Review

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Research Progresses in Understanding the Pathophysiology of Moyamoya Disease

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Key Words
Moyamoya disease · Pathophysiology · Angiogenesis · Endothelial progenitor cells · Genetics

Abstract
Background: The pathogenesis of moyamoya disease (MMD) is still unknown. The detection of inflammatory molecules such as cytokines, chemokines and growth factors in MMD patients' biological fluids supports the hypothesis that an abnormal angiogenesis is implicated in MMD pathogenesis. However, it is unclear whether these anomalies are the consequences of the disease or rather causal factors as well as these mechanisms remain insufficient to explain the pathophysiology of MMD. The presence of a family history in about 9–15% of Asian patients, the highly variable incidence rate between different ethnic and sex groups and the age of onset support the role of genetic factors in MMD pathogenesis. However, although some genetic loci have been associated with MMD, few of them have been replicated in inde-

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pendent series. Recently, *RNF213* gene was shown to be strongly associated with MMD occurrence with a founder effect in East Asian patients. However, the mechanisms leading from *RNF213* mutations to MMD clinical features are still unknown. ***Summary:*** The research on pathogenic mechanism of MMD is in its infancy. MMD is probably a complex and heterogeneous disorder, including different phenotypes and genotypes, in which more than a single factor is implicated. ***Key Message:*** Since the diagnosis of MMD is rapidly increasing worldwide, the development of more efficient stratifying risk systems, including both clinical but also biological drivers became imperative to improve our ability of predict prognosis and to develop mechanism-tailored interventions.

Introduction

Moyamoya disease (MMD) is a chronic cerebrovascular disorder characterized by progressive bilateral occlusion of the supraclinoid internal carotid artery (ICA) and its main branches, associated with the development of fine collateral networks, especially adjacent to the site of occlusion in the deep areas of the brain. The appearance of the latter on dynamic angiography was originally described in the Japanese literature using the expression 'moyamoya', which translates into English as 'a puff of cigarette smoke' [1, 2]. MMD is a rare disease more frequently occurring in Asian countries, particularly in Japan where an incidence up to 0.54 per 100,000 has been reported. However, although MMD has been described in all races and ethnicities worldwide, limited data are available in Western countries, where the incidence rate is probably about 10 times lower (about 0.086 per 100,000) than in Asia [3–8], and it probably remains a misdiagnosed cause of ischemic or hemorrhagic stroke [9–12].

Cerebrovascular events are the main presenting symptoms and are related both to the stenosis and occlusion of the ICAs (transient ischemic attack and ischemic stroke) and to the rupture of fragile collateral vessels (hemorrhagic stroke). Children with MMD usually present with ischemic attacks, whereas adults may have either ischemic or hemorrhagic events [13, 14]. Other manifestations include migraine-like headaches and movement disorders. The disease is characterized by individual variations in the degree of arterial involvement, progression of stenosis and response to the reduction of blood supply, which would explain the wide range of clinical presentations. The factors responsible for these different features are not well known.

Recent data support a geographical influence in disease manifestation. Several studies highlighted the differences between MMD presentation in Japanese and American patients. In comparison to Asian cases, Caucasian MMD patients are characterized by an older average age of presentation with lack of bimodal age distribution, prevalence of ischemic stroke type at all ages, more benign presenting symptoms and less common familial occurrence [7–14]. However, the basis of geographical differences in disease occurrence and presentation are still unknown, although environmental and genetic factors have been invoked as possibly influencing factors.

The diagnosis of MMD is made on the basis of certain diagnostic criteria [15, 16], originally based on cerebral catheter angiography. These criteria require the condition of a bilateral arterial involvement whereas patients with unilateral changes, otherwise typical of MMD, are classed as 'probable' cases, although some of these cases develop bilateral changes during follow-up [17]. In the modern era, non-invasive brain MRI and MR angiography can show sufficient abnormalities to make the diagnosis in many cases, although catheter angiography is still required to fully characterize the disease. Disease severity has been classified into 6 progressive stages according to Suzuki's classification [2]. However, this classification is purely based on angiographic features and does not take into account the clinical phenotype variability. Recently, more specific grading criteria, allowing the stratification of angiographic severity and clinical symptomatology, are being developed for MMD patients, finally aimed at assessing clinical symptoms and treatment risks [18].

Angiographic changes otherwise typical of MMD are seen also in association with several other diseases or acquired conditions including neck radiotherapy, hormonal abnormalities, autoimmune disorders, immunosuppressive therapies and infectious diseases as well as genetic disorders including sickle cell disease, protein C and S deficiency, Down syndrome and neurofibromatosis type 1 [19]. Such cases are often said to have moyamoya syndrome (MMS-associated or secondary angiopathy) rather than MMD-isolated angiopathy. However, the distinction is somewhat arbitrary since the obliterative angiopathy and collateral formation is often identical in appearance and consequences (especially in the genetic cases) and the associated conditions are better thought of as predisposing conditions rather than causes by themselves.

Nonetheless, the pathogenesis of this enigmatic disease remains so far unknown, but several hypotheses have been investigated. The report of increased levels of inflammatory molecules, cytokines, chemokines and growth factors in serum and cerebrospinal fluid from patients with MMD supports the assumption that angiogenesis anomalies are somehow implicated in disease pathogenesis. The association of the MMS with other genetic disorders, the presence of a family history in 9–15% of patients with MMD and the identification of a very strong association with a variant in the *RNF213* gene in East Asian MMD patients support the role of genetic factors in MMD pathogenesis, although these factors have yet to be identified in most patients.

A possible explanation of the different MMD pathophysiological characteristics leads to the hypothesis that more than one single factor is implicated, leading to the consideration of MMD as a multifactorial disease. It is believed that MMD is a complex disorder primarily caused by multiple gene and angiogenic abnormalities, in which unknown triggering environmental factors (including infections, immune failure and hemodynamic stress to specific vascular loci) seem indispensable for starting the first steps of the pathological changes in the disease [20, 21].

Herein, we propose an updated review on the pathogenesis of MMD focusing particularly on angiogenic, vasculogenic and genetic aspects.

Pathophysiological Features of MMD

The lack of animal models and of pathological specimens, but also the clinical heterogeneity and the limited data on disease course particularly in Western countries contribute to the incomplete disease knowledge. Research studies, aimed at clarifying the pathogenic mechanism of the disease, focused on 3 major fields: (1) pathological studies of affected tissues, (2) studies on the role of vasculogenesis and angiogenesis and (3) genetic studies.

MMD Histopathological Aspects

Histopathological studies of MMD-affected ICAs demonstrated several particular traits: (1) eccentric fibrocellular thickening of the intima, resulting from the abnormal proliferation of smooth-muscle-alpha-actin positive cells, (2) thinned media, (3) prominently tortuous, often duplicated, internal elastic lamina and (4) absence of inflammatory or atheromatous involvement [22]. Recent MRI studies have also shown significant outer-diameter narrowing of affected vessels, suggesting vascular constrictive changes, which were not observed in intracranial arterial stenosis caused by atherosclerosis [23, 24]. The abnormal proliferation of intimal cells leads to vessel occlusion and thrombosis [25] with consequent brain hypoxia inducing collateralization through the formation of dilated and tortuous perforating arteries. The moyamoya collateral vessels also display a thinned media with fibrin deposition in the vessel walls, fragmented elastic laminae, attenuated media and micro-aneurysms, putting these fragile deep vessels at risk of rupture [26].

As mentioned before, the particular MMD pathology is considered to be responsible for the occurrence of both ischemic and hemorrhagic stroke in these patients as at histological level, and MMD vessels lack any kind of inflammatory characteristics [27]. Although micro-thrombi have been detected in MMD vessels, this finding is not specific for MMD and might be interpreted as a result of chronic disease rather than the cause [28].

Moreover, MMD has been considered in the majority of clinical studies as a typical disease of anterior circulation. Despite this, posterior circulation involvement (mainly the posterior cerebral artery) has been mentioned since the early 1980s, and it has been repeatedly emphasized as one of the most important factors related to poor prognosis [29, 30]. Preliminary data indicate the involvement of some vascular wall progenitor cells in different vascular disease states, adding weight to the notion that the adventitia is integral to vascular wall pathogenesis [31]. In the contest of progenitor cells, the tunica adventitia has emerged as a progenitor-rich compartment with niche-like characteristics that support and regulate vascular wall progenitor cells. Due to these findings, more efforts should be given from the study of smooth muscle cells (SMCs) and pericytes derived from moyamoya-affected middle cerebral and posterior cerebral arteries specimens to explain if it is possible to identify a different disease origin, linked probably to the different embryological derivation [32].

Angiogenesis, Extracellular Matrix Remodeling

Many research projects have focused on MMD angiogenesis (sprouting of endothelial cells from existing vessels) and vasculogenesis (formation of new blood vessels from circulating bone-marrow-derived endothelial progenitor cells, EPCs), which are probably induced by the ischemic and hypoxic phenomena. The involvement of an abnormal angiogenesis and vasculogenesis in MMD is

sustained by the implementation of fragile collateral moyamoya vessels in order to revascularize the distal hypoperfused regions.

Increased expression of angiogenic factors such as hypoxia-inducing factor-1α, vascular endothelial growth factor (VEGF), basic fibroblast growth factor, granulocyte colony stimulating factor (G-CSF), transforming growth factor-β1 (TGFβ1) and hepatocyte growth factor was observed both in CSF and serum of MMD patients [33–36]. Significant expression of VEGF was found also around the affected vasculature and in glial cells [36]. These findings strongly suggest the existence of intracranial pro-angiogenic environment that may develop after the development of proximal cerebral artery stenosis. However, although there are no comprehensive investigations on the mechanistically-related protein functions, it seems likely that these factors are involved in the native revascularization. Recent studies also showed an impaired balance between matrix metalloprotease (MMPs) and their tissue inhibitors supporting the hypothesis that an excessive accumulation of SMCs and an abnormal production of extracellular matrix (ECM) components may induce vessel stenosis or occlusion [37, 38].

However, the results of these preliminary studies do not provide sufficient data to distinguish whether these abnormalities are simply a result or, are indeed, causative of the disease.

Endothelial Progenitor and SMC Involvement

EPCs are a subset of bone-marrow derived cells, firstly isolated and characterized in 1997 [39] that, following endothelial damage, are recruited into systemic circulation and are homed to sites of neovascularization through secretion of pro-angiogenic cytokines [40–42]. Since EPCs have been shown to have regenerative and proliferative potentials, they were proposed as a potential tool for studying human vascular diseases. A reduction of circulating EPCs has been related to endothelial dysfunctions in cerebrovascular as well as cardiovascular disease and peripheral atherosclerosis [43–45]. EPCs, from a biological point of view, should express at least one marker of immaturity and one additional marker reflecting endothelial commitment identified as CD34-, CD133- and KDR-positive cell population [46].

EPCs have been investigated to better understand and characterize MMD pathogenesis, with controversial results. Jung et al. [47] firstly reported in a cohort of 24 adults with MMD: (1) a reduced number of EPCs-colony forming units, (2) an impairment in EPC functional activity and (3) a higher yield of outgrowth cells. These findings were confirmed in MMD children, in whom the decreased levels of circulating EPCs, indicating impaired mobilization and defective function of these cells, have been related to the delayed repair of the damaged vessel and to the development of vessel occlusion [48].

On the contrary, Yoshihara et al. [49] demonstrated increased levels of CD34-positive cells associated with an unusually accelerated neovascularization near the occluded major cerebral artery in adult patients with angiographic evidence of moyamoya-like vessels. Moreover, Rafat et al. [50] found increased circulating EPCs in MMD suggesting that these cells could play a role in improving vasculogenesis and angiogenesis.

The high level of CD34+ and CD34+CXR4+ circulating cells in MMD has been associated with the increased level of SDF-1α that binds to CXCR4 receptor of CD34+ cells and mediates their migration from bone marrow to the periphery [51].

The controversial results of preliminary reports could be partially explained by differences in analytical methodologies, small sample size and characteristics of population studied (age, ethnicity). Further studies are required to elucidate the functional role of EPCs in MMD pathogenesis and to identify the factors by which EPCs induced changes and/or recruitment of the compensatory vascular network.

The potential pathogenic effect of EPCs is further highlighted by the ex vivo study by Sugiyama et al. [52] using intracranial artery specimens obtained from 2 MMD patients. This study provides the first strong indication that circulating EPCs may be involved in the intimal thickening of the supraclinoid ICA, which is the initiation site of MMD. In addition, Kang et al. [53] also demonstrated the possibility to differentiate EPCs from peripheral blood of MMD patients in smooth muscle progenitor cells (SPCs). The abnormal proliferation of these cells is thought to be responsible for the eccentric fibrocellular thickening of the intima, which is one of the most important MMD histopathological features [22]. The same group demonstrated on tube formation assay that SPCs tend to arrange irregularly and form thickened tubules; moreover, they showed an increased expression of genes involved in cell adhesion (integrin α3, BAI1-associated protein 2-like 1 and N-cadherin), cell migration, immune response and vascular development (Eph receptor A5 and MCAM) supporting the idea that these cells could provide a further experimental MMD cell model [53].

Genetic Factors in MMD

The role of genetic factors in MMD pathogenesis is supported by several observations: (1) the highly variable incidence rate between different ethnic groups, with a marked East–West gradient suggestive of a founder effect in East Asian countries, (2) the 9–15% proportion of familial cases described in the literature, particularly in East Asian Countries, (3) the high concordance rate observed in monozygotic twins and (4) the drop of mean age of onset from 30 years in sporadic cases to 11.8 years in familial cases.

Different patterns of inheritance have been suggested. Several studies reported pedigrees with parent–offspring transmission consistent with an autosomal dominant inheritance, most often with an incomplete penetrance [54–56]. Other studies reported pedigrees including only affected siblings, suggestive of a possible autosomal recessive transmission [57–60]. In line with these observations, a complex determinism with polygenic inheritance in most MMD cases and a Mendelian inheritance with genetic heterogeneity in some MMD patients have been proposed.

Several molecular genetics studies, mostly conducted on Asian MMD patients, have been published since the end of the 1990s. They included linkage studies, candidate gene association studies and genome-wide association studies (GWAS).

Genome-Wide Linkage Studies

A number of linkage studies has been conducted and are listed in table 1. Five main loci were linked to MMD (3p24.2p26, 6q25, 8q23, 12p12 and 17q25). Except for the 17q25 locus, none of these loci has been replicated in independent series. Yamauchi et al. [59] firstly identified a linkage to the 17q25 locus. This result was later replicated in several whole genome linkage analyses conducted on multigenerational families, allowing the progressive reduction of the candidate interval to a 1.5 Mb region on 17q25.3 [55, 56, 61].

Candidate Gene Association Studies

Many candidate gene association studies have been performed, based on various pathophysiological hypotheses. The first association studies investigated the role of human leukocyte antigens (HLAs), located on chromosome 6p21.3. In 1995, Aoyagi et al. [62] showed a significant association between HLA B51 and HLA B51-DR4 combination in Japanese MMD patients. Inoue et al. [63] genotyped HLA gene alleles in 71 Japanese and 525 control subjects in 1997 and also detected a positive association for DQB1*0502. Han et al. [64] studied 28 Korean patients and 198 controls and reported an association of MMD with HLA B35. These results were not confirmed by Hong et al. [65] who did not find any difference in HLA genotype between MMD and controls, except for an association between familial MMD (fMMD) and DRB1*1302 and DQB1*0609 alleles. More recently, Kraemer et al. [66] found that European patients with moyamoya angiopathy (including unilateral cases) carried more frequently than controls HLA DRB1*03, DRB1*13, A*02, B*08 and DQB1*03 antigens. However, the limited sample size of most studies and the lack of results replication make their interpretation quite difficult.

Based on the observation of an increased expression of pro-angiogenic and growth factors in patients' CSF, blood or tissues compared to controls, variations in the coding sequences and promoters of genes encoding for pro-angiogenic factors have been screened [67–73]. Some of these studies found associations between MMD and polymorphisms in growth factor genes such as platelet-derived growth factor receptor beta or TGFβ1, but replication was missing.

MMPs and metalloprotease tissue inhibitor pathways (TIMPs), which are known to regulate the interaction between SMCs and ECM, have also been investigated in MMD [74]. In line with the observation of a differential expression of these ECM remodeling enzymes between patients' and controls' biological samples, some studies showed an association of MMD with polymorphisms located in of TIMP2, MMP2, MMP3 genes or in their promoters [75–78]. Again, conflicting results between studies did not allow any conclusions to be drawn about the significance of these associations [73, 79, 80].

Results of candidate gene studies are listed in table 2.

GWAS

In 2011, Kamada et al. [81] performed a GWAS study including 72 Japanese MMD patients and 45 healthy Japanese controls, showing an association between MMD and a single locus on 17q25-ter ($p < 10^{-8}$). They confirmed this result in a locus-specific association study, showing a strong association between MMD and 20 SNPs spanning a 151 kb region within the RNF213 locus ($p < 10^{-6}$). The study also showed a very strong association with MMD of a single haplotype including 7 SNPs located in the 3′UTR of RNF213 ($p = 5.3 \times 10^{-10}$) supporting evidence for a founder effect in the Japanese population [81].

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Table 1. Candidate loci and genome-wide linkage analyses conducted in MMD

Studies	Populations	Pedigrees	Methods	Linkage analysis parameters	Results
Ikeda et al. [58], 1999	16 Japanese families (77 individuals genotyped, including 37 MMD patients)	– Affected parent and offspring: 3 families – Only affected siblings: 13 families	– Genome-wide linkage study on 8 families using 372 microsatellite markers – Candidate locus linkage study on 8 other families using 4 microsatellites markers on 3p24.2-p26	– Two point LOD scores under the following inheritance models: AR, AD with incomplete penetrance – MLSs under nonparametric model – Disease AF = 3.5×10^{-5}	Genome-wide linkage study: LOD scores under AR model = 1.49 and 3.18 and NPL scores = 2.31 and 1.80 for 2 markers located in 3p24.2-p26, contrasting with LOD scores <1 for the rest of genome 3p24.2-p26 locus specific linkage study: Maximal NPL score = 3.46 for one marker in this region
Inoue et al. [57], 2000	20 Japanese families	– Affected parent and offspring: 2 out of 16 families – Only affected siblings: 14 out of 16 families – 4 families not described	Chromosome 6 linkage analysis using 15 microsatellite markers	In each affected sibling pair, estimation of IBD (0, 1, 2) for each marker	– Linkage to a unique marker located at 6q25.2 in all 20 affected sibling pairs – Haplotypes shared between affected members for 16 families
Yamauchi et al. [59], 2000	24 families including 56 MMD patients	– Affected parent and offspring: 6 families – Only affected siblings: 18 families	Chromosome 17 linkage analysis using 22 microsatellite markers	– Two-point linkage analysis under a dominant model with incomplete penetrance (0.2, 0.5, 0.67) and a disease AF = 0.00001 – Two-point linkage analysis under a recessive model with penetrance of 0.2, 0.5, 0.67, 0.8 and 1, and an disease AF = 0.006 – Multipoint linkage analysis – APM method	Two point linkage analysis: – Maximal LOD score = 3.11 on 17q25 under the AD model – Maximal LOD score = 2.82 on 17q25 under the AR model Multipoint linkage analysis: – Linkage to a 9 cM region on 17q25, with a maximal LOD score = 4.58 APM method – p value $<1 \times 10^{-5}$ for 5 adjacent markers at 17q25
Sakurai et al. [60], 2004	12 nuclear Japanese families	12 nuclear families with MMD-affected sib-pairs (46 members, 12 sib pairs, 2 families lacking of paternal samples)	– Genome-wide linkage study using 391 microsatellites markers – Candidate region linkage study with 17 additional markers on 8q and 20 additional markers on 12p	Multipoint and single point non parametric analyses	– Significant linkage to 8q23 (MLS = 3.6 and NPL = 3.3) – Suggestive linkage to 12p12 (MLS = 2.3 and NPL = 2.5) – No linkage for the 3p, 6q and 17q loci previously reported (MLS = 1.7, 1.6 and 1.3, respectively)

Table 1. (continued)

Studies	Populations	Pedigrees	Methods	Linkage analysis parameters	Results
Mineharu et al. [61], 2008	15 Japanese families including 55 patients (43 definite MMD patients, 5 probable MMD patients and 7 patients with steno-occlusive lesions without collateral vessels)	Multigenerational families without consanguinity, consistent with an AD transmission with incomplete penetrance	– Genome-wide linkage analysis using 394 markers – Candidate region (17q25-qter) linkage analysis using 17 markers	– Two-point and multipoint parametric linkage analysis under a dominant model taking into account a possible locus heterogeneity (HLOD) Affected members only method Disease AF = 10^{-4} Phenocopy frequency = 10^{-5} – Non parametric linkage analysis – Analyses conducted under both narrow (definite MMD only) and broad (all patients) classifications	Genome-wide linkage analysis: – Significant evidence of linkage on 17q25-qter – Maximal multipoint LOD score and HLOD = 5.92 (narrow classification) and 7.33 (broad classification) – Maximal 2-point LOD score = 4.45 (narrow classification) and 5.48 (broad classification) – NPL = 4.51 (narrow) and 5.51 (broad classification) Fine mapping of the17q25-qter region: – Maximal multipoint LOD score = 6.57 (narrow) and 8.07 (broad classification) – Maximal HLOD = 6.81 (narrow) and 8.11 (broad) classification – Linkage to a critical interval of 3.5 Mb on 17q25.3 encompassing 94 annotated genes – Segregation of a disease haplotype in all families but one – Exclusion of 3p24-p26.1 and 8q23 previously mapped regions (LOD scores ≤–2.99)
Liu et al. [55], 2010	15 families included in the study of Mineharu 2008, with 2 more additional families	Multigenerational families satisfying an AD transmission with incomplete penetrance	17q25-qter candidate locus linkage analysis using 13 markers	Multipoint analysis under a dominant model Disease AF = 10^{-4} Phenocopy frequency = 10^{-5}	– Maximal LOD score = 9.67 on 17q25.3 – Linkage to a critical region of 2.1 Mb on 17q25.3 containing 40 genes
Kamada et al. [81], 2011	20 Japanese families	– Affected parent and offspring: 8 families – Only affected siblings: 12 families	Linkage study in 5 putative previously reported candidate loci (3p24-26, 6q25, 8q13-24, 12p12-13, 17q25) using 36 microsatellite markers	Multipoint analysis	– No locus with significant linkage – Suggestive linkage with the 17q25 locus (LOD score = 2.4 and NPL = 3.8)
Liu et al. [56], 2011	8 Japanese families	8 multigeneration families satisfying an AD transmission with incomplete penetrance	Genome-wide linkage analysis using 382 markers and fine-mapping markers for 17q25.3 region	Parametric multipoint analysis: – Affected members only method – Boostrap simulation analysis used for interpretation of LOD scores	– Significant linkage to 17q25.3 with a maximal LOD score = 8.52 – Linkage to a candidate region of 1.5 Mb on 17q25.3 containing 21 genes – Segregation of a shared disease haplotype in the 8 families

AD = Autosomal dominant; AR = autosomal recessive; AF = allele frequency; APM = affected pedigree members; HLOD = heterogeneity-adjusted logarithm of odds; LOD = logarithm of odds; MLS = multipoint LOD score; NPL = non parametric linkage score.

Cerebrovasc Dis 2016;41:105–118
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Table 2. MMD candidate gene studies

Reference	Patients background	Mean age of onset, years	Cases/ controls	Type of study	Type of analysis/gene	Main findings
Aoyagi et al. [62], 1995	Japanese	10	32/178 not CVD	Association	HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ	Positive association with HLA-B51 ($p < 0.002$, $p_c < 0.05$); HLA-B67 ($p < 0.01$, p_c NS); HLA-DR1 ($p < 0.05$, p_c NS), and combination B51-DR4 ($p < 0.002$) Negative association with HLA-Cw1 ($p < 0.05$, p_c NS)
Inoue et al. [63], 1997	Japanese	nr	71/525	Association	HLA-A, HLA-DRB1-DQA1-DQB1-DPA1-DPB	Positive association between MMD and HLA DQB1*0502 ($p < 0.025$) Negative association between MMD and DRB1*0405 and DQB1*0401 ($p < 0.01$ and $p < 0.025$)
Han et al. [64], 2003	Korean	34	28/198	Association	HLA-A, HLA-B, HLA class II	Association with HLA B35 ($p < 0.008$); no other associations
Hong et al. [65], 2009	Korean	7	70/207	Association	HLA-DR, HLA-DQ	HLA-DRB1*1302 associated with fMMD in comparison both to controls ($p_c = 0.008$) and non fMMD ($p_c = 0.02$); HLA-DQB1*0609 associated to fMMD vs. both to controls ($p_c = 0.02$), and nfMMD ($p_c = 0.02$). HLA-DQB1*0502 associated to fMMD vs. nfMMD ($p = 0.02$). Increased frequency of DRB1*1302-DQB1*0609 haplotype in fMMD vs. controls ($p = 0.0003$), and nfMMD ($p = 0.0003$)
Kraemer et al. [66], 2012	German, Croatian, Spain, Polish	31	33 MMA including 22 MMD	Association	HLA-A, HLA-B, HLA-DRB1, HLA-DQB1	Significant association for HLA-DRB1*03 and HLA-DRB1*13 in all 33 MMA patients ($p_c \leq 0.001$); and in 22 MMD patients ($p_c \leq 0.001$ and $p = 0.011$, respectively) Significant association with HLA-A*02, HLA-B*08 ($p_c < 0.001$) and HLA-DQB1*03 ($p_c = 0.003$) for all 33 MMA patients
Kang et al. [75], 2006	Korean	4	61/50	Association	TIMP2: exon 2–5; TIMP4: exon 1–5	Significant more frequency of –418 G/C htz in TIMP2 promoter region in fMMD vs. MMD ($p = 0.005$), and fMMD vs. controls ($p = 0.001$)
Paez and Yamamoto [79], 2007	Japanese	nr	48/52	Association	TIMP2	No significant differences of –418 G/C between patients and controls
Li et al. [76], 2010	Chinese	28	208/224	Association	6 SNP in promoters of MMP-2-3-9-13 and TIMP-2 genes	MMP-3, MMP-1171 5A/6A and 5A/5A genotypeswere associated with a reduced risk of MMD in comparison to controls ($p_c = 0.042$) and with a reduced risk of fMMD vs. controls ($p_c = 0.048$)
Roder et al. [67], 2010	German, Switzerland	16	39/68	Association	9 exons of ACTA 2	One new mutation in a MMD patient, exon 6 (R179H; c536G>R); no differences in the other found SNPs between MMD and controls
Shimojima et al, [68] 2009	Japanese	nr	53/nr	Association	ACTA 2	No mutations
Roder et al. [69], 2010	German, Switzerland	15	40/68	Association	13 SNPs of bFGF, CRABP1, PDGFRβ, TGFB1	Association of 2 SNPs: rs382861 (A/C) ($p = 0.0373$) promoter region of PDGFRβ, and rs1800471 (C/G) ($p = 0.0345$, in the first exon of TGFβ1)
Park et al. [70], 2011	Korean	23	93/328	Association	eNOS –922 A>G, –786T>C, 4a4b VNTR, and 894 G>T	The 4a4b tandem repeat polymorphism in intron 4 of eNOS is associated with adult MMD ($p = 0.029$)
Park et al. [71], 2012	Korean	21	107/243	Association	VEGF (–2578, –1154, –634, and 936), and KDR (–604, 1192, and 1719)	VEGF-634G allele is associated with pediatric MMD and poor collateral vessel formation

Table 2. (continued)

Reference	Patients background	Mean age of onset, years	Cases/ controls	Type of study	Type of analysis/gene	Main findings
Liu et al. [72], 2012	Japanese	15	45/79	Association	Exon 1 of TGFβ1	No association between the rs1800471 SNP and MMD
Wang et al. [73], 2013	Chinese	43	96/96	Association	5 SNPs in PDGFRβ, MMP-3, TIMP2, RNF213 genes	G/A genotype of rs112735431 and G/G genotype rs 148731719 in RNF213 are associated with MMD ($p = 0.018$ and $p < 0.01$)
Kamada et al. [81], 2011	Japanese	nr	72/45	Association	GWAS Case–control study for the p.R4859K polymorphism in RNF213 gene	Significant association ($p < 10^{-8}$) for c.14576G>A (p.R4859K) in exon 60 of RNF213 gene, detected in 95% of MMD families, 73% of non-familial MMD and 1.4% of controls p.R4859K polymorphism increase risk of MMD (OR 190.8, $p = 1.2 \times 10^{-43}$)
Miyatake et al. [83], 2012	Japanese	0–57 range	204/283	Association	RNF213	c.14576G>A polymorphism in RNF213 gene was associated both to fMMD (95.1%)and sporadic MMD (79.2%) with an OR 259 ($p < 0.001$) c.14576G>A polymorphism found in 1.8% of controls
Wu et al. [85], 2012	Chinese	36	170/507	Association	RNF213: mutation R4810K	p.R4810K mutation greatly increased the risk for MMD (OR 36.7, $p = 6.1^{-15}$)
Mineharu et al. [87], 2013	Japanese	36	1	Case report	RNF213	p.R4810K variant found
Liu et al. [82], 2013	German, Czech	31	38/41	Association	GWAS	Not significant associations but suggestive associations with SNP located in 1q23.3, 2p22.1, 13q14.11, 17p13.3 and 20q13.33
Miyawaki et al, [84] 2012	Japanese	48 dMMD 49 uMMD	30/110	Association	c.14576G>A of RNF213	Association between c.14576G>A and dMMD (OR 144, $p < 0.0001$), uMMD (OR 54, $p = 0.0001$) and non MMD intracranial major artery stenosis ro occlusion (OR 16.8, $p < 0.0001$) c.14576G>A found in 1.8% of controls
Cecchi et al. [88], 2014	Multi-ethnic cohort from the USA (European, Hispanic, Black and Asian descent)	26.7	110	Association	Sequencing of exons 43–45, and 60 of RNF213 gene for 86 probants and WESfor 24 probants	56% (9/16) of MMD patients of Asian descent had p.R408K polymorphism in RNF213 p.R4810K polymorphism not found in the 94 MMD patients of non-asian descent 11 additional RNF213 rare variants (p.C3997Y, p.I4076V, p.D4013N, p.R4019C, p.E4950_F4951ins7, p.K4732T, p.V5163I, p.D4237E, p.R3922Q, p.A529del, p.K4115del) were identified in 8/82, 2/6 and 1/16 patients from European, Hispanic and Asian descent respectively.

MMA = Moyamoya angiopathy; dMMD = definite MMD; uMMD = unilateral MMD; nfMMD = non-familial MMD; nr = not reported; p_c = corrected p; NS = not significant.

In 2013, a GWAS conducted in Caucasians, including 38 unrelated German and Czech patients and 41 German controls, suggested possible associations with 7 SNPs (located on 1q23.3, 2p22.1, 13q14.11, 17p13.3, 20q13.33, 3p22.1 and 4q22.3; $p < 10^{-5}$) but failed to identify a significant association with MMD. Direct sequencing in 5 patients of 8 genes included in these candidate regions revealed 79 variants including 5 missense variants, commonly found in Caucasian control population, making them unlikely to be responsible for MMD. No association with *RNF213* polymorphism was found in Caucasian patients [82] (table 2).

RNF 213 and MMD

Following the identification of the association between MMD and RNF213, a second Japanese research team established linkage to the *RNF213* locus at 17q25.3 in 8 multigenerational MMD families and identified, by whole exome sequencing, RNF213 as a major candidate gene for MMD [56]. Mutational analysis followed by case–control association studies revealed a strong association between MMD in East Asian countries and a single missense mutation in *RNF213* (p.R4810K, also designated as p.R4859K according to the NM transcript considered), leading to an aminoacid substitution from Arginine to Lysine in the C-terminal part of the protein. This mutation was found in 90% of Japanese, 79% of Korean and 23% of Chinese MMD cases and strongly increased the risk to develop MMD with an OR 338.9 ($p = 10^{-100}$) in Japanese, OR 135.6 ($p = 10^{-25}$) in Korean and OR 14.7 ($p = 10^{84}$) in Chinese populations [56]. Further independent studies confirmed this association in Japanese patients. Miyatake et al. [83] showed the presence of this mutated allele in 95.1% of fMMD cases and 79.2% of sporadic MMD cases, with an OR 259 ($p < 0.001$).

Miyawaki et al. [83] found the mutated allele in 85.4% of MMD patients (OR 292.8, $p < 0.0001$) and in 21.9% in non-MMD intracranial major artery stenosis occlusion (OR 14.9, $p = 0.01$). This association was also replicated in Chinese Han patients, although at a lower level, with the presence of p.R4810K variant in 13% of MMD Han patients (OR 36.7, $p = 6 \times 10^{-15}$) [85]. Of note, in these studies, the p.R4810K variant was found in 1–2% of Japanese controls and in 0.4% of Chinese Han controls, and therefore, it should be considered as a MMD susceptibility variant rather than a MMD causing variant. It was also suggested that presence of the p.R4810K variant, when present in an homozygous state, was associated with an earlier onset and a more severe disease course, suggesting a value of this variant as a biomarker for predicting prognosis [83, 86, 87].

If the role of p.R4810K variant in *RNF213* gene as a susceptibility variant for MMD is clear in East Asian subjects, neither this variant nor the founder haplotype have been detected in Caucasian patients [81, 82, 88]. A recent study, conducted in the United States, showed the presence of p.R4810K in 56% of unrelated MMD of Asian descent (Korean, Japanese and Chinese but also Indian and Bangladeshi ethnicities) whereas it was not identified in European or Hispanic Americans. Analysis of familial cases showed co-segregation of p.R4810K with the MMD phenotype, but with an incomplete penetrance [88].

Some additional *RNF213* rare variants were identified in Asian and Caucasian MMD patients negative for p.R4810K [56, 81, 88]. These variants were mostly missense variants except 3 molecular variants reported by Cecchi et al. [88], which consisted of 1 in-frame insertion and 2 small in-frame deletions. Except for 1 missense variant (p.D4013N) detected in 2 unrelated Caucasian patients from 2 distinct studies, all variants were private. Interestingly, p.R4810K variants and almost all additional variants were located in the C-terminus part of the RNF213 protein.

The exact mechanism by which the RNF213 would be involved in MMD pathogenesis remains unknown. RNF213 encodes for a large cytosolic protein ubiquitously expressed, and containing a ring-finger domain (suggestive of an E3 ubiquitin ligase domain) and an AAA-ATPase domain. In-vitro functional studies showed that the p.R4810K variant did not alter stability, intracellular distribution or ubiquitin activities [56]. Zebrafish knockdown for RNF213 was reported to have severely abnormal sprouting vessels in the head region, especially from the optic vessels [56].

Genetically engineered mice that lack *RNF213* do not exhibit abnormalities in brain vasculature under physiological conditions [89, 90]. However, after carotid artery ligation, knockout mice did not present the transitory intimal and medial hyperplasia found in their wild-type littermates and had significantly thinner intimal and medial layers than wild type mice, suggesting a possible role of *RNF213* in arterial wall remodeling [91]. Finally, recent experimental studies performed on p.R4810K-mutated cells showed a reduced angiogenic activity, and in another study, cycle cell perturbation with increased genomic stability [92, 93].

However, the exact mechanism by which RNF213 molecular variant lead to MMD clinical features is still unknown.

Discussion

The pathophysiological mechanisms of MMD remain poorly understood. Although, the results from experimental studies conducted so far highlight the presence of abnormalities in angiogenic pathway and cellular proliferative signaling cascade at the base of both native revascularization and vessel stenosis or occlusion, these findings are still inadequate to fully explain MMD biological mechanisms.

Several elements, including the different incidence rate between ethnicities and the high rate of familial occurrences, support the role of genetic factors in MMD. A very strong association between MMD and a missense variant in RNF213 (p.R4810K) has been reported by several studies in East Asian patients. This variant, which is present in 1–2% of the Japanese control population, was found in more than 90% of MMD patients [82, 83, 87, 88]. However, although this variant has been established as a susceptibility factor for MMD in East Asia, it may explain only part of the disease susceptibility in this population and it is probably not involved in Caucasian patients.

However, the identification of the additional genes that are most likely involved in MMD was hampered by several factors, including (1) the complex pattern of inheritance and genetic heterogeneity of MMD, (2) the limited samples size used so far to map and identify those genes, (3) the fact that investigated gene or SNPs might not have a causative effect on the pathogenesis of MMD (might rather only be related to some disease aspect) and (4) the genetic methodology, that in most cases was the candidate gene approach, limiting the number of explored polymorphisms in any study whereas, probably, many common genetic variants contribute to the risk of MMD.

The results of the available studies, as well as our clinical and research experience in MMD, support the idea that probably one single mechanism is unable to explain the complex disease pathogenesis. MMD angiopathy is a heterogeneous, multifaceted disease in which, probably, different pathogenic processes contribute to the disease onset and progression [94]. According to this concept, an intriguing hypothesis, the so-called 'double-hit mechanism' has been proposed, supported by the association between MMD angiopathy and several acquired and genetic conditions, including definite entities such as sickle cell disease, protein C and S deficiency, Down syndrome and neurofibromatosis type 1 as well as the recently identified *RNF213* mutations in East Asians. MMD could result from a set of linked and subsequent events in which environmental factors may influence the development of arteriopathy in genetically susceptible individuals. In particular, it has been supposed that in specific genetic and acquired conditions, several factors such as infectious agents, immunological responses but mostly an overlapping insult of endothelium attributed to flow dynamics such as shear stress, which may be related to SMC migration at internal carotid terminal, may trigger to ICA stenosis [19]. The involvement of epigenetic factors may also explain the extreme variability in clinical phenotype, in progression rate and disease susceptibility in East Asians and Caucasians [95].

Ultimately, the impression is that our understanding of the disease is not assisted by the variability of disease phenotype and the arbitrary diagnostic criteria applied so far, including uncertainty whether to distinguish between disease or syndrome, or consider the overall MMD angiopathy. The application of the available diagnostic criteria, although appealing for clinical management, may provide poor reliable and confounding subgroups classification that may finally hamper the identification of definite phenotypes. Moreover, although the impact of ethnicity is becoming increasing important, the risk stratification by ethnicity is still not defined due to the lack of data on European population [96].

Since the diagnosis of MMD is rapidly increasing worldwide, these considerations support the need for developing more specific and efficient stratifying risk systems, including deep clinical and radiological phenotyping but also the identification of disease biomarkers through genomic and metabolomic studies [95]. The identification of at-risk phenotypes and/or specific biological drivers could improve our ability to predict prognosis and to develop individually tailored interventions [95].

The extensive application of high-throughput technologies, such as GWASs, or novel sequencing technologies, such as next generation sequencing, may help to overcome limitations of previous genetic investigations, mostly in familial cases. However, given the disease complexity, an integrated approach including advanced genomic technologies, biochemical and functional studies but also a strong clinical approach, including detailed phenotyping in order to identify clinically homogeneous subgroups of patients and collaborative efforts to collect large MMD patients series and DNA samples seem to be the best strategy to maximize our understanding of the mysteries of MMD pathogenesis.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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