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メタデータ	言語: 出版者: Wiley 公開日: 2021-11-12 キーワード (Ja): キーワード (En): age of mutation, East Asia, Jomon people, Moyamoya disease, RNF213, Yayoi immigrants 作成者: Koganebuchi, Kae, Sato, Kimitoshi, Fujii, Kiyotaka, Kumabe, Toshihiro, Haneji, Kuniaki, Toma, Takashi, Ishida, Hajime, Joh, Keiichiro, Soejima, Hidenobu, Mano, Shuhei, Ogawa, Motoyuki, Oota, Hiroki メールアドレス: 所属:
URL	http://hdl.handle.net/20.500.12000/50005

ORIGINAL ARTICLE

An analysis of the demographic history of the risk allele R4810K in *RNF213* of moyamoya disease

Kae Koganebuchi^{1,2,8}  | Kimitoshi Sato³ | Kiyotaka Fujii³ | Toshihiro Kumabe³ | Kuniaki Haneji⁴ | Takashi Toma⁴ | Hajime Ishida⁴ | Keiichiro Joh⁵ | Hidenobu Soejima⁵ | Shuhei Mano⁶ | Motoyuki Ogawa^{1,7} | Hiroki Oota^{1,7,8}

¹ Department of Biological Structure, Kitasato University Graduate School of Medical Sciences, Sagami-hara, Kanagawa, Japan

² Faculty of Medicine, Advanced Medical Research Center, University of the Ryukyus, Nishihara, Okinawa, Japan

³ Department of Neurosurgery, Kitasato University School of Medicine, Sagami-hara, Kanagawa, Japan

⁴ Department of Human Biology and Anatomy, Graduate School of Medicine, University of the Ryukyus, Nishihara, Okinawa, Japan

⁵ Division of Molecular Genetics and Epigenetics, Faculty of Medicine, Department of Biomolecular Sciences, Saga University, Saga, Japan

⁶ Department of Mathematical Analysis and Statistical Inference, The Institute of Statistical Mathematics, Tachikawa, Tokyo, Japan

⁷ Department of Anatomy, Kitasato University School of Medicine, Sagami-hara, Kanagawa, Japan

⁸ Department of Biological Sciences, Graduate School of Science, University of Tokyo, Bunkyo-ku, Tokyo, Japan

Correspondence

Hiroki Oota, Department of Biological Sciences, Graduate School of Science, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

Email hiroki_oota@bs.s.u-tokyo.ac.jp

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Abstract

Background: *Ring finger protein 213 (RNF213)* is a susceptibility gene of moyamoya disease (MMD). A previous case-control study and a family analysis demonstrated a strong association of the East Asian-specific variant, R4810K (rs112735431), with MMD. Our aim is to uncover evolutionary history of R4810K in East Asian populations.

Methods: The *RNF213* locus of 24 MMD patients in Japan were sequenced using targeted-capture sequencing. Based on the sequence data, we conducted population genetic analysis and estimated the age of R4810K using coalescent simulation.

Results: The diversity of the *RNF213* gene was higher in Africans than non-Africans, which can be explained by bottleneck effect of the out-of-Africa migration. Coalescent simulation showed that the risk variant was born in East Asia 14,500–5100 years ago and came to the Japanese archipelago afterward, probably in the period when the known migration based on archaeological evidences occurred.

Conclusions: Although clinical data show that the symptoms varies, all sequences harboring the risk allele are almost identical with a small number of exceptions, suggesting the MMD phenotypes are unaffected by the variants of this gene and rather would be more affected by environmental factors.

KEYWORDS

age of mutation, East Asia, Jomon people, Moyamoya disease, RNF213, Yayoi immigrants

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1 | INTRODUCTION

Moyamoya disease (MMD) is a disorder characterized by spontaneous occlusion of the circle of Willis with the development of a fragile network of basal collateral vessels similar to a puff of smoke on a cerebral angiogram. MMD was reported as a disease of bilateral internal carotid arteries in 1957 (Takeuchi & Shimizu, 1957). The term “moyamoya” means “puffs of smoke” in Japanese, was used for this disease in 1969 (Suzuki & Takaku, 1969) and is used worldwide even today. MMD occurs frequently in East Asia, including Japan, but it is rare in Europe and Africa (Goto & Yonekawa, 1992). Though the majority of MMD cases are sporadic, familial cases have also been substantially reported in previous studies (Kim, 2016). A family history of MMD is found in approximately 10–15% of patients (Kuriyama et al., 2008). Several previous studies have revealed the loci associated with the MMD in East Asia: 3p26–p24.2 (Ikeda et al., 1999), 6q25 (Inoue et al., 2000), 17q25 (Liu et al., 2010; Mineharu et al., 2006), and 8q23 (Sakurai et al., 2004). A genome-wide association study and a pedigree analysis have identified the same susceptibility gene, *Ring finger protein 213* (*RNF213*), which is located at 17q25 (Kamada et al., 2011; Liu et al., 2011); the *RNF213* gene is a regulator of cytoplasmic lipid droplets (Sugihara et al., 2019). The two genetic studies demonstrate a strong association of the variant R4810K in the *RNF213* gene (rs112735431) with MMD in the East Asian population with an extremely high odds ratio (approximately 110). The allele frequencies of R4810K in the MMD cases are 48.1% in Japanese, 39.5% in Korean, and 12.5% in Chinese (Liu et al., 2011), which has never been found in MMD patients with European ancestry (Kobayashi et al., 2016; Liu et al., 2011). A very low frequency of R4810K (0.00–2.84%) has been found in healthy subjects in East Asia (Liu et al., 2011, 2012; Takamatsu et al., 2017). It is rare that for a single risk variant, such high penetrance has been shown in East Asians, while patients with MMD have very diverse symptoms (Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis, & Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases, 2012).

Although many variants associated with common (multifactorial) diseases are usually shared by populations around the world, their penetrance is generally low (Schork et al., 2009). On the other hand, the penetrance of risk alleles for Mendelian disorders that are observed only in certain families is generally high (Antonarakis et al., 2010). Previous studies on celiac disease and Crohn's disease have revealed that these diseases show intermediate characteristics between Mendelian disorders and common diseases (Nakagome et al., 2010, 2012; Zhernakova et al., 2010), which is thought to reflect the history of the population.

The MMD patients have various diagnostic characters, while the most of East Asian patients have R4810K, especially in Japanese: 70%~90% of patients have the risk allele (Liu et al., 2011; Takamatsu et al., 2017). The questions are whether the diagnostic diversity is owing to the other mutations on the *RNF213* gene, and how/when the lineage harboring R4810K spread in the East Eurasian continent, especially into the Japanese archipelago. In the present study, our purpose is disclosing population genetic characteristics and spread process of the risk allele of MMD found in East Asian populations. We recently reported sequences of the 214-kb region covering the *RNF213* gene for 24 MMD patients (Koganebuchi et al., 2018). In this study, we perform population genetics analysis of *RNF213* using the sequence data to elucidate how this risk allele has been maintained in East Asians and estimate the age of the risk allele. For a greater understanding of MMD, we discuss the evolution of the risk allele under the peopling history of Japanese.

2 | MATERIALS AND METHODS

2.1 | DNA samples of MMD cases

All patients were diagnosed with MMD according to the criteria issued by the Japanese Ministry of Health, Labor, and Welfare (Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis, & Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases, 2012). Blood samples were collected from unrelated 30 MMD patients at Kitasato University Hospital, Kanagawa Prefecture, Japan. Information on family histories and onset of symptoms was obtained by interview. Each patient was observed various symptoms such as transient ischemic attack, stroke, cerebral hemorrhage, headache, and unilateral or bilateral involvement. All individuals provided written informed consent to participate in this genetic research project. This project was approved by the ethical committees at Kitasato University School of Medicine. Genomic DNA was extracted from blood using the DNA Extractor WB Kit (Wako Pure Chemical Corporation, Japan).

2.2 | DNA samples of healthy individuals in Japan

We analyzed four local populations in the Japanese archipelago: Northern Kyushu, the Okinawa islands, the Miyako islands and the Ishigaki islands (Figure S1). The three islands are included in the Ryukyu islands. The 47 Ryukyu islanders (15 Okinawa, 16 Miyako, and 16 Ishigaki islanders) who were originally described in Matsukusa

et al. (2010) were examined, and they were partially similar to the population described in Sato et al. (2014). Saliva samples of Northern Kyushu were collected from 43 healthy individuals at Saga University. All subjects provided written informed consent to participate in this genetic research project. This project was approved by the ethical committees at Faculty of Medicine, University of the Ryukyus or the Saga University School of Medicine, respectively. We confirmed by interview that the birthplaces of four grandparents were the Saga and/or the Fukuoka prefectures and labeled them as “Northern Kyushu.” Genomic DNA was extracted from the saliva samples following a modified protocol (Quinque et al., 2006) or a modified protocol of Oragene (DNA Genotek, Canada) saliva sample purification using the Puregene DNA Purification Kit (Qiagen, Germany) (<http://www.dnagenotek.com/US/pdf/PD-PR-00212.pdf>).

2.3 | Polymerase chain reaction amplification

We amplified the 967 bp region, including the risk variant R4810K (rs112735431), by PCR using a pair of primers: 5'-ACA TGG GCC CAA GGG ACA GAT TTC-3' and 5'-ACA GGG ATG GGC CGA GTC AGG-3'. For details on the PCR amplification conditions, see the Supporting Information text.

2.4 | Direct sequencing analysis

The DNA sequencing reactions were performed using the BigDye[®] Terminator v3.1 Cycle Sequencing Kit (Life Technologies, USA) using the diluted PCR primers according to the commercial protocol. For details on the direct sequencing conditions, see the Supporting Information text.

2.5 | Haplotype estimation and analysis of 1000 Genomes data

To initially explore LD and haplotype patterns, we selected 13 SNPs (Figure S2) in *RNF213* that were polymorphic in all four global populations, Yoruba in Ibadan, Nigeria (YRI), Utah Residents (CEPH) with Northern and Western European Ancestry (CEU), Han Chinese in Beijing, China (CHB), and Japanese in Tokyo, Japan (JPT), in the 1000 Genomes Project. A total of 414 individuals (108 YRI, 99 CEU, 103 CHB, 104 JPT) were involved in the analyses. The 10–20 kb intervals were taken between the 13 SNPs. The SNPs were chosen when the expected heterozygosity was estimated to be greater than 0.2 in at least three of the four

populations in the 1000 Genomes Project. This is because the SNPs shared among diverse populations at intermediate frequencies are likely to be old and appeared before the out-of-Africa (about 70,000 years ago), and such SNPs are possible to provide high r^2 -values than low-frequency alleles (Nordborg & Tavaré, 2002; VanLiere & Rosenberg, 2008). For details on the haplotype estimation, see the Supporting Information text.

2.6 | Population genetic statistics

Intrapopulation genetic diversity was shown by nucleotide diversity (π). The π of exons and introns was estimated by using VCFtools (version 0.1.13) (Danecek et al., 2011) with a 1,000 bp window size and 100 bp stepping size, and those averages were calculated.

We compared the linkage disequilibrium (LD) of *RNF213* among JPT, CHB, CEU, and YRI: we calculated two statistics of pairwise linkage disequilibrium, D' and r^2 , using Arelquin3.5 (Excoffier & Lischer, 2010).

2.7 | *RNF213* sequences of the 1000 Genomes Project data

VCF files of the 1000 Genomes Phase 3 containing a genomic region of the *RNF213* gene (about 138 kb) were obtained using the Data Slicer web tool (<http://www.internationalgenome.org/data-slicer/>), including JPT, CHB, CEU, and YRI. The VCF files were converted to FASTA files using vcf-consensus function included in the VCFtools (version 0.1.13) software package (Danecek et al., 2011).

2.8 | *RNF213* sequencing data of the MMD patients

We used nucleotide sequence data of 214-kb region covering the *RNF213* gene for 24 individuals, which we previously reported (Koganebuchi et al., 2018). In the previous study, we first sequenced the *RNF213* locus including the R4810K site for the 30 MMD patients by Sanger PCR-direct sequencing, and found 22 individuals had the risk allele. Second, we sequenced the 214-kb region covering the *RNF213* gene using MiSeq (Illumina, USA) for the 22 with the risk allele and 2 individuals without the risk allele for comparison. Hereafter, we call the 24 subjects “MY individuals” in this study. We labeled two sequences as 1 and 2 in the heterozygote: for instance, two sequences from an individual, MY1, were labeled MY1_1 and MY1_2. For details on the MiSeq sequencing procedure, see the Supporting Information text.

2.9 | Constructing the *RNF213* gene sequence tree

To select an outgroup sequence of the *RNF213* gene tree, we constructed a phylogenetic tree using YRI individuals and the human ancestral reference sequence (https://ftp.1000genomes.ebi.ac.uk/vol1/ftp/technical/reference/human_ancestor_GRCh37_e59.tar.bz2) provided by the 1000 Genome Project. Finally, a sequence of NA18498 (NA18498_1) was selected as the outgroup for the *RNF213* gene tree because NA18498_1 was placed at a branch that was the nearest to the human ancestral reference sequence.

The total number of diploid sequences in phylogenetic analysis, including MY, JPT (128 individuals) and NA18498_1, was 257. Finally, we obtained a dataset of 135,539 bp of aligned sequences. All positions containing gaps and missing data were eliminated, and a total of 135,041 bp was used in subsequent phylogenetic analysis. For details on the multiple alignment of the sequences, see the Supporting Information text.

Phylogenetic analyses were performed using the program MEGA7 (Kumar et al., 2016). Pairwise sequence divergences were calculated under the Tamura-Nei model (Tamura & Nei, 1993). Phylogenetic trees were constructed with the neighbor-joining (NJ) method (Saitou & Nei, 1987). The reliability of the tree was evaluated using 100 bootstrap replicates.

2.10 | Estimating the age of R4810K

We conducted coalescent simulations using GENETREE software version 9.0 (Griffiths, 2007) to generate maximum likelihood estimates for the scaled population mutation rate (θ_{ML}), the coalescent tree and the age of mutations for R4810K using MY and JPT. We also used BEAST version 2.5.2 (Bouckaert et al., 2019) to estimate the age of mutation. For details on the analyses, see the Supporting Information text.

3 | RESULTS

3.1 | Allele frequency of *RNF213* R4810K of healthy individuals

We looked into the allele frequency of the *RNF213* R4810K allele and found a frequency of 1.16% of the risk allele in Northern Kyushu (Figure S3), which was almost the same as that shown in previous studies (1.38% of Honshu and 1.85% of Northern Kyushu) (Liu et al., 2012; Takamatsu et al., 2017). In the Ryukyu islands, only on Ishigaki island,

the risk allele was shown at a little higher frequency (3.12%) (one risk allele in 32 chromosomes), but it was not found in the Miyako islands and the Okinawa islands at all (0.00%) (Figure S3). The frequency of the total population of the Ryukyu Islands (1.06%) was a little lower than that of other Japanese populations. Thus, we found a regional difference in the risk allele frequencies between the mainland and the Ryukyu islands in the Japanese archipelago.

3.2 | Nucleotide diversity

We examined the average π of *RNF213* in four global populations (JPT, CHB, CEU, YRI) from the 1000 Genomes Project (Figure S4) and found that the π of exons ($0.42 - 0.77 \times 10^{-3}$) was lower than that of introns ($1.01 - 1.39 \times 10^{-3}$). The diversity of exons was higher in YRI (0.77×10^{-3}) than in the other populations ($0.42 - 0.50 \times 10^{-3}$). The diversity of introns was also higher in YRI (1.39×10^{-3}) than the others ($1.01 - 1.17 \times 10^{-3}$). Nucleotide diversities of the entire *RNF213* gene in each population were higher than the averages of those of exons ($0.37 - 0.47 \times 10^{-3}$) and introns ($0.64 - 0.87 \times 10^{-3}$) in whole-genome data of the 1000 Genomes Project (Mu et al., 2011). Thus, this locus was a relatively highly polymorphic region.

3.3 | Linkage disequilibrium

We calculated LD values (D' and r^2) of *RNF213* in the global populations (Figures 1 and S5). Pairs of SNPs that showed higher LD were found in JPT, CHB, and CEU than in YRI. We found two high LD regions (blocks) in CEU, JPT, and CHB but not in YRI. The LD pattern of JPT was slightly different from CEU and CHB: a high LD was found in the region including rs112935431, corresponding to the risk allele, R4810K. However, this difference was not statistically significant because the risk allele frequency was too low (0.010) to show significant LD.

3.4 | Haplotype analysis

We looked into 13 SNP haplotype frequencies of global populations from the 1000 Genomes Project (YRI, CEU, JPT, and CHB). We found that 12 of 172 haplotypes accounted for $\geq 2\%$ of the total 414 individuals and named the 12 common haplotypes H1–H12 (Figure 2A). We combined frequencies of the remaining haplotypes (Residual). Comparing the total number of haplotypes among the populations, YRI (82) showed more haplotypes than CEU (58), JPT (64) and CHB (56), indicating that YRI was the most diverse population of the *RNF213* gene among the global

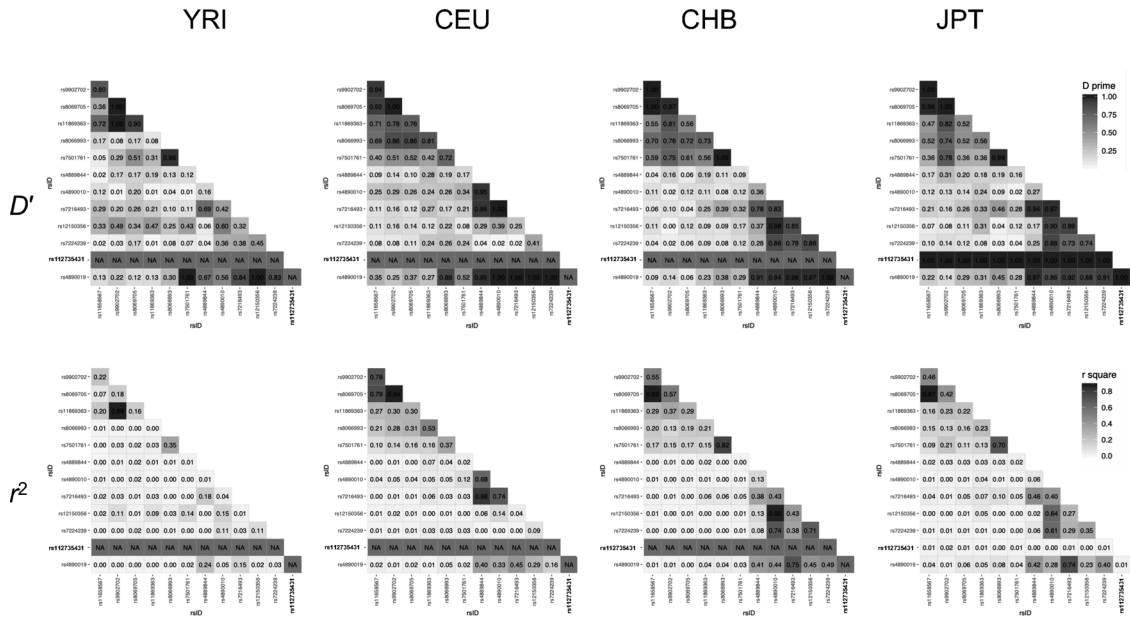


FIGURE 1 Heatmap matrixes of pairwise LD statistics D' and r^2
Note: The upper sides of the heatmaps are from the 5' end. The lower sides of the heatmaps are from the 3' end

populations; four haplotypes (H1, H6, H9, H11) account for 13.0% in YRI. The non-African populations, CEU and CHB–JPT, showed eight (H1, H2, H4, H7–H9, H11, H12) and nine haplotypes (H2–H5, H7–H11) that accounted for 49.5% and 63.1%–46.6%, respectively. Six haplotypes (H2, H4, H7, H8, H9, H11) were common among the non-African populations (CEU and JPT–CHB), while nine haplotypes (H2–H5, H7–H11) were shared between East Asian populations (CHB and JPT). Though 4 of the 12 common haplotypes (H1, H6, H9, H11) were found in YRI, almost all haplotypes, except for H3 and H10, were found in at least one of the seven African populations in the 1000 Genomes Project (Table S2). Thus, the pattern of haplotype frequencies was explained simply by bottleneck effect of the out-of-Africa migration that was shown in many previous studies (Jakobsson et al., 2008; Li et al., 2008; Ramachandran et al., 2005).

A haplotype harboring R4810K was found only in JPT that was shared by two sequences included in the residual of *RNF213* haplotypes estimated using 13 SNP sites. To understand the evolutionary history of the *RNF213* haplotypes, we constructed a phylogenetic network of 13 haplotypes (12 common haplotypes and the haplotype harboring R4810K) and the human ancestral reference sequence as the ancestral haplotype (Figure 2B). The four populations of the 1000 Genomes project did not have the ancestral haplotype. Because H3 and H10 were not found in the African populations (Table S2) but in the East Asian populations, and located at the edges of the network (Figure 2B), it is likely that the two haplotypes were born outside

of Africa after the out-of-Africa migration. The network showed two reticulations indicating at least two (probably more) past recombination events within the *RNF213* locus. Although two separate evolutionary directions from the ancestral haplotype would be often interpreted to be an evidence of balancing selection (Bamshad & Wooding, 2003), there has been no conventional statistical test to distinguish between balancing selection and random genetic drift.

The topology of the *RNF213* haplotype network can be explained by both of them. First, this does not have really two separate directions: the network contained furthermore invisible reticulations caused by multiple recurrent mutations and/or recombinations in the locus. Second, if it is truly balancing selection, more than two haplotypes should show remarkably higher frequencies. However, there were no outstanding high-frequency haplotypes, suggesting no evidence of strong balancing selection in the genomic region. H4 showed a relatively higher frequency than the other haplotypes, and the haplotype harboring R4810K likely arose from H4.

3.5 | Genotypes of the R4810K site on the MMD cases

We analyzed genotypes of the R4810K site in the 30 MMD cases by direct sequencing. Homozygous healthy alleles were found in 8 individuals, while 22 individuals had heterozygous alleles. The number of homozygous risk alleles

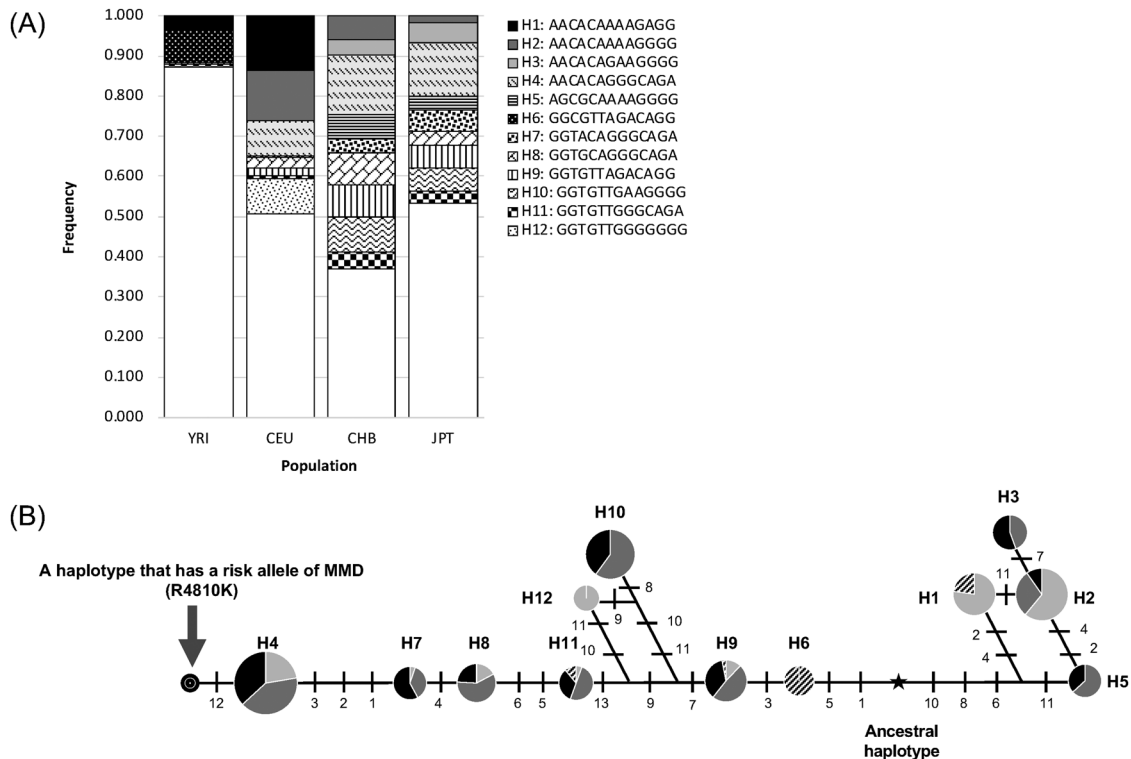


FIGURE 2 *RNF213* 13 SNP haplotypes (A) Haplotype frequencies in each geographic population. Abbreviations of the populations are the same as in the Section 2. Haplotypes with $\geq 2\%$ frequency in the total population are numbered from H1 to H12, and those with $< 2\%$ frequency in the total population are shown as residual. (B) A phylogenetic network for 13 haplotypes of 13 SNPs from *RNF213* constructed by the median-joining method. Pie charts represent 12 major haplotypes (see Figure 2A). The circle sizes are proportional to the world average of frequencies for the 12 major haplotypes with subdivisions showing the frequencies of the haplotypes in the geographic populations: JPT (black), CHB (dark gray), CEU (light gray), and YRI (black shaded lines). The star indicates the ancestral haplotype. The double circle indicates the risk allele-harboring haplotype. The black bars and the numbers on the branches represent the SNP positions of the haplotype in Figure S2. The presence of the same number multiple times suggests repeat mutations and/or recombinations. The ambiguity in the evolution of the haplotypes is indicated by the two pathways from the ancestral haplotype

was zero. Thus, 73.3% of the cases were heterozygotes. A previous study reported a similar genotype frequency in a Japanese MMD patient cohort (Takamatsu et al., 2017).

For targeted-capture sequencing using MiSeq, we selected all 22 MMD patients harboring the risk allele and randomly chosen the 2 of 8 MMD patients without risk allele. These 2 MMD patients were analyzed for comparison to the 22 MMD patients harboring the risk allele. Hereafter, we analyzed the 24 MMD patients (MY individuals) in total.

3.6 | NJ tree of *RNF213*

We constructed an NJ tree of *RNF213* using the nucleotide sequence data of MY (24 patients) and JPT (104 individuals) (Figure 3A and B). Out of the 48 MY sequences, 22 sequences harbored R4810K. Out of the 22 sequences, 20 sequences clustered with 2 sequences, NA18977_1 and NA 19070_2, harboring R4810K in JPT. We call it the

“R4810K cluster.” The remaining two sequences, MY02_1 and MY21_1, were placed in the other nodes. As shown in Figure S6, the two sequences showed two sequential gaps at approximately 14 and 40 kb regions from the 5' end, indicating past recombination events. Namely, the two sequences were plausibly born by multiple recombinations that occurred between a sequence in the R4810K cluster and a sequence placed at the branches that were closer to the root than the R4810K cluster. Out of the 20 clustered sequences harboring R4810K, 16 sequences were completely the same (Figure 3B). Thus, the sequences harboring R4810K had very high similarity with each other.

3.7 | Estimation of the ages of two mutations

To estimate the ages of R4810K and a mutation shared by the MY cluster (mutation nos. 6 and 1 in Figure S7, respectively), we looked for a nonrecombining region

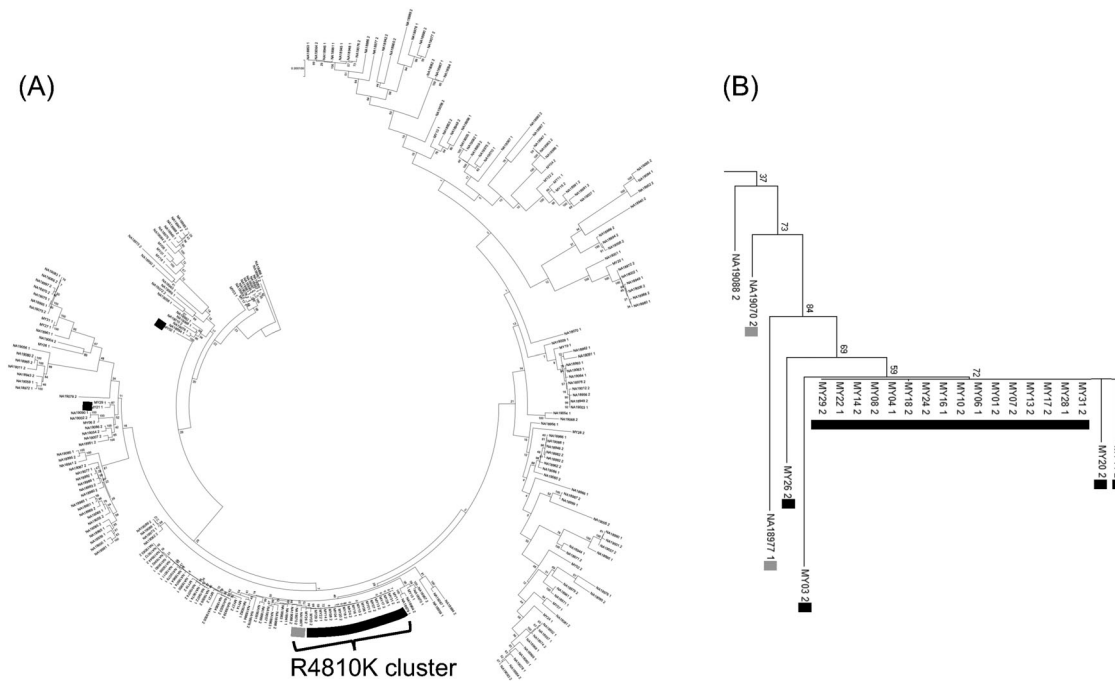


FIGURE 3 Phylogenetic tree for *RNF213* based on 136-kbp nucleotide sequences constructed by the neighbor-joining (NJ) method. *Note:* The analysis involved 257 nucleotide sequences because the tree was constructed using nucleotide sequence data of an outgroup sequence and individuals in MY and JPT populations, which provided two sequences each. The genetic distance was estimated with the Tamura-Nei model. Bootstrapping ($\times 100$) was performed. The black highlights represent sequences harboring R4810K found in MY, while the gray highlights represent the sequences harboring R4810K found in JPT of the 1000 Genomes Project database. (A) The NJ tree of the *RNF213* gene. (B) A part of the NJ tree of the *RNF213* gene focused on the R4810K cluster

harboring the R4810K site. We analyzed all 24 sequences harboring R4810K in MY, JPT and the outgroup sequence (NA19088_2) and found the nonrecombining region (79,723 bp) fitting the infinitely many-site model using GENETREE (Figure S7). We found seven polymorphic sites in the nonrecombining region (Tables S3 and S4) and a cluster including the patients (MY cluster) in the coalescent tree (Figure S7).

Using the nonrecombining region, we estimated the ages by GENETREE and BEAST2 (Table 1). We used two models, constant and exponential growth rate, for the estimation but found no difference between the estimated ages under the two models with GENETREE: the ages of R4810K and the shared mutation in the MY cluster were approximately 11,000 and 6500 years ago, respectively. The estimations with BEAST2 were different between the two models: the ages of R4810K and the shared mutation in the MY cluster were approximately 14,000 and 5900 years ago, or 5100 and 4200 years ago, respectively. Due to large standard errors, the 95% confidence intervals of the ages of R4810K and MY overlapped among the four runs.

The estimated age of R4810K and the mutation shared in the MY patients slightly varied between GENETREE and BEAST2 (Table 1). Though the two programs are based

on coalescent simulation, they have different algorithms of genealogy sampling: GENETREE adopts independent sampling, whereas BEAST2 adopts correlated sampling. Independent sampling assumes a restrictive mutation model: infinitely many sites model. The correlated sampling method allows various mutational models but has more difficulties producing an exhaustive sample of high-quality genealogies (Kuhner, 2009), which might give different estimations between GENETREE and BEAST2. The estimation of GENETREE can provide a stricter result than that of BEAST2.

4 | DISCUSSION

4.1 | East Asia origin of the risk allele R4810K

The comparison of diversity among the *RNF213* sequences from YRI, CEU, CHB and JPT gives us the genetic characteristics of the gene. The π values of African populations are higher than those of non-African populations, which is a typical pattern of bottleneck effect in the out-of-Africa expansion (Figure 2). Comparing the averages of all genes

TABLE 1 Time estimates (in years \pm SD) for the TMRCA of 24 chromosomes harboring R4810K and coalescent tree nodes of MMD cases

	GENETREE (constant)	GENETREE (population growth)	BEAST2 (constant)	BEAST2 (population growth)
R4810K	11,553 \pm 4044	10,545 \pm 3374	14,465 \pm 4626	5107 \pm 2590
MY	6730 \pm 2256	6244 \pm 1953	5884 \pm 2816	4189 \pm 1870

in the entire genome, the average π of exons was smaller than that of introns, which is common in neutral genes. Meanwhile, both the exon and intron π in *RNF213* were higher than the averages of the 1000 Genomes (Figure S4). The mutation rate of the *RNF213* gene (see Section 2) was higher than that of the whole genome in a recent study (approximately 0.5×10^{-9} mutations per nucleotide per year) (Sally, 2016). Such higher mutation rates are characteristics of genes related to the immune system (Martinson et al., 1999), which is often useful for environmental adaptation. However, the currently known function of *RNF213* is related to fat metabolism (Sugihara et al., 2019).

The comparison of *RNF213* haplotypes revealed the expansion process of the gene and occurrence of R4810K after the out-of-Africa migration of modern humans. The risk allele haplotype was born by a single nucleotide substitution from H4 that three non-African populations, JPT, CHB, and CEU, shared, but YRI did not (Figure 2B). When we looked at H4 in all African data from the 1000 Genomes Project, one chromosome of Gambians in western Africa shared H4 (0.44%) (Table S2). H7 and H8 that were placed at the nearest branch of H4 in the haplotype network (Figure 2B) were not shared in the African populations except for one chromosome that contained H8 in the Kenya (Table S2). From these results, it is likely that H4 was born outside of Africa after the out-of-Africa migration, or disappeared in the African populations though H4 was born in Africa. The observation of H4 in Gambian and H8 in Kenyan at very low frequency might be explained by back-migration from non-African populations (e.g., colonization in the early modern period) or by some Gambians/Kenyans having non-African ancestry, though this remains to be shown. However, there is no evidence for the hypothetical explanations. We should examine more African populations to see the origin of H4. It is much clearer that the R4810K mutation was born in East Asia, because the allele was found only there.

4.2 | R4810K brought by ancient immigrants

The high similarity of sequences harboring R4810K showed a recent common ancestor. The 22 sequences of MY harboring R4810K with no recombination were approximately 80 kb (Figure S6). Of 22, 16 sequences were

exactly the same sequence type (Figure S6), indicating that the MY patients in the present study are closely related genetically, notwithstanding we collected the MY patient samples from different families. The similarity of the sequences MY harboring R4810K just fits the peopling history discussed next.

Recent population genomic studies of ancient/modern samples have revealed peopling history of Japanese (Gakuhari et al., 2020; Jinam et al., 2012; Kanzawa-Kiriyama et al., 2017, 2019; Nakagome et al., 2015; Sato et al., 2014). According to archeological records, the Jomon culture spanned ~16,000–3000 years ago in the entire Japanese archipelago after the Upper Paleolithic period (Mizoguchi, 2013). The people who had the Jomon culture, what we call the Jomon people, were aboriginal hunters–fishers–gatherers. The Japanese archipelago was connected to the East Eurasian continent via the northern island, Hokkaido, until the end of the Last Glacial Maximum, and separated from the continent around 18,000 years ago. The Jomon people were, therefore, isolated from the other populations in East Eurasia (Kaifu et al., 2015). Around 3000 years ago, immigrants came to the Japanese archipelago from East Asia and introduced paddy rice farming. This culture was called Yayoi culture, and the people who had the Yayoi culture were called Yayoi immigrants. Based on our ancient genome analysis of a Jomon individual, the divergence time between the Jomon people and the Yayoi immigrants is dated back to the common ancestor of present-day East Eurasian and Native American (40,000–26,000 years ago) (Gakuhari et al., 2020).

According to previous genetic studies, R4810K is found in Chinese, Korean, and Japanese (Figure S3). In our estimation, R4810K arose approximately 14,500–5100 years ago (Table 1), corresponds to the Early to Middle Jomon period, though the estimated age includes wide-range deviation. Based on the current geographical distribution of R4810K, it is likely that R4810K arose in the East Asian continent. Because the age of the mutation shared in the MY cluster (the split time of the grey arrow of Figure S7) was more recent than that of R4810K (the split time is shown by the black arrow of Figure S7), we speculate that the ancestor of the MY patients examined in this study came to the Japanese archipelago together with the immigrants from the East Asian continent. By analyzing the ancient genome of bones from Korea and China in this period, we might be able to reveal the whole picture of the *RNF213* gene.

The distribution of R4810K in the Japanese archipelago could fit “the dual structure model” of peopling history in the Japanese archipelago, which is based on morphological anthropology (Hanihara, 1991; Ishida et al., 2009; Matsumura, 2001). The recent genetic and genomic population studies have strongly supported that Ryukyu islanders showed a lower genetic contribution of the Yayoi immigrants than the Hondo people (Koganebuchi et al., 2012; Matsukusa et al., 2010; Nakagome et al., 2015; Sato et al., 2014). When comparing the allele frequency of R4810K among the six sampling sites of the Japanese archipelago, we found the risk allele at higher frequencies in Hondo and Northern Kyushu than in the Ryukyu islands (Figure S3). Thus, it is plausible that the R4810K frequency distribution pattern is formed by the demographic history explained by the dual structure model. The exception, relatively high frequency (3.12 %) of the R4810K allele in the Ishigaki population, would be drift due to the small sample size (16 individuals) and also be an influence of migration from Hondo to the Ishigaki island occurred before the grandparents’ generation of the subjects, however, the diversity of the *RNF213* gene harboring R4810K in the Ryukyu Islands and Kyushu, as well as those in mainland East Asia, is required to reveal the detailed expansion process of R4810K in the future.

4.3 | Diagnostic variation and genetic diversity

Our analysis shows that the R4810K was maintained by demography in spite of its deleterious effects, which likely agrees with diagnostic characteristics. MMD shows some different diagnostic characteristics between the homozygote and heterozygote of the risk allele (Miyatake, Miyake, et al., 2012; Miyatake, Touho, et al., 2012). The R4810K homozygotes were highly associated with early-onset MMD (age at onset <5 years old), severe symptomatic manifestations at diagnosis, and poor prognosis (Kim et al., 2015). MMD patients with the R4810K heterozygote develop later onset (after reproductive age) and show less severe symptoms than homozygote patients. There is no advantageous phenotype reported in the individuals harboring R4810K so far. Thus, the R4810K mutation could be brought to descendants as the R4810K heterozygote regardless of its deleterious effect.

Mendelian disease alleles are highly effective, and their frequencies are very rare because the alleles are generally found in particular family lineages, while common disease alleles are shared among global populations (Manolio et al., 2009). Risk alleles of common disease appeared before human population divergences (approximately ~200,000 years ago), while Mendelian disease alle-

les are likely to be very recent mutations (approximately some hundreds or decades ago) (Nakagome & Oota, 2012). R4810K is East Asian-specific and the age of the mutation is approximately 12,000–5000 years. Thus, the age and the pattern of distribution of the MMD risk allele are intermediate between Mendelian and common disease. Though the *RNF213* sequences with the risk allele were very similar to each other, there is high diversity of diagnostic characteristics of the MMD cases (e.g., transient ischemic attack, cerebral infarction, intracranial bleeding, headache) (Kuroda & Houkin, 2008), suggesting that *RNF213* genetic variations cannot explain the high diversities of the phenotypes or MMD. Rather, the interaction with the other genes and the environment could explain the high phenotypic diversity of MMD, which is considered an important issue to be addressed in the near future.

ACKNOWLEDGMENTS

We thank Dr. Shoji Kawamura, Dr. Minoru Yoneda, Dr. Takafumi Katsumura, and Dr. Ryosuke Kimura for many discussions and suggestions about our research. The study was supported by grants from JSPS KAKENHI (<https://www.jsps.go.jp/j-grantsinaid/>) Grants-in-Aid to HO (17H05132, 19H04526, 19H05350), for Scientific Research B to HO (24370099, 17H03738) to HI (22370087), for Scientific Research on Innovative Areas to HO (19H04526), to HI (16H06408), and for Scientific Research B to SM (24300109). KK was supported by the JSPS Fellowship (<https://www.jsps.go.jp/j-pd/>, 15J10824).

AUTHOR CONTRIBUTION

Study design: Kae Koganebuchi and Hiroki Oota. *Sample collection:* Kae Koganebuchi, Kimitoshi Sato, Kiyotaka Fujii, Toshihiro Kumabe, Kuniaki Haneji, Takashi Toma, Hajime Ishida, Keiichiro Joh, Hidenobu Soejima, and Hiroki Oota; *Data analysis:* Kae Koganebuchi. *Supervision:* Shuhei Mano and Motoyuki Ogawa. *Manuscript preparation:* Kae Koganebuchi and Hiroki Oota.


CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The sequences were reported in our previous study (Koganebuchi et al., 2018) and were deposited in the DDBJ Sequence Read Archive (<http://trace.ddbj.nig.ac.jp/dra/>, DRR129157–129180). We used the “DRR” sequence data in the analyses of this study.

ORCID

Kae Koganebuchi  <https://orcid.org/0000-0002-6972-2218>

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SUPPORTING INFORMATION

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How to cite this article: Koganebuchi K, Sato K, Fujii K, et al. An analysis of the demographic history of the risk allele R4810K in *RNF213* of moyamoya disease. *Ann Hum Genet.* 2021;85:166–177. <https://doi.org/10.1111/ahg.12424>