlusion seen in MMD. Nonetheless, the exact molecular mechanism whereby these disturbed cell types contribute to the progression of MMD needs to be further investigated in the future.[187]

1. Interleukin-1β

Interleukin-1β (IL-1β) is produced by endothelial cells, smooth muscle cells and macrophages and its secretion is induced by microbial products that stimulate toll-like receptors. Thus the presence of increased levels of IL-1β among MMD patients implies that an inflammatory molecule may be involved in the disease process.[188] Elevated levels of IL-1β result in activation of endothelial and smooth muscle cell proliferation, macrophage activation and endothelial dysfunction. Further, IL-1β increases the vascular permeability by release of prostaglandin E2.[188]

2. T-cells

Weng et al. revealed an increased level of peripheral Treg and Th17 cells in MMD patients compared with healthy controls.[192] Serum expression of Treg-related TGF-β and IL-10 was enhanced in MMD patients compared with the control group and Th17-related IL-17, TNF-α, IL-6 and IL-23 were significantly higher in MMD.[192] Further, this study found that the Treg cells from MMD patients had a lower immunosuppressive function compared to those from healthy controls. Imbalance of Treg/Th17 is involved in several human autoimmune diseases and Treg depletion can induce autoimmunity.[192] The study suggested that function imbalance in Treg/Th17 may also contribute to the pathophysiology of MMD. Another conclusion of this study was that Suzuki's angiographic stage is positively correlated with the level of Treg cells, TGF-β, but not Th17 and IL-17.[192]

3. Peripheral blood mononuclear cells

A study by Nagata et al. in 2019 investigated the peripheral blood mononuclear cells (PBMNCs) in MMD patients.[226] It was seen that PBMNCs obtained and cultured from patients with MMD did not produce as much IL-10 as the PBMNCs cultured from the control group. This is suggesting a potential role of IL-10 in the pathogenesis of MMD.[226] IL-10 is a cytokine with anti-inflammatory properties and it improves the function of ECFCs through the activation of the STAT3 signaling pathway. IL-10 is secreted by multiple immune cells such as macrophages, dendritic cells, B cells, and T cells. Loss of IL-10 is associated with autoimmune pathologies.[226] The results of this study indicate that the vascular abnormalities observed in MMD patients might be caused by this

insufficiency of IL-10. Further, IL-10 insufficiency might induce platelet-derived-growth factor (PDGF) activity which is a proinflammatory cytokine. Kang et al. did find significantly higher levels of PDGF in MMD patients.[188] Increased levels of PDGF predisposes vascular progenitor cells to differentiate into a SMC lineage which induces a SMC proliferation, typically seen in MMD patients.[188, 226]

4. Cluster of differentiation 163 and C-X-C Motif Chemokine Ligand 5

A study by Fujimura et al. investigated the serum levels of soluble cluster of differentiation 163 (CD163) and C-X-C Motif Chemokine Ligand 5 (CXCL5) in MMD patients.[193] Soluble CD163+ is an activation marker for CD163+M2-polarized macrophages which produce chemokines to recruit immune cells in a variety of autoimmune disorders such as rheumatoid arthritis, pemphigus vulgaris etc. Additionally, activation of these M2 macrophages leads to increased serum CXCL5 which is a cytokine that has been correlated with the severity of these autoimmune diseases.[193] The study demonstrated a significantly increased serum levels of both soluble CD163 and CXCL5 in MMD patients compared to healthy controls.[193] No differences in serum level were found between wild-type or variant genotypes of the *RNF213* gene.[193] These results shed light on the novel pathogenesis of MMD through CD163+ M2-polarized macrophages and it suggests that patients with MMD may have increased autoimmune activity.[193] The heightened serum levels of CD163 and CXCL5 in MMD patients can partly explain the higher prevalence of autoimmune diseases in MMD patients but the link between the development of MMD and enhanced autoimmunity is still unknown.[193]

5. ***Immunoglobulin G***

A recent immunohistochemical study of three MMD patients who underwent autopsy showed aberrant expression of IgG in the internal elastic lamina of the ICA and the MCA.[92] This too could be a sign of involvement of an autoimmune response in the MMD pathogenesis. It was suggested that the IgG deposits may underlie the disruption of the internal elastic lamina and facilitate migration of SMCs into the intima. [29, 92]

Lipid metabolism

Lipid metabolism is very important in central nervous system because it is the most cholesterol-rich organ in the body. Any cholesterol present in the nervous system is synthesized de novo and is efficiently recycled within the CNS, having a long half-life of 1-5 years. [207, 227] Apolipoproteins are

proteins that bind lipids to form lipoproteins and they transport the lipids through the circulatory and lymphatic systems.[207] Astrocytes are the major source of apolipoprotein J (ApoJ) and apolipoprotein E (ApoE) in the CSF.[207, 227]

A study by Koh et al. reported that the ApoE precursor is downregulated in the serum of moyamoya patients.[228] A study by Kashiwazaki et al. demonstrated that ApoE, ApoE precursor, and ApoJ too are downregulated in the CSF of MMD patients.[207]

Apo E is a glycoprotein that transports cholesterol and other lipids in the plasma and the CNS by binding to cell-surface ApoE receptors.[207] The concentration of ApoE is known to be highest in the liver and the brain and it is the most abundant CSF apolipoprotein. Synthesis of ApoE is stimulated by CNS injury.[207, 227] It functions as an essential mediator in maintaining and repairing cell membrane in the CNS during or after injury. Further, ApoE protects the astrocytes against hypoxia-induced apoptosis.[207] Thus, the downregulation of ApoE and its precursors may provoke cerebrovascular dysfunction and progress occlusive changes in the terminal portion of the internal carotid arteries. It may also be involved in neuronal vulnerability against ischemia.[207]

ApoJ, also known as clusterin, is a glycoprotein that serves as both a lipid-transport protein and a molecular chaperone in the cellular stress response. ApoJ is found in all body fluids including CSF.[207] ApoJ is upregulated in response to cerebral ischemia and binds to stabilize proteins. In extracellular space, ApoJ inhibits an inflammatory response. Thus, normal levels of ApoJ may play a neuroprotective role against cerebral ischemia and contribute to the remodeling of the CNS.[207] Further, ApoJ prevents endothelial apoptosis by inhibiting caspase-3 activation.[207] Thus, ApoJ may also play a crucial role in keeping a balance between cell proliferation and death. Based on these observations, downregulation of ApoJ may activate the caspase-3-involved apoptosis pathway of endothelial cells in MMD.[207]

Environmental factors

Apart from the genetic hypotheses, some environmental factors have been proposed as an etiological factor in MMD.[4]

1. Irradiation

Radiation therapy can degrade both the wall of blood vessels and the elastic tissue on the inner vascular walls. This can lead to occlusions at the intracranial part of the internal carotid artery, which can result in MMS.[21] This means that frequent irradiation of head and neck regions, for example in acute paediatric patients with lymphoblastic lymphoma or intracranial tumors, could

induce MMS.[7, 21] The younger the patient and the higher the dose of radiation, the higher the risk of developing MMS.[21]

2. Infection

Yamada et al. found high levels of Propionibacterium acnes antibodies in the serum of MMD patients, both children and adults.[21, 229] This suggests that P. acnes and its induced immune factors may contribute to the occurrence of MMD.[21] In an adult MMD study, the human immunodeficiency virus (HIV) could initiate vascular lesions in the brain. This could result in MMD.[21] An infectious illness prior to the onset of MMD may occur, so infection has been proposed as a cause.[7]

Discussion

The contributions of genetic factors have been assumed since the initial recognition of MMD due to familial diagnoses and regional differences. Since then, many association analyses and linkage analyses have been conducted. In 2011, researchers identified *RNF213* as a susceptibility gene in East Asian population with an odds ratio of 190.8 which indicates a strong association between *RNF213* and MMD. In comparison, the strongest known genetic cause (*APOE4* gene) of Alzheimer disease has an odds ratio of 3,6 in heterozygous carriers.[232]

Although the identification of *RNF213* greatly advanced the work of etiologic studies, it does not explain why the group of *RNF213* p.R4810K heterozygous carriers, which is the majority of the Korean and Japanese MMD patients, is composed of various MMD phenotypes (for example pediatric versus adult population, hemorrhagic versus ischemic symptoms, unilateral versus bilateral etc.) suggesting that many unknown additional factors other than *RNF213* contribute to the development of the disease. The so-called double-hit theory is probably insufficient in explaining this spectrum in phenotypes. Another possible visualization to explain the mechanism of MMD is to use the ‘pinball’ metaphor. This model represents how individual cells roll down a slope to different outcomes or cell fates depending upon the epigenetic phenomena encountered.[118] The balls rolling down represent individual East Asian people in which interaction of multiple other factors contribute to the development and different clinical expression of MMD. Figure 5 gives an example of a pinball model in MMD.

There are still some other critical knowledge gaps in the understanding of MMD.

First, MMD encompasses a broad spectrum of distinct diseases and underlying processes with some angiographic features in common.[230] The current diagnosis of MMD is based on the presence of angiographic criteria. However, it is seen that the moyamoya angiopathy can occur as a single entity or in combination with an underlying disease called MMS. However, it is difficult to distinguish between underlying diseases that occur concomitantly in the moyamoya vasculopathy and underlying diseases in the context of a syndrome. This raises the question whether there should be a distinction between MMD and MMS. Because there may be other distinctive phenotypes buried within the catch-all term of 'moyamoya' and because the key angiographic features defining these clinically important subgroups have not yet been defined, a broader diagnostic criterion is needed to illustrate this entire spectrum of MMD.

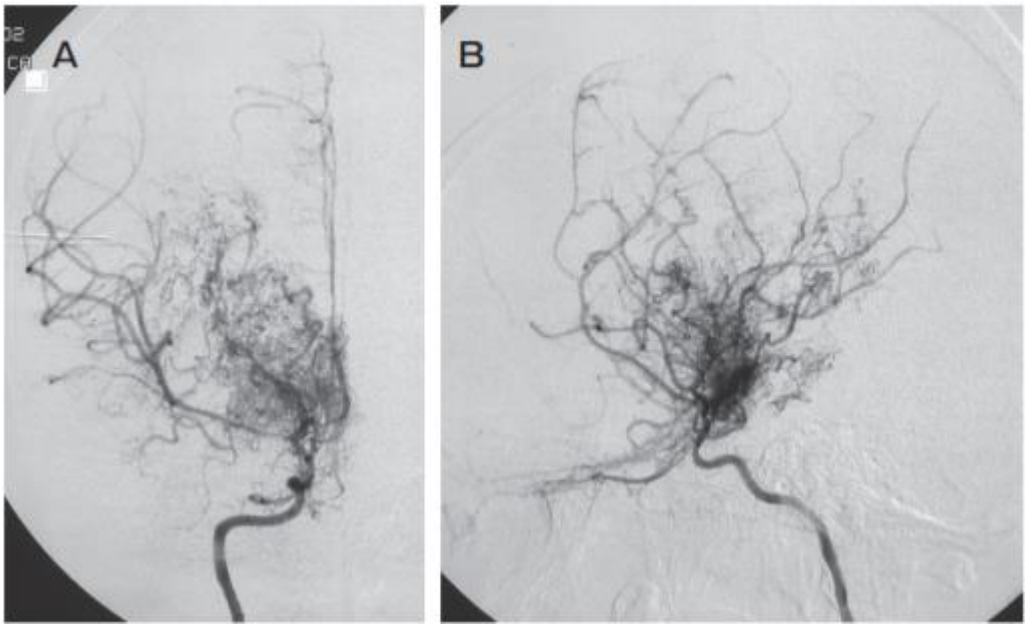
Another deficiency in the understanding of MMD is the inability to accurately predict prognosis for an individual patient. Currently, to identify patients at risk of progression, the clinical practice relies on an imperfect combination of angiographic staging, clinical history and radiographic studies which attempt to quantify cerebral blood flow and vasoreactivity. The predictive prognostic value of these assessments vary across institutions. There is a need to define universal specific biomarker profiles and specific radiological signatures to improve risk stratification in MMD patients.

Conclusion

MMD is a rare cerebrovascular disease with a largely unknown and probably multifactorial cause. Although the worldwide incidence of MMD is low, it is an important cause of cerebral ischemic or hemorrhagic stroke with potential permanent and devastating neurological deficits. Knowledge of the pathophysiology of this disorder is important to identify potential therapeutic interventions to stop or slow the progression of the disease and improve the long-term prognosis of MMD patients. Studies have shown a familial linkage in 10-15% of the MMD patients in which the mode of inheritance tends to be autosomal dominant with incomplete penetrance. MMD is associated with several loci on chromosomes 3, 4, 6, 8, 10 and 17. The *RNF213* gene is identified as an important susceptibility gene in East-Asian MMD patients. Evidence has also shown involvement of pro-angiogenetic, inflammatory and environmental factors in the MMD pathogenesis. The understanding of the MMD pathophysiology at molecular and genetic levels continues to expand and it is hoped that novel knowledge will help guide innovative treatment modalities in the future.

Figures

Figure 1: Frontal (A) and lateral (B) projection angiography in moyamoya disease.



Injection of the right internal carotid artery showing severe narrowing at the terminal portion of the ICA and formation of abundant collaterals resembling a “puff of smoke” at the base of the brain.[27]

(From Hishikawa T, Sugiu K, Date I. (2016) Moyamoya Disease: A Review of Clinical Research. Acta Med Okayama 70(4):229-36.)

Figure 2: overview of the systematic search and exclusion factors.

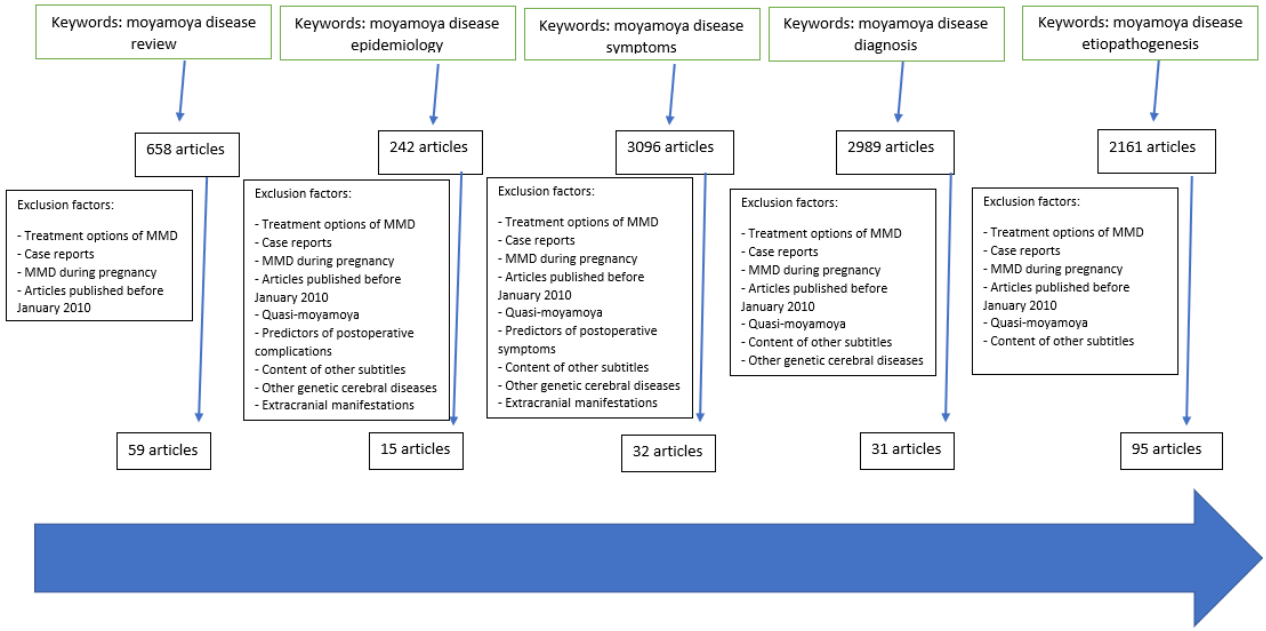
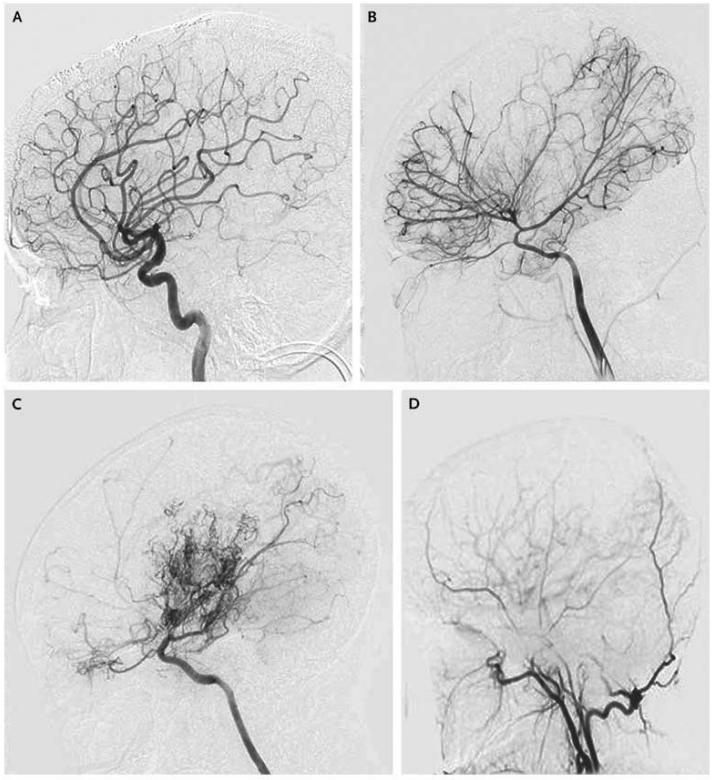


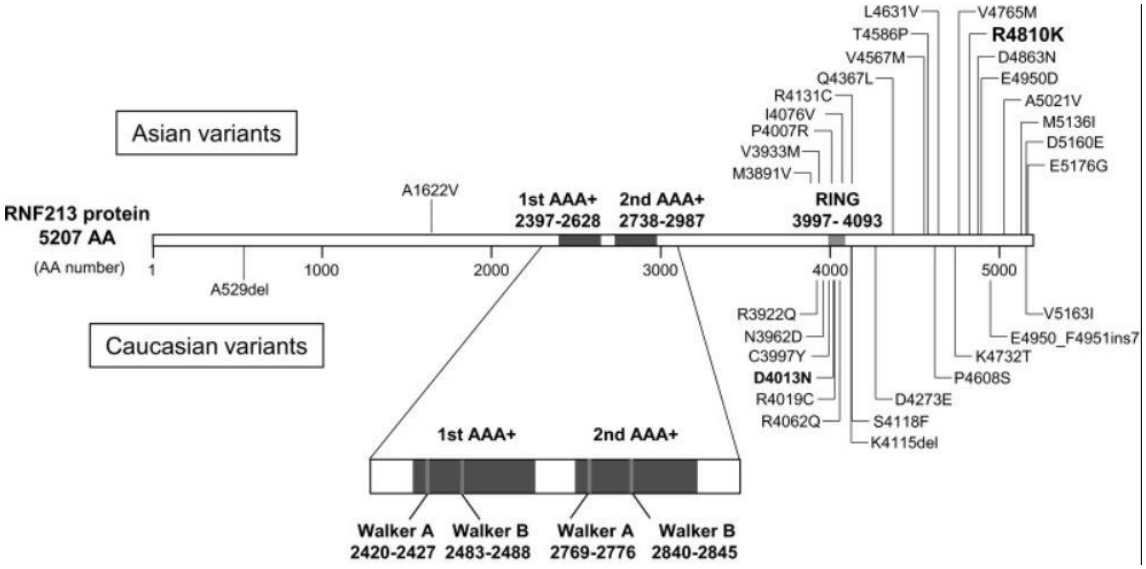
Figure 3: The angiographic progression in MMD.



Panel A shows a normal angiogram after injection of the ICA. Panel B shows Suzuki grades I to II with narrowing of the ICA before the development of extensive collateral vessels. Panel C shows Suzuki grades III to IV, with significant narrowing of the ICA and characteristic “puff-of-smoke” collaterals. There is diminished cortical perfusion as compared with the findings shown in Panels A and B. Panel D shows Suzuki grades V to VI. The occlusion of the ICA results in disappearance of the puff-of-smoke collaterals, since they are supplied by the ICA. Cortical perfusion is markedly reduced, with supply derived from the posterior (basilar) circulation (which is not visible without a vertebral-artery injection) and collateral vessels of the external carotid artery.[231]

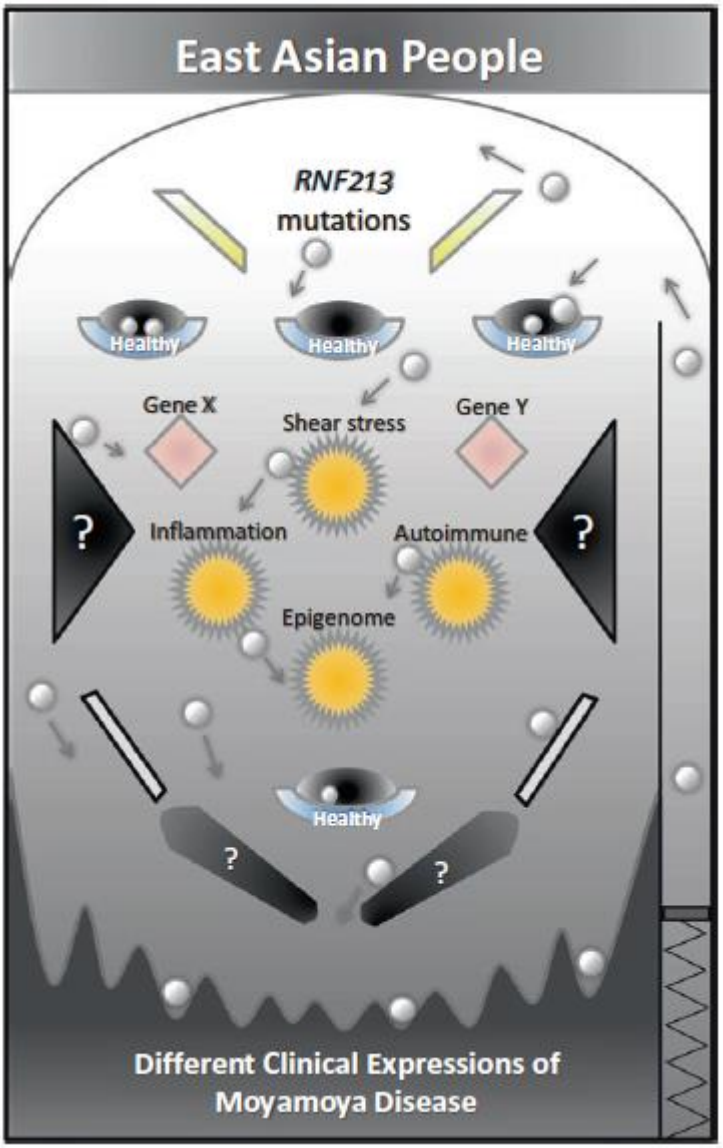
(From Scott R, Smith E. (2009) Moyamoya disease and moyamoya syndrome. N Engl J Med. 360(12):1226-37)

Figure 4: overview of all identified *RNF213* variants in Asian and Caucasian population.[50]



(From Koizumi A, Kobayashi H, Hitomi T et al. (2016) A new horizon of moyamoya disease and associated health risks explored through RNF213. Environ Health Prev Med. 21(2):55-70.)

Figure 5: pinball model representing the development of MMD.[91]



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