Founder genetic variants of *ABCC4* and *ABCC11* in the Japanese population are not associated with the development of subacute myelo-optico-neuropathy (SMON)

Hideki Matsumoto¹ | Hideo Sasai¹,² | Norio Kawamoto¹ | Masato Katsuyama³ | Makoto Minamiyama⁴ | Satoshi Kuru⁴ | Toshiyuki Fukao¹,² | Hidenori Ohnishi¹,² | SMON research group members

¹Department of Pediatrics, Gifu University Graduate School of Medicine, Gifu University, Gifu, Japan
²Clinical Genetics Center, Gifu University Hospital, Gifu, Japan
³Radioisotope Center, Kyoto Prefectural University of Medicine, Kyoto, Japan
⁴Department of Neurology, National Hospital Organization Suzuka National Hospital, Mie, Japan

Correspondence
Hideki Matsumoto, Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido 1-1, Gifu 501-1194, Japan.
Email: hmatsumoto-gifu@umin.ac.jp

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Abstract

**Background:** Subacute myelo-optico-neuropathy (SMON) is a severe neurological disorder associated with clioquinol administration, which frequently occurred in Japan during the 1950s and 1960s. The unique genetic background of the Japanese population is considered to be strongly involved in the development of this neurological disease. Recently, genetic variants of *ABCC4* (OMIM: 605250) and *ABCC11* (OMIM: 607040), which are particularly common in the Japanese population, were suggested as possible genetic susceptibility factors for the development of SMON.

**Methods:** We analyzed 125 Japanese SMON patients who provided consent for this study. Patient DNA was collected from peripheral blood, and genetic analysis was performed for *ABCC4* rs3765534 (c.2268G>A, p.Glu857Lys) and *ABCC11* rs17822931 (c.538G>A, p.Gly180Arg) polymorphisms using the Sanger sequencing method and/or TaqMan PCR method. The frequency distribution of each polymorphism was compared with that in healthy Japanese people recorded in two genomic databases (Human Genomic Variation Database and Integrative Japanese Genome Variation Database), and each genotype was compared with the clinical features of patients.

**Results:** The frequencies of *ABCC4* rs3765334 and *ABCC11* rs17822931 polymorphisms in SMON patients and healthy Japanese people were not significantly different in the multifaceted analysis.

**Conclusion:** We conclude that the *ABCC4* rs3765334 and *ABCC11* rs17822931 polymorphisms are not associated with the development of SMON.

**Keywords**
*ABCC11, ABCC4, clioquinol, Japanese, subacute myelo-optico-neuropathy*
1 | INTRODUCTION

Subacute myelo-optico-neuropathy (SMON), a neurological disorder associated with clioquinol administration, is a serious drug-induced disorder. Reports have indicated that 1%–4% of patients who were administered clioquinol developed SMON. SMON has occurred in ~10,000 people, and ~5% of SMON patients have died from the disease (Meade, 1975). In recent years, because of the aging of patients, the number of surviving SMON patients has decreased each year. In our report in 2019, ~1100 SMON patients with various neurological sequelae were still alive in Japan. The pathomechanism of this neurological disease is considered to be dependent on the dose of clioquinol (Sobue et al., 1973). SMON and similar disorders have also been reported in European and Indian populations (Gilland, 1984; Ricoy et al., 1982; Wadia, 1984), but the most severe form of this neurological disease occurs with a high frequency in Japan (Kono, 1971; Meade, 1975; Nakae et al., 1973). Therefore, it is possible that the unique genetic background of Japanese people induces susceptibility to this neurological disease caused by clioquinol administration. Clioquinol was considered a useful medication with strong antibacterial activity during the 1950s and 1960s in Japan. Recently, clioquinol has been suggested for the treatment of neurodegenerative diseases such as Alzheimer’s disease (Billings et al., 2016; Cherny et al., 2001) and tumors (McInerney et al., 2018; Perez et al., 2016). Therefore, it is important to analyze the effects of genetic background on clioquinol metabolism before considering the introduction of clioquinol and its analogues in Japan to prevent the recurrence of SMON.

In 2019, Perez et al. (2019) suggested an association among clioquinol administration, the development of SMON in Japanese people, and ABCC4 (OMIM: 605250) and ABCC11 (OMIM: 607040) polymorphisms. ABCC4 and ABCC11 genes are related to the cAMP transport pump. ABCC4, which is encoded by the ABCC4 gene, is associated with the transport of lipophilic organic anions across the plasma membrane and may also be involved in prostaglandin-mediated cAMP signaling in ciliogenesis (Hardy et al., 2019). The ABCC4 rs3765534 polymorphism has been reported to dramatically reduce transporter function by disrupting localization of the ABCC4 protein in the plasma membrane (Krishnamurthy et al., 2008). ABCC11, encoded by the ABCC11 gene, is associated with transporting lipophilic organic anions across the plasma membrane, similar to ABCC4 (Toyoda et al., 2016). The ABCC11 rs17822931 polymorphism is involved in apocrine gland secretion and has been associated with a certain type of earwax and the onset of axillary osmidrosis (Super Science High School Consortium, 2009; Toyoda et al., 2009). The ABCC4 rs3765534 (c.2269G>A, p.Glu757Lys) and ABCC11 rs17822931 (c.538G>A, p.Gly180Arg) polymorphisms are both more common in Japanese people than in Europeans. To confirm the above-mentioned hypothesis reported by Perez et al. (polymorphisms in ABCC4 and ABCC11 are associated with clioquinol administration and development of SMON in Japanese people), we performed a genetic analysis using a large database of Japanese SMON patients.

2 | MATERIALS AND METHODS

2.1 | Recruitment of SMON patients

The participants were Japanese SMON patients who participated in the "SMON health examination by the SMON research group members" (health screening specifically for SMON patients provided through a national policy) from 2016 to 2020 (total number of patients screened 297). Peripheral blood samples of 125 SMON patients who gave written informed consent were collected from collaborating institutions.

2.2 | DNA extraction

Genomic DNA was extracted from blood samples and collected in tubes containing EDTA using the Sepa Gene Kit® (EIDIA Co., Ltd.) according to the manufacturer’s manual. DNA extraction was performed using a single extraction method. After extraction, DNA was stored at 4°C until use. ABCC4 (NM_005845.5) rs3765534 and ABCC11 (NM_032583.3) rs17822931 polymorphisms were analyzed by the Sanger sequencing method and/or the TaqMan PCR method.

2.3 | Single nucleotide polymorphism (SNP) genotyping assay using the Sanger sequencing method

The following primers were used for SNP analysis: ABCC4 rs3765534 polymorphism in ABCC4 exon 18: forward 5’-TCGACTGAGACTCTGATCTGT-3’ and reverse 5’-CATGAAGCTTCTTCCAAA-3’ and ABCC11 rs17822931 polymorphism in ABCC11 exon 4: forward 5’-CTAAGTGCCAGGACATGCTTGTGATGC-3’ and reverse 5’-TTCAGTGCTTCTGGTGATGC-3’. The sequences were analyzed using a BigDye® Terminator v1.1 Cycle Sequencing Kit (Cat. No. 4337450; Applied Biosystems,) and an Applied Biosystems 3130xl Genetic Analyzer (Applied Biosystems).
2.4 SNP genotyping assay using the TaqMan PCR method

PCR was performed using a StepOne RealTime PCR System (48-well format; Applied Biosystems), TaqMan GTXpress Master Mix (Cat. No. 4401892; Applied Biosystems), and TaqMan SNP genotyping assay mix (ABCC4 rs3765534 polymorphism, Assay ID C__27478235_20, Cat. No. 4362691, ABCC11 rs17822931 polymorphism, Assay ID C__25999969_20, Cat. No. 4362691, Thermo Fisher Scientific Inc.) using a general protocol according to the manufacturer’s instructions.

2.5 Statistical analysis of polymorphisms

The frequencies of the ABCC4 rs3765334 (Ref: G/Alt: A) and ABCC11 rs17822931 (Ref: G/Alt: A) polymorphisms for different races were collected from the Genome Aggregation Database (gnomAD; Karczewski et al., 2020). Then, we compared the frequency distributions of the ABCC4 rs3765334 and ABCC11 rs17822931 polymorphisms in SMON patients and healthy Japanese people (in the Human Genomic Variation Database (HGVD; Higasa et al., 2016; Narahara et al., 2014) and Integrative Japanese Genome Variation Database (iJGVD; Tadaka et al., 2018). These comparisons were analyzed with dominant and recessive genetic models. The statistical analysis was performed using Prism 9 (GraphPad Software, LLC). The statistical significance of the differences was determined by Pearson’s chi-square test, and Yate’s continuity correction was applied as needed. Statistical significance was set as p < .05.

3 RESULTS

A summary of the clinical information of SMON patients enrolled in this study is shown in Table 1. Many SMON patients are still living with sequelae of variable severity. The frequencies of ABCC4 rs3765334 and ABCC11 rs17822931 polymorphisms among the races registered in the gnomAD are shown in Table 2. Compared with other races, the allele frequency of ABCC4 rs3765334 Alt (A) was much higher in the Japanese population. The allele frequencies of ABCC11 rs17822931 Ref (G) and Alt (A) were reversed in the East Asian population, including Japanese people, compared with other populations. The frequency distributions of ABCC4 rs3765334 and ABCC11 rs17822931 polymorphisms in SMON patients and healthy Japanese people listed in the databases (HGVD and iJGVD) are shown in Table 3. Statistical analysis showed no significant difference in the frequency of these two polymorphisms between SMON patients and healthy Japanese people.

4 DISCUSSION

In this study, we evaluated the genetic variants of ABCC4 and ABCC11 that were recently suggested as possible genetic susceptibility factors for SMON. However, the ABCC4 rs3765534 and ABCC11 rs17822931...

| TABLE 1 | Summary of the clinical information of subacute myelo-optico-neuropathy patients |
|Entry| Data|
|---|---|
|Male: female| 40: 85|
|Age at onset of SMON (mean [SD])| 30.4 years old (±8.4)|
|Age at the time of blood sampling (mean [SD])| 80.3 years old (±8.0)|
|Degree of visual impairment |
|1: 6 (4.8%), 2: 4 (3.2%), 3: 7 (5.6%), 4: 12 (9.6%), 5: 41 (32.8%), 6: 54 (43.2%), n.d.: 1 (0.8%)|
|Degree of gait disturbance |
|1: 55 (44.0%), 2: 15 (12.0%), 3: 27 (21.6%), 4: 0 (0.0%), 5: 7 (5.6%), 6: 15 (12.0%), 7: 5 (4.0%), 8: 1 (0.8%)|
|Degree of superficial sensory impairment (tactile sensation) |
|1: 9 (7.2%), 2: 48 (38.4%), 3: 40 (32.0%), 4: 16 (12.8%), 5: 9 (7.2%), n.d.: 3 (2.4%)|
|Degree of superficial sensory impairment (pain) |
|1: 9 (7.2%), 2: 37 (29.6%), 3: 34 (27.2%), 4: 36 (28.8%), 5: 6 (4.8%), n.d.: 3 (2.4%)|
|Degree of abnormal perception |
|1: 25 (20.0%), 2: 68 (54.4%), 3: 22 (17.6%), 4: 8 (6.4%), n.d.: 2 (1.6%)|

Abbreviation: n.d., no data.

1. Total blindness, 2. light/dark only, 3. preocular manual valve, 4. preocular exponential valve, 5. mildly reduced, 6. almost normal.

2.1 Unable to walk, 2. wheelchair, 3. needs assistance, 4. grasping, 5. crutches, 6. single cane, 7. unsteady walking, 8. slight unsteady walking.

3.1 Severely decreased, 2. moderately decreased, 3. mildly decreased, 4. hypersensitive, 5. none.

4.1 Severe, 2. moderate, 3. mild, 4. almost none.
polymorphisms showed no significant difference in frequency between SMON patients and healthy Japanese people. Furthermore, we found many SMON patients who lacked these two polymorphisms. The association between the development of SMON and these two polymorphisms could not be verified, at least in terms of allele frequency.

Tateishi et al. reported an association between the development of SMON and clioquinol administration in experiments with an animal disease model (Tateishi et al., 1971), and this association was verified because the occurrence of new SMON cases completely disappeared after clioquinol use was banned (Nakae et al., 1973). However, the specific mechanism by which clioquinol causes nerve damage and induces SMON has not been elucidated. At present, several hypotheses regarding the pathomechanism of SMON have been proposed. Kawamura et al. (2014) reported that the neurological damage associated with the disease is caused by reactive oxygen species, Schaumburg et al. and Kimura et al. showed that copper deficiency was caused by copper chelation by clioquinol (Kimura et al., 2011; Schaumburg & Herskovitz, 2008), and Katsuyama et al. (2012) showed that double-strand DNA breaks induced by clioquinol cause ATM activation and concomitant activation of p53. Katsuyama et al. (2021) also showed that zinc influx was caused by the ionophore effect of clioquinol, and copper accumulation was caused by oxidation of ATOX1. However, none of these factors have been shown to be linked to susceptibility to SMON. Although clioquinol-induced neurological disorders have been reported in European (Gilland, 1984; Ricoy et al., 1982) and Indian populations (Wadia,

### Table 2 Frequency distribution of the ABCC4 rs3765334 and ABCC11 rs17822931 polymorphisms among the population reported in the Genome Aggregation Database (dataset: v2.1.1)

| Population            | ABCC4 (rs3765334) | ABCC11 (rs17822931) |
|-----------------------|-------------------|---------------------|
| Japanese              | 0.1908 (29)       | 0.8289 (126)        |
| Korean                | 0.08793 (335)     | 0.9872 (3767)       |
| Other East Asian      | 0.05787 (833)     | 0.8391 (12097)      |
| South Asian           | 0.05214 (1592)    | 0.406 (12397)       |
| Latino/Admixed American | 0.04282 (1514) | 0.2365 (5935)       |
| European (non-Finnish)| 0.009986 (1288)   | 0.1615 (5712)       |
| European (Finnish)    | 0.008921 (224)    | 0.1304 (16822)      |
| Ashkenazi Jewish      | 0.005696 (59)     | 0.1076 (1115)       |
| African/African-American| 0.003086 (77)    | 0.0279 (696)        |
| Other                 | 0.01664 (120)     | 0.1722 (1243)       |
| Total                 | 0.02186 (6173)    | 0.2169 (61266)      |

### Table 3 Frequency distribution of the ABCC4 rs3765334 and ABCC11 rs17822931 polymorphisms in subacute myelo-optico-neuropathy patients and healthy Japanese people in genetic databases (Human Genomic Variation Database and Integrative Japanese Genome Variation Database)

| Gene (SNP)          | Population               | Genotype | Statistical analysis |
|---------------------|--------------------------|----------|----------------------|
| ABCC4 (rs3765334)   | SMON patients            | Ref/Ref  | Ref/Alt              |
|                     | Healthy Japanese population (HGVD) | 93       | 28                |
|                     |                          | 880      | 301               |
|                     |                          | 29       | 1210              |
| ABCC11 (rs17822931) | SMON patients            | 3        | 21                |
|                     | Healthy Japanese population (HGVD) | 27       | 176               |
|                     |                          | 940      | 1143              |

| Gene (SNP)          | Population               | Allele frequency | Statistical analysis |
|---------------------|--------------------------|-------------------|----------------------|
| ABCC4 (rs3765334)   | SMON patients            |                   |                      |
|                     | Healthy Japanese population (HGVD) | 214     | 36                 |
|                     | Healthy Japanese population (iJGVD) | 2061   | 359                |
|                     |                          | 2420              |
|                     |                          | 8104              | 1442               |
|                     |                          | 9546              |
| ABCC11 (rs17822931) | SMON patients            |                   |                      |
|                     | Healthy Japanese population (HGVD) | 27      | 223               |
|                     | Healthy Japanese population (iJGVD) | 230   | 2056              |
|                     |                          | 2286              |
|                     |                          | 1231              | 8315               |
|                     |                          | 9546              |

*Using Yate’s continuity correction.
In recent years, many reports have described the beneficial effects of clioquinol and similar substances for neurodegenerative and oncological diseases. Therefore, it is important to elucidate the mechanism responsible for susceptibility to SMON. Several reports have found that the metal chelating effect of clioquinol may be useful in preventing the development of Alzheimer’s disease (Billings et al., 2016; Cherny et al., 2001). Several reports have also found that the inhibitory effect of clioquinol on ATP binding cassette subfamily C (ABCC) transporter function may be useful for inhibiting the growth of hematological tumors (McInerney et al., 2018; Perez et al., 2016). Because ABCC4, 5, and 11 are transporters that can be affected by clioquinol, Perez et al. analyzed the regional distribution of polymorphisms of the associated genes in the Japanese population (Super Science High School Consortium, 2009) in combination with reports on the residential areas of SMON patients (Kono, 1971) and reported that the ABCC4 rs3765534 and ABCC11 rs17822931 polymorphisms were candidate gene variants associated with the development of SMON (Perez et al., 2019). However, the association between these polymorphisms and the development of SMON was not demonstrated in in vitro functional experiments, and the frequencies of these polymorphisms in SMON patients are still unknown. Our study reports the frequencies of these polymorphisms in surviving SMON patients, but the association between the development of SMON and these two polymorphisms could not be verified.

One hypothesis is that the development of SMON is associated with a unique Japanese genetic background. To prevent a similar drug-induced disorder in the future, it is important to understand the pathogenesis of SMON. Therefore, we will continue to search for other genetic factors associated with SMON development using the largest database of SMON patients. It is assumed that oxidative stress in neurons may play a key role in the development of SMON (Kawamura et al., 2014). We are currently focusing on the cytoplasmic two-electron reductase encoded by the NQO1 gene (OMIM: 125860, NM_000903.3), which is an enzyme associated with oxidative stress, as one possible factor. In addition, comprehensive analysis, including genome-wide association studies, is required in future research. Two limitations in this study should be noted. We have obtained the largest dataset of SMON patients worldwide, but it is unlikely that there will be any new SMON patients in the future. Therefore, it would be impossible to collect more patients than those included in our study. The second limitation of this study is the lack of data, including the total dose and duration of clioquinol administration in SMON patients. In addition, we were not able to determine the patients’ residential areas at SMON onset to perform detailed research on environmental factors.

5 | CONCLUSION

No clear association was found between the ABCC4 rs3765534 and ABCC11 rs17822931 polymorphisms and the development of SMON. It will be necessary to investigate other genetic background factors involved in the development of SMON in the future.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
ETHICAL CONSIDERATIONS
This study was carried out under approval by the ethics review committee on medical research of Gifu University (Protocol number: 29-209), and the research collaborator’s institution also provided ethical approval.

DATA AVAILABILITY STATEMENT
Research data are not shared.

ORCID
Hideki Matsumoto https://orcid.org/0000-0002-5538-0739

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