Epilepsy with \textit{SLC35A2} Brain Somatic Mutations in Mild Malformation of Cortical Development with Oligodendroglial Hyperplasia in Epilepsy (MOGHE)

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\textbf{Purpose:} This study presents the characteristics of patients with mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE) with \textit{SLC35A2} somatic variants in the brain who underwent epilepsy surgery and showed clinical improvement in seizures.

\textbf{Methods:} We collected 10 patients with \textit{SLC35A2} somatic mutations in the brain who underwent surgery to treat drug-resistant epilepsy at Severance Children's Hospital from 2014 to 2019 and retrospectively reviewed their genetic profiles, neuropathologic results, clinical features, pre-operative evaluations, and post-operative outcomes.

\textbf{Results:} Six of the 10 patients with \textit{SLC35A2} somatic mutations in the brain had Lennox Gastaut syndrome (LGS) evolving from infantile spasms (IS), three had LGS, and one had IS. The median value of variant allele frequencies (VAFs) was 5.7\% (1.7\% to 5.8\%; range, 1.4\% to 22.9\%). Non-sense mutations were the most common (50\%), followed by missense mutations (40\%) and a splicing site mutation (10\%). Eight patients (80\%) had good post-operative outcomes, with freedom from disabling seizures in five (Engel class I) and rare disabling seizures in three (Engel class II). Four of the eight patients who could be assessed for social quotient (SQ) after surgery showed SQ improvements by $12.2 \pm 6.4$. Although all patients were finally diagnosed with MOGHE, seven (70\%) were initially diagnosed with gliosis, two with mild malformation of cortical development, and one with no abnormality.

\textbf{Conclusion:} All patients with \textit{SLC35A2} brain somatic mutations, even with low VAFs, had refractory epilepsy such as LGS or IS, and were finally diagnosed with MOGHE. This report is the first in Korea to our knowledge.

\textbf{Keywords:} Malformations of cortical development; Drug resistant epilepsy; Lennox Gastaut syndrome
Introduction

Malformations of cortical development (MCDs) refer to a wide range of cortical lesions from disruption of neurogenesis, proliferation, apoptosis, or migration [1,2]. The concept of MCDs was introduced in pediatric patients with developmental delay and epilepsy. A classification of those malformations was proposed in 1996 [3]. This classification was revised and updated in 2012 including mild MCD (mMCD) or focal cortical dysplasia (FCD), which features a small proportion of abnormal brain cells and disorganized cortical lamination [4]. Furthermore, mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE), which is characterized by increased proliferation of oligodendroglia in the white matter and deep gray matter, was proposed as a new histopathologic entity in 2017 [5].

Ample evidence has established that FCD is associated with intractable epilepsy requiring surgical resection of the lesion [1,6]. Remarkable advances in genetic technologies and molecular biology have revealed that somatic mutations in brain cells are associated with FCD [7,8]. Moreover, a low-level brain somatic mutation burden—even with a variant allele frequency (VAF) less than 1%—is enough to cause intractable epilepsy [9,10]. Therefore, deep sequencing with a high read depth (more than 1,000 ×) is necessary to identify the causative gene variant [10,11]. Genes related to epilepsy have been identified, including SLC35A2 and genes encoding the mechanistic target of rapamycin (mTOR) pathway proteins (AKT3, DEPDCS, MTOR, PIK3CA, TSC1, and TSC2) [8,10,11].

SLC35A2, which is located at Xp11.23, encodes a uridine diphosphate (UDP)-galactose transporter, a member of the nucleotide-sugar transporter family that transports galactose from the cytosol or nucleus into Golgi vesicles [9,12]. Germline loss of function variants in SLC35A2 resulting in producing abnormal truncated glycans that lack galactose have been identified in multiple patients with epileptic encephalopathy [13,14]. In addition, brain mosaic mutations in SLC35A2 are now considered one of the major genetic causes of intractable epilepsy, and recent studies have reported the histopathologic features of SLC35A2 somatic variants [12].

In this study, we present the clinical characteristics of patients with SLC35A2 somatic mutations in the brain who were finally diagnosed with MOGHE.

Materials and Methods

1. Selection of subjects
We retrospectively collected a series of patients with intractable pediatric epilepsy who underwent epilepsy resection surgery and were confirmed to have SLC35A2 brain somatic mutations from January 2013 to December 2019 at the Epilepsy Research Institute of Severance Children's Hospital. Ten cases were enrolled, including six patients (patient numbers 1, 2, 3, 4, 5, and 7) who were previously reported in 2018, three patients (patient numbers 8, 9, and 10) reported in 2019, and one patient (patient number 6) reported in 2021 [10,12,15]. We reviewed all data available for these 10 patients, which comprised their demographic characteristics, clinical features, pre-operative investigations, genetic profiles, operation details (including the pathologic analysis), and post-operative outcomes with medical records.

All patients were informed about the study and agreed to the collection of human tissues, and the protocols were approved by Severance Hospital and the KAIST Institutional Review Board and Committee on Human Research (IRB No. 4-2017-0119).

2. Pre-operative evaluations
The pre-operative investigations included neurologic examinations, development tests, and evaluations for determining the surgical area. The epileptogenic area was determined through the interpretation of long-term video-electroencephalogram (EEG)-monitoring data and confirmed by imaging studies including high-resolution magnetic resonance imaging (MRI), fluoro-deoxy-glucose (FDG) positron emission tomography (PET), and subtraction ictal single-photon emission computed tomography (SPECT) co-registered to MRI (SISCOM).

The development level was measured considering both cognitive level and social function, and it was classified as follows: normal (intelligence quotient/developmental quotient > 70), mild delay (50 to 70), moderate delay (35 to 49), severe delay (20 to 34), and profound delay (< 20). The cognitive level was assessed using the Korean Bayley Scales of Infant Development-II, the Korean Wechsler Preschool & Primary Scale of Intelligence-IV or the Korean Wechsler Intelligence Scale for Children-IV according to the patient’s age. The social quotient (SQ), as an indicator of general adaptive function, was scored in all patients using the Korean version of the Social Maturity Scale (SMS) based on the Vineland Social Maturity Scale, fifth version.

3. Genetic profiles and pathologic analysis through brain samples
Surgery proceeded in two stages: inserting intracranial EEG and determining the surgical margin according to the protocol of the Epilepsy Research Institute, Severance Children's Hospital [10,16]. All brain samples were freshly frozen (FFZ) or formalin-fixed paraffin-embedded (FFPE).
For DNA extraction from brain tissue, we used QIAamp DNA Mini kits (Qiagen, Germantown, MD, USA) from FFZ brain samples and QIAamp DNA FFPE kits (Qiagen, Hilden, Germany) from FFPE, as described in the previous report [10]. Site-specific amplicon sequencing for genetic analysis of SLC35A2 with read depth > 100,000 × and region-specific primers with the Illumina Nextera single index (Illumina, San Diego, CA, USA) for validation sequencing for somatic mutations was performed, as previously described [10,15].

Histopathologic analyses were conducted twice; the first one was done at the time of surgery by the Department of Pathology at Severance Children’s Hospital with the International League against Epilepsy (ILAE) classification [17]. Because MOGHE was first introduced in 2017 [5] and has not yet been included in the ILAE classification, a reanalysis was performed with hematoxylin and eosin staining, as well as anti-NeuN to look for heterotopic neurons (Clone A60, Millipore, Temecula, CA, USA) and anti-oli2 to identify oligodendroglial cells (clone JP18953, IBL International, Hamburg, Germany) immunostaining. The reanalysis was conducted by an expert neuropathologist without knowing the genetic information and previous pathologic results at Schoen Klinik, Vogtareuth, Germany in 2020 [12].

Results

We enrolled a total of 10 patients with intractable pediatric epilepsy confirmed to have SLC35A2 brain somatic variants.

1. Demographics and clinical features
As shown in Table 1, six of the 10 patients were male (60%). All patients suffered from daily seizures and had refractory epilepsy with focal epileptic findings on EEG, making them candidates for epilepsy surgery. The mean age of seizure onset was 12.2 ± 12.1 months old (range from 3 months to 3 years 2 months of age). Seventy percent of patients were diagnosed with infantile spasms presenting with spasms, and six of those patients progressed to Lennox Gastaut syndrome (LGS) with various types of seizures, including focal impaired-awareness seizures, focal motor seizures, and myoclonic seizures. Thirty percent of cases had only LGS, of whom two (2/3) experienced generalized seizures with head drop and one (1/3) had focal impaired-awareness seizures and spasms.

The degree of developmental delay was determined through an analysis of the cognitive level and social function; 10% of patients had low average development, 50% showed mild delay, 10% had moderate delay, 10% presented severe delay, and 20% had profound delay. The average IQ was 45.7 ± 22.2, corresponding to a moderate delay.

2. Genetic profiles
SLC35A2 brain somatic mutations were confirmed by site-specific amplicon sequencing (read depth > 100,000 ×). Nonsense mutations were found in 50% of patients, missense mutations in 40%, and a splicing site mutation of 10%. The SLC35A2 VAFs ranged from 1.4% to 22.9% (median VAF, 5.7% [range, 1.7% to 5.8%]), and patients were assigned numbers based on the VAFs in descending order. Patients 1, 2, and 3, who had high VAFs (more than 15%), all had nonsense mutations, while patients 8, 9, and 10, who had low VAFs (less than 5%), were all identified as having missense mutations (Table 1).

3. Pre-operative evaluations, operation details, and post-operative outcomes
As presented in Table 2, four patients (40%) underwent epilepsy surgery twice, three of whom (3/4) had resection surgery after localization of the lesion following corpus callosotomy. All these patients initially had negative findings on MRI, but localization by

Table 1. Demographics, clinical features, and genetic profiles

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age of seizure onset</th>
<th>Diagnosis of epilepsy</th>
<th>Type of seizures</th>
<th>Development level</th>
<th>Genomic variant</th>
<th>Protein change</th>
<th>Variant type</th>
<th>Brain VAF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>3 mo</td>
<td>LGS from IS</td>
<td>FIAS, spasms</td>
<td>Mild delay</td>
<td>c.589C&gt;T</td>
<td>p.Gln197Ter</td>
<td>Nonsense</td>
<td>22.9</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>3 yr 2 mo</td>
<td>LGS</td>
<td>FIAS, spasms</td>
<td>Low average</td>
<td>c.502C&gt;T</td>
<td>p.Gln168Ter</td>
<td>Nonsense</td>
<td>18.0</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>3 mo</td>
<td>LGS from IS</td>
<td>FIAS, focal motor, spasms</td>
<td>Profound delay</td>
<td>c.760G&gt;T</td>
<td>p.Glu254Ter</td>
<td>Nonsense</td>
<td>15.8</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>13 mo</td>
<td>LGS from IS</td>
<td>FIAS, spasms</td>
<td>Severe delay</td>
<td>c.703A&gt;C</td>
<td>p.Asn235His</td>
<td>Missense</td>
<td>10.0</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>5 mo</td>
<td>LGS from IS</td>
<td>Myoclonic, spasms</td>
<td>Mild delay</td>
<td>c.553C&gt;T</td>
<td>p.Gln185Ter</td>
<td>Nonsense</td>
<td>6.0</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>7 mo</td>
<td>LGS from IS</td>
<td>FIAS, spasms</td>
<td>Moderate delay</td>
<td>c.359_360del</td>
<td>p.Leu120HifsTer7</td>
<td>Nonsense</td>
<td>5.5</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>6 mo</td>
<td>LGS from IS</td>
<td>Spasm</td>
<td>Mild delay</td>
<td>c.275−1G&gt;T</td>
<td>-</td>
<td>Splicing site</td>
<td>5.0</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>2 yr 6 mo</td>
<td>LGS</td>
<td>GT, head drop</td>
<td>Mild delay</td>
<td>c.842G&gt;A</td>
<td>p.Gly281Asp</td>
<td>Missense</td>
<td>3.7</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>11 mo</td>
<td>LGS</td>
<td>GT, head drop</td>
<td>Profound delay</td>
<td>c.671T&gt;C</td>
<td>p.Leu224Pro</td>
<td>Missense</td>
<td>3.7</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>6 mo</td>
<td>IS</td>
<td>Spasm</td>
<td>Mild delay</td>
<td>c.359T&gt;C</td>
<td>p.Leu120Pro</td>
<td>Missense</td>
<td>1.4</td>
</tr>
</tbody>
</table>

VAF, variant allelic frequency; LGS, Lennox Gastaut syndrome; IS, infantile spasms; FIAS, focal impaired-awareness seizure; GT, generalized tonic.

https://doi.org/10.26815/acn.2022.00073
<table>
<thead>
<tr>
<th>No.</th>
<th>Age at last surgery</th>
<th>Surgery count</th>
<th>Scalp EEG</th>
<th>MRI findings</th>
<th>PET findings (decreased FDG uptake area)</th>
<th>Resection topology</th>
<th>Initial histology</th>
<th>Histology reanalysis</th>
<th>Follow-up period</th>
<th>Engel class</th>
<th>No. of last AED</th>
<th>Pre-operative SQ (age of test)</th>
<th>Post-operative SQ (age of test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 yr 5 mo</td>
<td>1</td>
<td>Rt. posterior quadrant</td>
<td>Normal</td>
<td>Rt. inferior frontal and temporal</td>
<td>Rt. frontal and Rt. posterior quadrant</td>
<td>Gliosis</td>
<td>MOGHE</td>
<td>4 yr 1 mo</td>
<td>1C</td>
<td>3</td>
<td>55.26 (3 yr 4 mo)</td>
<td>48.28 (7 yr 0 mo)</td>
</tr>
<tr>
<td>2</td>
<td>6 yr 3 mo</td>
<td>2 (after resection surgery)</td>
<td>Lt. temporal</td>
<td>Normal</td>
<td>Lt. parietal and superior temporal</td>
<td>Lt. temporo-occipital</td>
<td>Gliosis</td>
<td>MOGHE</td>
<td>2 yr 8 mo</td>
<td>1A</td>
<td>1</td>
<td>88.55 (3 yr 8 mo)</td>
<td>88.4 (7 yr 6 mo)</td>
</tr>
<tr>
<td>3</td>
<td>5 yr 2 mo</td>
<td>2 (after CC)</td>
<td>Lt. posterior quadrant, Lt. frontal</td>
<td>Normal</td>
<td>Lt. hemisphere</td>
<td>Lt. fronto-temporal, Lt. amygdalo-hippocampus and Lt. posterior quadrant</td>
<td>Gliosis</td>
<td>MOGHE</td>
<td>6 yr 3 mo</td>
<td>2B</td>
<td>4</td>
<td>11.8 (5 yr 0 mo)</td>
<td>11.85 (7 yr 2 mo)</td>
</tr>
<tr>
<td>4</td>
<td>5 yr 1 mo</td>
<td>2 (after CC)</td>
<td>Lt. parietal</td>
<td>Normal</td>
<td>Lt. fronto-parietal</td>
<td>Lt. temporal</td>
<td>nMCD</td>
<td>MOGHE</td>
<td>5 yr 9 mo</td>
<td>1A</td>
<td>0</td>
<td>36.8 (5 yr 0 mo)</td>
<td>34.28 (8 yr 1 mo)</td>
</tr>
<tr>
<td>5</td>
<td>4 yr 0 mo</td>
<td>1</td>
<td>Rt. frontal</td>
<td>FCD on Rt. frontal lobe</td>
<td>Lt. fronto-parietal</td>
<td>Lt. frontal, Rt. parietal and Lt. inferior frontal</td>
<td>Gliosis</td>
<td>MOGHE</td>
<td>2 yr 8 mo</td>
<td>1A</td>
<td>2</td>
<td>54.56 (3 yr 10 mo)</td>
<td>66.04 (4 yr 10 mo)</td>
</tr>
<tr>
<td>6</td>
<td>9 yr 0 mo</td>
<td>1</td>
<td>Rt. posterior quadrant</td>
<td>Normal</td>
<td>Rt. anterior temporal</td>
<td>Rt. temporal</td>
<td>nMCD</td>
<td>MOGHE</td>
<td>11 mo</td>
<td>2B</td>
<td>1</td>
<td>46.43 (8 yr 10 mo)</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>2 yr 8 mo</td>
<td>1</td>
<td>Rt. posterior quadrant</td>
<td>Slightly increased white matter T2 signal around Rt. temporo-parietal lobes</td>
<td>no official reading</td>
<td>Rt. posterior quadrant</td>
<td>Normal</td>
<td>MOGHE</td>
<td>2 yr 2 mo</td>
<td>1A</td>
<td>0</td>
<td>50.4 (2 yr 6 mo)</td>
<td>71.28 (3 yr 10 mo)</td>
</tr>
<tr>
<td>8</td>
<td>6 yr 1 mo</td>
<td>1</td>
<td>Lt. frontal</td>
<td>FCD on Lt. frontal lobe</td>
<td>Lt. medio-anterior frontal and inferior parietal</td>
<td>Lt. fronto-temporal</td>
<td>Gliosis</td>
<td>MOGHE</td>
<td>2 yr 9 mo</td>
<td>2A</td>
<td>2</td>
<td>50.36 (5 yr 10 mo)</td>
<td>55.79 (7 yr 2 mo)</td>
</tr>
<tr>
<td>9</td>
<td>10 yr 2 mo</td>
<td>2 (after CC)</td>
<td>Lt. temporal (main), Lt. frontal and Lt. occipital</td>
<td>Mild cerebellum volume decrease</td>
<td>Lt. superior frontal and medial parietal</td>
<td>Lt. frontal, Lt. posterior quadrant, amygdalo-hippocampus, splenium, corpus callosum, disconnected occipital and temporal</td>
<td>Gliosis</td>
<td>MOGHE</td>
<td>2 yr 6 mo</td>
<td>3A</td>
<td>3</td>
<td>12 (10 yr 1 mo)</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>2 yr 1 mo</td>
<td>1</td>
<td>Lt. fronto-temporal</td>
<td>Normal</td>
<td>Lt. superior frontal, lateral inferior parietal, and lateral temporal</td>
<td>Rt. frontal and Rt. temporal</td>
<td>Gliosis</td>
<td>MOGHE</td>
<td>4 yr 0 mo</td>
<td>3A</td>
<td>2</td>
<td>50.48 (2 yr 1 mo)</td>
<td>61.54 (3 yr 2 mo)</td>
</tr>
</tbody>
</table>

EEG, electroencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; FDG, fluoro-deoxy-glucose; AED, anti-epileptic drug; SQ, social quotient; Rt., right; MOGHE, mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy; Lt., left; CC, corpus callosum; mMCD, mild malformation of cortical development; FCD, focal cortical dysplasia.
In this study, we presented the clinical features of patients with SLC35A2 brain somatic variants showing the pathologic characteristics of MOGHE. SCL35A2 somatic variants have been reported in correlation with neuropathologic phenotypes with MOGHE [12]. The definition, classification, clinical phenotypes, MRI findings, pathology, and correlated genetic variants of MCD remain a challenging topic, and updates in this field continue [20]. As the concept of MOGHE has been introduced relatively recently, its clinical importance is underestimated in practice [5].

In our study, most of the mutations in SLC35A2 were nonsense mutations (50%), including one frameshift deletion, and this category included the three patients with the highest VAFs. Brain tissues with the p.Gln197Ter variant from patient 1 and the p.Glu254Ter variant from patient 3 showed aberrant patterns in terms of pathogenicity, and patient 2, with the p.Gln168Ter variant, showed changes in UDP-galactose transport as previously reported [13,15]. SLC35A2 is involved in transporting UDP-galactose from the cytosol to the Golgi apparatus and completing glycosylation by attaching galactose to N-acetylglucosamine. Loss of function of SLC35A2 can cause problems with N-glycosylation in this process. Abnormal N-glycosylation of brain development affects neural transmission, myelination, and neuronal migration, leading to clinical neurologic symptoms such as congenital disorders of glycosylation (CDG) [21], and the phenotype of MOGHE involves increased heterotopic neurons in the white matter and oligo-2 positive cell clusters in the white matter and gray-white matter junction. Ultimately, these findings appear as a blurred gray-white matter junction and hypomyelination on brain MRI. Most patients in our study presented normal MRI findings (70%), while three patients had increased T2 signal intensity on the lesion. The MRI findings of MOGHE are known to involve an increased laminar signal at the corticomedullary junction on T2 and fluid attenuated inversion recovery in subtype I in younger children or an increased signal of the adjacent white matter in subtype II in older children [18]. Therefore, somatic brain variants of SLC35A2, which likely occur in a neuroglial progenitor cell during neurogenesis, are thought to have potential as a genetic marker for MOGHE [12].

In this study, the three patients with the low VAFs (less than 5%) were all missense mutations, which means that a low mutation burden is sufficient to cause intractable epilepsy. Of particular note, patient 10 with a VAF of 1.4% and patient 9 with a VAF of 3.7% belonged to Engel class III, with only partially controlled seizures after epilepsy surgery. The variant burden in the brain may also govern aspects of the clinical presentation, but this mechanism is still unclear [9]. Further research is needed to determine whether the VAF in a fraction of cells in the blood is proportional to the VAF in brain somatic mutations and could be used as a factor to determine clinical severity.

Considering the reports that the symptoms of SLC35A2-CDG patients improved after taking galactose supplementation, which may partially increase cytosolic UDP-galactose and thereby facilitate galactosylation through alternative UDP-galactose transport into the Golgi [12,22], precision treatment can be considered to
control the symptoms of patients with SLC35A2 somatic brain mutations who cannot undergo epilepsy surgery or continue to have seizures after surgery.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Conceptualization: SHK, JSL, HDK, and HCK. Data curation: HJK, DSK, SHK, JHL, AK, and HCK. Formal analysis: HJK, AK, SHK, JSL, and HCK. Funding acquisition: HDK and HCK. Methodology: DSK, SHK, JHL, AK, SHK, JSL, HDK, and HCK. Project administration: HJK. Visualization: HJK. Writing-original draft: HJK. Writing-review & editing: HDK and HCK.

Acknowledgements

This study was supported by the Team Science Award of Yonsei University College of Medicine (6-2021-0007) and a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI21C1659).

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