RESEARCH ARTICLE

Clinical Features, Neuropathology, and Surgical Outcome in Patients With Refractory Epilepsy and Brain Somatic Variants in the *SLC35A2* Gene

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Abstract

Background and Objectives

The *SLC35A2* gene, located at chromosome Xp11.23, encodes for a uridine diphosphate–galactose transporter. We describe clinical, genetic, neuroimaging, EEG, and histopathologic findings and assess possible predictors of postoperative seizure and cognitive outcome in 47 patients with refractory epilepsy and brain somatic *SLC35A2* gene variants.

Methods

This is a retrospective multicenter study where we performed a descriptive analysis and classical hypothesis testing. We included the variables of interest significantly associated with the outcomes in the generalized linear models.

Results

Two main phenotypes were associated with brain somatic *SLC35A2* variants: (1) early epileptic encephalopathy (EE, 39 patients) with epileptic spasms as the predominant seizure type and moderate to severe intellectual disability and (2) drug-resistant focal epilepsy (DR-FE, 8 patients) associated with normal/borderline cognitive function and specific neuropsychological deficits. Brain MRI was abnormal in all patients with EE and in 50% of those with DR-FE. Histopathology review identified mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy in 44/47 patients and was inconclusive in 3. The 47 patients harbored 42 distinct mosaic *SLC35A2* variants, including 14 (33.3%) missense, 13 (30.9%) frameshift, 10 (23.8%) nonsense, 4 (9.5%) in-frame deletions/duplications, and 1 (2.4%) splicing variant. Variant allele frequencies (VAFs) ranged from 1.4% to 52.6% (mean VAF: 17.3 ± 13.5). At last follow-up (35.5 ± 21.5 months), 30 patients (63.8%) were in Engel Class I, of which 26 (55.3%) were in Class IA. Cognitive performances remained unchanged in most patients after surgery. Regression analyses showed that the probability of achieving both Engel Class IA and Class I outcomes, adjusted by age at seizure onset, was lower when the duration of epilepsy increased and higher when postoperative EEG was normal or improved. Lower brain VAF was associated with improved postoperative cognitive outcome in the analysis of associations, but this finding was not confirmed in regression analyses.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The SLC35A2 Study Group is listed at Appendix 2

Glossary

ASM = antiseizure medication; **CV-LFB** = cresyl violet-Luxol fast blue; **DR-FE** = drug-resistant focal epilepsy; **EE** = epileptic encephalopathy; **FCD** = focal cortical dysplasia; **ID** = intellectual disability; **IED** = interictal epileptiform discharge; **mMCD** = mild malformation of cortical development; **MOCHE** = mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy; **VAF** = variant allele frequency.

Discussion

Brain somatic *SLC35A2* gene variants are associated with 2 main clinical phenotypes, EE and DR-FE, and a histopathologic diagnosis of MOGHE. Additional studies will be needed to delineate any possible correlation between specific genetic variants, mutational load in the epileptogenic tissue, and surgical outcomes.

SLC35A2 (solute carrier family 35 member A2) gene, located at chromosome Xp11.23, encodes for a uridine diphosphate–galactose transporter, i.e., a multipass membrane protein that permits the transport of galactose into Golgi vesicles for protein and sphingolipid glycosylation. De novo variants in the *SLC35A2* gene have been associated with a congenital disorder of glycosylation presenting with epileptic encephalopathy (EE) as a prominent feature.[1,2] Somatic *SLC35A2* variants were initially reported in 3 patients with nonlesional focal epilepsies and in 2 with suspected focal cortical dysplasia (FCD) on MRI.[3] Histopathology revealed FCD type Ia in 2 of the nonlesional patients and gliosis in the remaining 3.[4] Somatic *SLC35A2* variants were subsequently identified in five[5] additional patients with nonlesional focal epilepsies and in one[6] with diffuse cortical dysplasia on MRI. Histopathology revealed mild malformation of cortical development (mMCD)[7] in 4 patients and gliosis or no abnormality in the remaining 2. Seven additional patients with epileptic spasms and somatic *SLC35A2* variants have been reported,[6,8,9] with histopathologic features consistent with mMCD type 2 in four[7] and FCD type I in three.[4] More recently, in 2 additional patients operated for drug-resistant epilepsy, *SLC35A2* brain somatic variants were demonstrated in tissue specimens harboring FCDIc with concomitant oligodendroglial hyperplasia.[10] A multicenter study[11] reevaluated histopathology in most previously reported patients with brain somatic *SLC35A2* variants plus 9 additional patients and identified a mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE), which is a recently defined histopathologic entity featuring clustered oligodendroglial hyperplasia with increased proliferative activity in the white matter involving the gray-white matter junction.[12] Two additional patients with somatic brain *SLC35A2* variants and MOGHE were subsequently reported.[13] In the recently updated FCD classification, MOGHE has been proposed as a new category to be included.[14] Although various series[13,15-18] have explored the clinical, EEG, and neuroimaging features and postoperative seizure outcome in patients with MOGHE, limited information is available regarding specific brain somatic *SLC35A2* variants and their associated outcomes after surgery. In this study of 47 patients with brain somatic *SLC35A2* gene variants, we analyzed clinical, neuroimaging, EEG, histopathologic, and genetic findings and assessed factors influencing postoperative seizure and cognitive outcomes.

Methods

Study Design and Population

This is a retrospective, multicenter study involving 9 epilepsy surgery centers, from Europe (5 centers), the United States (3 centers), and South Korea (1 center) and including 47 patients identified through multiple diagnostic and research series. Each center provided observations according to epilepsy surgery and brain somatic *SLC35A2* gene variants. Exclusion criteria were as follows: (1) constitutional (germline) *SLC35A2* gene variants and (2) additional constitutional or somatic variants affecting other genes and providing an alternate explanation for the patient's condition. We considered constitutional (germline) the *SLC35A2* variants exhibiting an allele variant frequency (VAF), defined as the ratio between the number of reads supporting the variant and reference alleles, between 0.45 and 0.55 in the brain tissue of female patients (i.e., 45%–55%), and above 0.9 in the brain tissue of male patients. All patients included in the study had been registered prospectively in each center's database; only pseudo-anonymized information was shared among the investigators.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Pediatric Ethics Committee of Tuscany Region, Italy (no 300/2021). Written informed consent (consent for research) was obtained from all participants (or guardians of participants) in the study.

Study Protocol

For each patient, centers were asked to provide pseudo-anonymized information on the following items: (1) general characteristics: sex, age at seizure onset and at first and last surgery, early development, neurologic examination, cognitive assessment (IQ/global developmental quotient) categorized as normal/borderline scores and mild, moderate, and severe intellectual disability (ID), extraneurologic manifestations; (2) type

Table 1 Somatic *SLC35A2* Variants Identified in the 47 Patients Included in the Study

Pt code	Sex	Variant (HGVS) NM_001042498.3	Brain VAF (%)**	Blood VAF (%)	ACMG evidence criteria	Previous report of the Pt (code[Ref.])/previous report of the variant[Ref.] in a different Pt	Epileptic syndrome
MEY_01	F	c.248T>C p.(Leu83Pro)	7%	0%	PS2, PM2, and PP3 (LP)	-/-	EE
MEY_02	F	c.385C>T p.(Gln129*)[a]	2%	0%	PVS1, PS2, and PM2 (P)	-/variant[11]	EE
MEY_03	F	c.844G>A p.(Gly282Arg)	2%	0%	PS1, PS2, PM2, PP3, and PP5 (P)	-/variant[31]	EE
MEY_04	M	c.905C>T p.(Ser302Phe)[a]	4%	0%	PS2, PM2, and PP3 (LP)	-/variant[11]	EE
MEY_05	M	c.837_847del p.(Phe280Thrfs*10)	23%	0%	PVS1, PS2, and PM2 (P)	-/-	EE
MEY_06	M	c.424C>T p.(Gln142*)	7%	0%	PVS1, PS2, and PM2 (P)	-/-	EE
MEY_07	M	c.625T>C p.(Ser209Pro)	18%; 23%	0%	PS2, PM2, and PP3 (LP)	-/-	EE
SK-01	M	c.589C>T p.(Gln197*)	23%	0%	PVS1, PS2, and PM2 (P)	Pt EPI219,[5] mMCD219,[47] KR5[11]/-	EE
SK_02	M	c.502C>T p.(Gln168*)	18%	0%	PVS1, PS1, PS2, and PM2 (P)	Pt EPI340,[5] mMCD340,[47] KR6[11]/variant[28,29]	EE
SK_03	M	c.760G>T p.(Glu254*)	16%	0%	PVS1, PS2, and PM2 (P)	Pt LGS150[5], mMCD150,[47] KR4[11]/-	EE
SK_04	F	c.703A>C p.(Asn235His)	10%	0%	PS2, PM2, and PP3 (LP)	Pt LGS150,[5] mMCD150,[47] KR1[11]/-	EE
SK_05	F	c.553C>T p.(Gln185*)	6%	0%	PVS1, PS2, and PM2 (P)	Pt EPI147,[5,47] KR3[11]/-	EE
SK_06	F	c.359_360del p.(Leu120Hisfs*7)[a]	5.5%	NA	PVS1, PS2, and PM2 (P)	Pt KR10[11]/-	EE
SK_07	M	c.275-1G>T	5%	0%	PVS1, PS2, and PM2 (P)	Pt EPI044[5,47], KR2[11]/-	EE
SK_08	M	c.842G>A p.(Gly281Asp)	3.67%	NA	PS2, PM2, PM5, and PP3 (LP)	Pt 1428,[47] KR8[11]/-	EE
SK_09	F	c.671T>C p.(Leu224Pro)	3.66%	NA	PS2, PM2, PM5, and PP3 (LP)	Pt 1429,[47] KR9[11]/-	EE
SK_10	M	c.359T>C p.(Leu120Pro)	1.4%	NA	PS2, PM2, and PP3 (LP)	Pt 3995,[47] KR7[11]/-	EE
EH_01	F	c.910T>C p.(Ser304Pro)	0.4%; 27%	0%	PS2, PM2, and PP3 (LP)	Pt case 1[3]/-	(NL)DR-FE
EH_02	M	c.337_339dup p.(Leu113dup)	3.8%; 6.1%	0%	PS2, PM2, and PM4 (LP)	Pt case 2[3]/-	(NL)DR-FE
EH_03	M	c.634_635del p.(Ser212Leufs*9)[a]	0%; 9%	0%	PVS1, PS2, and PM2 (P)	Pt case 3[3]/-	(NL)DR-FE
EH_04	M	c.435C>A p.(Tyr145*)	2.8%	0%	PVS1, PS2, and PM2 (P)	Pt MCD47[9]/-	EE
PRG_01	M	c.385C>T p.(Gln129*)[a]	33%	NA	PVS1, PS2, and PM2 (P)	Pt NL1[11]/-	EE
PRG_02	F	c.265C>T p.(Gln89*)	6%	0%	PVS1, PS2, and PM2 (P)	-/-	EE
PRG_03	M	c.482_484del p.(Asn161_Arg162delinsSer)	31%	0%	PS2, PM2, and PM4 (LP)	-/-	(NL)DR-FE
VOG_01	M	c.206C>T p.(Thr69Ile)	14%	NA	PS2, PM2, and PP3 (LP)	Pt DE-1[11]/-	EE
VOG_02	F	c.603_606dup p.(Leu203Argfs*20)	21%	NA	PVS1, PS2, and PM2 (P)	Pt DE-2[11]/-	EE
VOG_03	M	c.569_572del p.(Gly190Alafs*158)	41%	NA	PVS1, PS2, and PM2 (P)	Pt DE-3[11]/-	EE
VOG_04	M	c.335_339dup p.(Lys114Argfs*32)	52%	NA	PVS1, PS2, and PM2 (P)	Pt DE-4[11]/-	EE
VOG_05	F	c.905C>T p.(Ser302Phe)[a]	7%	NA	PS2, PM2, and PP3 (LP)	Pt DE-5[11]/-	EE
VOG_06	M	c.580_616dup p.(Val206Alafs*28)	9%	NA	PVS1, PS2, and PM2 (P)	Pt DE-6[11]/-	EE
VOG_07	F	c.359_360del p.(Leu120Hisfs*7)[a]	30%	NA	PVS1, PS2, and PM2 (P)	Pt DE-7[11]/-	EE
VOG_08	M	c.112_116delinsTGGTGGTCCAGAATG p.(Ile38Trpfs*59)	33%	NA	PVS1, PS2, and PM2 (P)	Pt DE-8[11]/-	EE

Continued

Table 1 Somatic *SLC35A2* Variants Identified in the 47 Patients Included in the Study *(continued)*

Pt code	Sex	Variant (HGVS) NM_001042498.3	Brain VAF (%)**	Blood VAF (%)	ACMG evidence criteria	Previous report of the Pt (code[Ref.])/previous report of the variant[Ref.] in a different Pt	Epileptic syndrome
VOG_09	F	c.935C>T p.(Ser312Phe)[a]	33%	NA	PS2, PM2, PM5, and PP3 (LP)	Pt DE-9[11]/-	EE
AP_01	M	c.164G>T p.(Arg55Leu)	50.8%	0%	PS2, PM2, PM5, and PP3 (LP)	Pt case 4[3], MCD37[9]/-	EE
AP_02	M	c.747_757dup p.(Ala253Glyfs*100)	18.8%	0%	PVS1, PS1, PS2, and PM2 (P)	Pt case 5[3], MCD38[9]/variant[30]	EE
AP_03	M	c.547C>T p.(Gln183*)	3%	0%	PVS1, PS1, PS2, and PM2 (P)	Pt MCD63[9]/variant[30]	EE
PAR_01	M	c.801C>G p.(Tyr267*)	12.1%	0%	PVS1, PS2, and PM2 (P)	Pt FCD-1,[8] FR-1[11]/-	EE
PAR_02	M	c.634_635del p.(Ser212Leufs*9)[a]	2%; 22.6%	0%	PVS1, PS2, and PM2 (P)	Pt FCD-2,[8] FR-2[11]/-	EE
PAR_03	M	c.886_888del p.(Leu296del)	22.4%	0%	PS2, PM2, and PM4 (LP)	Pt FCD-3,[8] FR-3[11]/-	EE
PAR_04	M	c.804dup p.(Pro269Thrfs*25)	32.7%	0%	PVS1, PS2, and PM2 (P)	Pt FCD-4,[8] FR-4[11]/-	EE
PAR_05	F	c.918_929del p.(Leu307_Val310del)	13%	0%	PS2, PM2, and PM4 (LP)	Pt FR-5[11]/-	EE
PAR_06	M	c.287_288del p.(His96Profs*7)	25%	0%	PVS1, PS2, and PM2 (P)	Pt FR-6[11]/-	EE
BET_01	F	c.935C>T p.(Ser312Phe)[a]	8.02%	NA	PS2, PM2, PM5, and PP3 (LP)	Pt (without genetic data)[17]/variant[11]	EE
BET_02	F	c. 515T>C p.(Leu172Pro)	3.02%	NA	PS1, PS2, PM2, and PP3 (P)	Pt (without genetic data)[17]/variant[29]	DR-FE
BET_03	F	c.640G>C p.(Gly214Arg)	7.98%	NA	PS2, PM2, and PP3 (LP)	Pt (without genetic data)[17]/-	DR-FE
BET_04	F	c.364_365insC p.(Tyr122Serfs*6)	15.14%	NA	PVS1, PS2, and PM2 (P)	Pt (without genetic data)[17]/-	DR-FE
BET_05	M	c.675dup p.(Gly226Argfs*29)	40.42%	NA	PVS1, PS2, and PM2 (P)	Pt (without genetic data)[17]/-	DR-FE

Abbreviations: DR = drug resistant; EE = epileptic encephalopathy; FCD = focal cortical dysplasia; FE = focal epilepsy; HGVS = Human Genome Variation Society; LP = likely pathogenic; mMCD = mild malformation of cortical development; NA = not available; NL = nonlesional; P = pathogenic; PM2 = absent from controls; PM4 = protein length changes as a result of in-frame deletions/insertions; PM5 = novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before; PP3 = multiple lines of computational evidence support a deleterious effect on the gene or gene product; PS1 = same amino acid change as a previously established pathogenic variant regardless of nucleotide change; PS2 = de novo (used for mosaic variants); PVS1 = null variant; VAF = variant allele frequency.
[a] Variants identified in more than 1 patient in this study.

of seizures[19] and of epilepsy[20] and age at seizure onset; (3) last preoperative interictal scalp EEG before surgery (background activity and interictal epileptiform discharges [IEDs]); (4) preoperative scalp ictal EEG findings classified according to the lobar localization and lateralization of the ictal discharge[21]; (5) results of invasive recordings,[21,22] if performed; (6) neuroimaging findings, i.e., topography and characteristics of the brain abnormalities, if any; (7) surgical treatment (age at surgery, type of surgery, e.g., lesionectomy, lobectomy, hemispherotomy, and corticectomy, multiple surgeries, and completeness of the resection assessed on postoperative brain MRI; (8) histopathology[4,12,23]; (9) duration of follow-up; (10) postoperative interictal scalp EEG at first follow-up (background activity and IEDs); (11) seizure outcome at last follow-up[24]; (12) persistence of antiseizure medications (ASMs) at last follow-up; (13) cognitive outcome classified as worsened, improved, and unchanged according to postoperative neuropsychological testing at last follow-up; and (14) genetic findings on brain tissue, i.e. *SLC35A2* gene variant, variant type (missense, nonsense, frameshift, in-frame deletion, and splicing variants), VAF in brain and blood samples, gnomAD frequency,[25] pathogenicity and conservation scores.

Genetic Study

Next-generation sequencing was performed from fresh-frozen or formalin-fixed paraffin-embedded samples. Blood-derived DNA, when available, was also tested to confirm the brain specificity of the *SLC35A2* mosaic variants. Variant discovery was performed in the different centers with deep whole-exome sequencing or targeted panels including a variable number of genes involved in, or candidate for, FCDs, mTOR pathway genes, and a subset of epilepsy-associated genes including *SLC35A2*. Matched blood and brain tissues were analyzed in 28 of 47 (59.6%) patients (detailed methods are described in the eMethods, links.lww.com/WNL/C456).

Neuropathologic Evaluation

Reassessment of the 47 cases obtained from multiple centers was performed by an expert neuropathologist (I.B.) as reported previously.[11] Digitally scanned slides were made accessible for online microscopic evaluation providing

Table 2 Molecular Characteristics of the 42 Variants Identified in the *SLC35A2* Gene

Code	Sex	Variant (HGVS) NM_001042498.3	Variant type	GnomAD database	Pathogenicity predictions (SIFT, MutationTaster, PolyPhen-2, and MutationAssessor)[b]	Conservation score (GERP)[b]
MEY_01	F	c.248T>C p.(Leu83Pro)	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	5.33
MEY_02	F	c.385C>T p.(Gln129*)[a]	Nonsense	Absent	NA	NA
MEY_03	F	c.844G>A (p.Gly282Arg)	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	5.86
MEY_04	M	c.905C>T p.(Ser302Phe)[a]	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	5.33
MEY_05	M	c.837_847del p.(Phe280Thrfs*10)	Frameshift	Absent	NA	NA
MEY_06	M	c.424C>T p.(Gln142*)	Nonsense	Absent	NA	NA
MEY_07	M	c.625T>C p.(Ser209Pro)	Missense	Absent	Deleterious, disease causing, probably damaging, and medium impact	5.33
SK-01	M	c.589C>T p.(Gln197*)	Nonsense	Absent	NA	NA
SK_02	M	c.502C>T p.(Gln168*)	Nonsense	Absent	NA	NA
SK_03	M	c.760G>T p.(Glu254*)	Nonsense	Absent	NA	NA
SK_04	F	c.703A>C p.(Asn235His)	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	5.86
SK_05	F	c.553C>T p.(Gln185*)	Nonsense	Absent	NA	NA
SK_06	F	c.359_360del p.(Leu120Hisfs*7)[a]	Frameshift	Absent	NA	NA
SK_07	M	c.275-1G>T	Splicing	Absent	New acceptor site predicted (SSF, MaxEnt, NNSPLICE, and GeneSplicer)	NA
SK_08	M	c.842G>A p.(Gly281Asp)	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	4.99
SK_09	F	c.671T>C p.(Leu224Pro)	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	5.33
SK_10	M	c.359T>C p.(Leu120Pro)	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	5.57
EH_01	F	c.910T>C p.(Ser304Pro)	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	4.16
EH_02	M	c.337_339dup p.(Leu113dup)	In-frame duplication	Absent	NA	NA
EH_03	M	c.634_635del p.(Ser212Leufs*9)[a]	Frameshift	Absent	NA	NA
EH_04	M	c.435C>A p.(Tyr145*)	Nonsense	Absent	NA	NA
PRG_01	M	c.385C>T p.(Gln129*)[a]	Nonsense	Absent	NA	NA
PRG_02	F	c.265C>T p.(Gln89*)	Nonsense	Absent	NA	NA
PRG_03	M	c.482_484del p.(Asn161_Arg162delinsSer)	In-frame deletion	Absent	NA	NA
VOG_01	M	c.206C>T p.(Thr69Ile)	Missense	Absent	Deleterious, disease causing, possibly damaging, and high impact	4.81
VOG_02	F	c.603_606dup p.(Leu203Argfs*20)	Frameshift	Absent	NA	NA
VOG_03	M	c.569_572del p.(Gly190Alafs*158)	Frameshift	Absent	NA	NA
VOG_04	M	c.335_339dup p.(Lys114Argfs*32)	Frameshift	Absent	NA	NA
VOG_05	F	c.905C>T p.(Ser302Phe)[a]	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	5.33
VOG_06	M	c.580_616dup p.(Val206Alafs*28)	Frameshift	Absent	NA	NA
VOG_07	F	c.359_360del p.(Leu120Hisfs*7)[a]	Frameshift	Absent	NA	NA

Continued

Table 2 Molecular Characteristics of the 42 Variants Identified in the *SLC35A2* Gene *(continued)*

Code	Sex	Variant (HGVS) NM_001042498.3	Variant type	GnomAD database	Pathogenicity predictions (SIFT, MutationTaster, PolyPhen-2, and MutationAssessor)[b]	Conservation score (GERP)[b]
VOG_08	M	c.112_116delinsTGGTGGTCCAGAATG p.(Ile38Trpfs*59)	Frameshift	Absent	NA	NA
VOG_09	F	c.935C>T p.(Ser312Phe)[a]	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	4.8
AP_01	M	c.164G>T p.(Arg55Leu)	Missense	Absent	Deleterious, disease causing, damaging, and medium impact	4.61
AP_02	M	c.747_757dup p.(Ala253Glyfs*100)	Frameshift	Absent	NA	NA
AP_03	M	c.547C>T p.(Gln183*)	Nonsense	Absent	NA	NA
PAR_01	M	c.801C>G p.(Tyr267*)	Nonsense	Absent	NA	NA
PAR_02	M	c.634_635del p.(Ser212Leufs*9)[a]	Frameshift	Absent	NA	NA
PAR_03	M	c.886_888del p.(Leu296del)	In-frame deletion	Absent	NA	NA
PAR_04	M	c.804dup p.(Pro269Thrfs*25)	Frameshift	Absent	NA	NA
PAR_05	F	c.918_929del p.(Leu307_Val310del)	In-frame deletion	Absent	NA	NA
PAR_06	M	c.287_288del p.(His96Profs*7)	Frameshift	Absent	NA	NA
BET_01	F	c.935C>T p.(Ser312Phe)[a]	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	4.8
BET_02	F	c. 515T>C p.(Leu172Pro)	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	5.13
BET_03	F	c.640G>C p.(Gly214Arg)	Missense	Absent	Deleterious, disease causing, probably damaging, and high impact	5.33
BET_04	F	c.364_365insC p.(Tyr122Serfs*6)	Frameshift	Absent	NA	NA
BET_05	M	c.675dup p.(Gly226Argfs*29)	Frameshift	Absent	NA	NA

Abbreviations: HGVS = Human Genome Variation Society; NA = not available.
[a] Variants identified in more than 1 patient in this study.
[b] Pathogenicity prediction and conservation score are available only for missense and/or splice site variants.

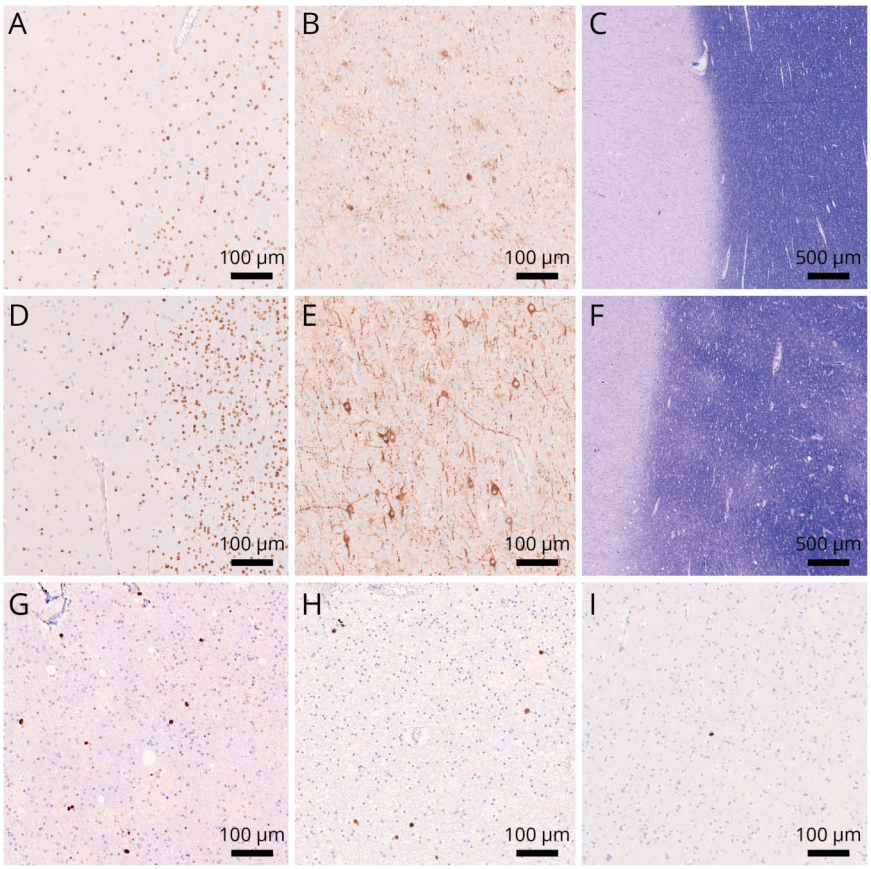
hematoxylin and eosin staining of all tissue blocks, cresyl violet–Luxol fast blue (CV-LFB) stainings, and/or immunohistochemistry for NeuN, MAP2, Olig2, and KI-67 in selected cases. The diagnosis of MOGHE was given if clusters of oligodendroglial cells were recognized at a density of >2000/mm^2 at the gray-white matter junction (Figure 1, D and G), and an excess of heterotopic neurons in the white matter >20/mm^2 was confirmed[12] (Figure 1E). In cases with available CV-LFB, these areas of the white matter also displayed a patchy loss of myelination (Figure 1F).

Statistical Analysis

We performed a descriptive statistical analysis to summarize the following variables of interest: type of variant, i.e., truncating (nonsense, frameshift, and splice variants) vs nontruncating (missense and in-frame deletions); percentage of mosaicism (VAF) in brain tissue (when multiple surgeries or surgical biopsies were performed we referred to the highest value); preoperative cognitive level, categorized as normal/borderline, mild, moderate, and severe ID; type of epilepsy, categorized in EE and drug-resistant focal epilepsy (DR-FE); age at seizure onset; preoperative interictal scalp EEG classified as showing focal, diffuse, or multifocal IEDs on the basis of widely accepted international standards[26,27] and through consensus-based discussions involving at least 2 expert epileptologists in each center; having undergone invasive recordings; brain neuroimaging, categorized as normal and abnormal; topography of brain abnormalities, if any, classified as unilobar or multilobar; age at last surgery; duration of epilepsy (seizure onset to surgery); type of surgery; completeness of resection; histopathology[4,12]; and postoperative interictal scalp EEG categorized as normal (no epileptiform abnormalities and only breach rhythm), abnormal worsened (increased IED frequency and/or worsening of background activity), abnormal improved (decreased IED frequency and/or better organized background activity), and unchanged in comparison with the last interictal EEG before surgery.

First, we performed the analysis of association between selected preoperative clinical variables (cognitive level, type of epilepsy, age at seizure onset, neuroimaging, and interictal EEG) and the genetic variables (VAF and type of variant). Then, we analyzed

Figure 1 Histopathology in Patients With Brain Somatic *SLC35A2* Gene Variants



(A–C) Normal histology findings at the gray-white matter junction of the frontal lobe in a 3-year-old girl with early-onset EE. (A) OLIG2 immunohistochemistry showing a normal cell density; on the left = deep neocortex; on the right = white matter; bound antibodies were colored in brown with methylene blue counterstaining, which applies to all immunostainings shown in this panel with the exception of C and F. (B) MAP2 immunohistochemistry depicting few scattered heterotopic neurons and their neuropil in the deep white matter (<10 neurons/mm^2). (C) Nissl–Luxol fast blue representing compact myelination in dark blue; on the left = deep neocortex; on the right = white matter. Scale bar in A = 100 µm, applies also to B, D–E, and G–I. (D–F) Same stainings as those shown above from the same 3-year-old girl and the same surgical sample but taken from a region with MOGHE. (D) OLIG2 immunohistochemistry with an increase of the oligodendroglial cell density >2,200/mm^2 at the gray-white matter junction, gray matter on the left as above. (E) MAP2 immunohistochemistry depicting many scattered heterotopic neurons and their neuropil in the deep white matter (>30 neurons/mm^2). (F) Nissl–Luxol fast blue representing patchy losses of myelination (pale areas on the right). Scale bar in F = 500 µm applies also to C. (G–H) Another hallmark of MOGHE is increased proliferation of oligodendroglia, as indicated by immunohistochemical labeling of the Ki67 epitope. (G) Note the increased proliferation activity in MOGHE, similar to a dysembryoplastic neuroepithelial tumor (H); focal cortical dysplasia ILAE type 1A has a comparatively low proliferation activity (I). EE = epileptic encephalopathy.

all the variables of interest in relation to 3 different seizure outcomes: Engel Class IA vs IB-IV; Engel Class I vs Class II-IV and persistence with ASM at last follow-up, and to cognitive outcome classified as improved, worsened, or unchanged.

For each outcome, we performed the following:

1. Pearson χ^2 test or Fisher exact test of independence on tables of frequency for each categorical variable of interest.
2. Analysis of variance or Kruskal-Wallis rank test and Student *t* test or Wilcoxon signed-rank test, in accordance with the Shapiro-Wilk normality test, for each continuous variable of interest.

We included the variables of interest significantly associated with the outcomes in the generalized linear models; when necessary, we used exact methods. Level of significance was set at 5% two sided. Results for quantitative variables are expressed as mean ± SD or median (range). We conducted all statistical analyses using STATA version 16.0 (StataCorp. 2016. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP).

Data Availability

The main findings of this study are included in the main text, tables, figures, and supplemental material (links.lww.com/WNL/C456). Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

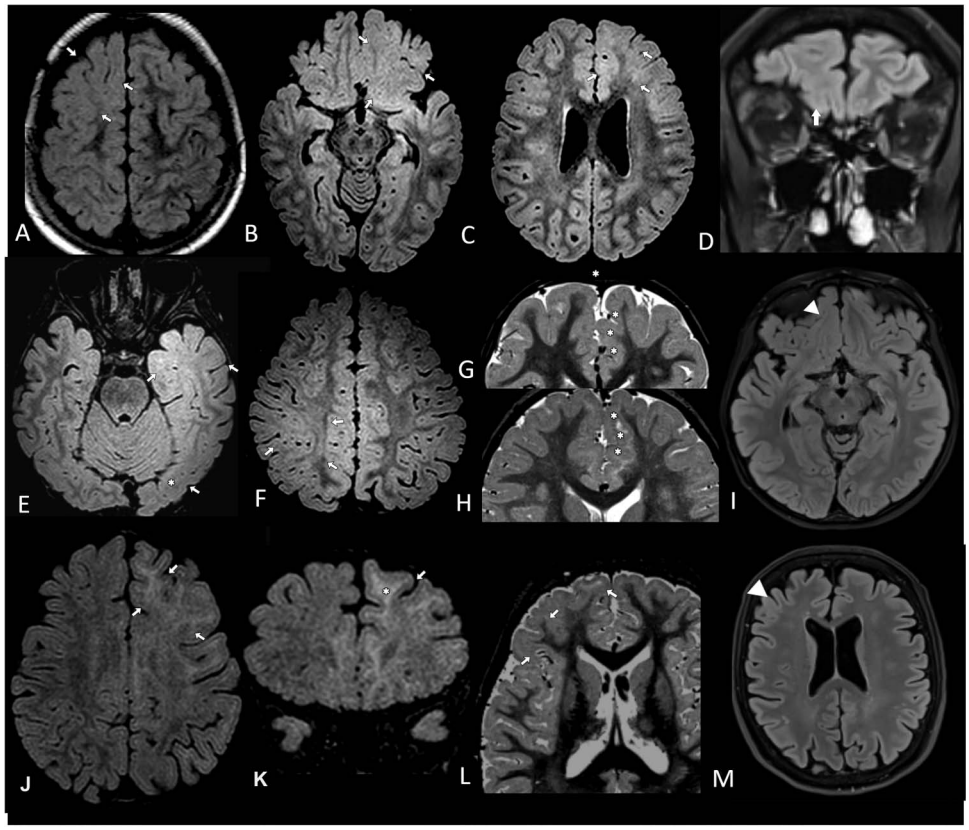
Results

Descriptive Analysis

We included in this study 47 patients (18 F, 38.3%), 9 of whom were never reported in previous studies. The mean age was 3.0 ± 5.3 years (range 3 months-24 years) at seizure onset and 9.4 ± 11 years (range 2–59 years) at last surgery.

All but 3 patients were in polytherapy at the time of surgery. No ASM, alone or in combination, proved more effective in controlling seizures (see eTable1 for details on pharmacologic treatment, links.lww.com/WNL/C456). Two main epilepsy syndromes were associated with *SLC35A2* somatic variants: EE and DR-FE. Specifically, 39 (83%) patients had an EE, featuring epileptic spasms, associated or not with other types of seizures in 35, and focal and generalized seizures, such as absences, myoclonic or tonic seizures in 4; 8 (17%) patients had DR-FE, with or without focal to bilateral tonic-clonic seizures.

Figure 2 MRI Findings in Patients With Brain Somatic *SLC35A2* Gene Variants



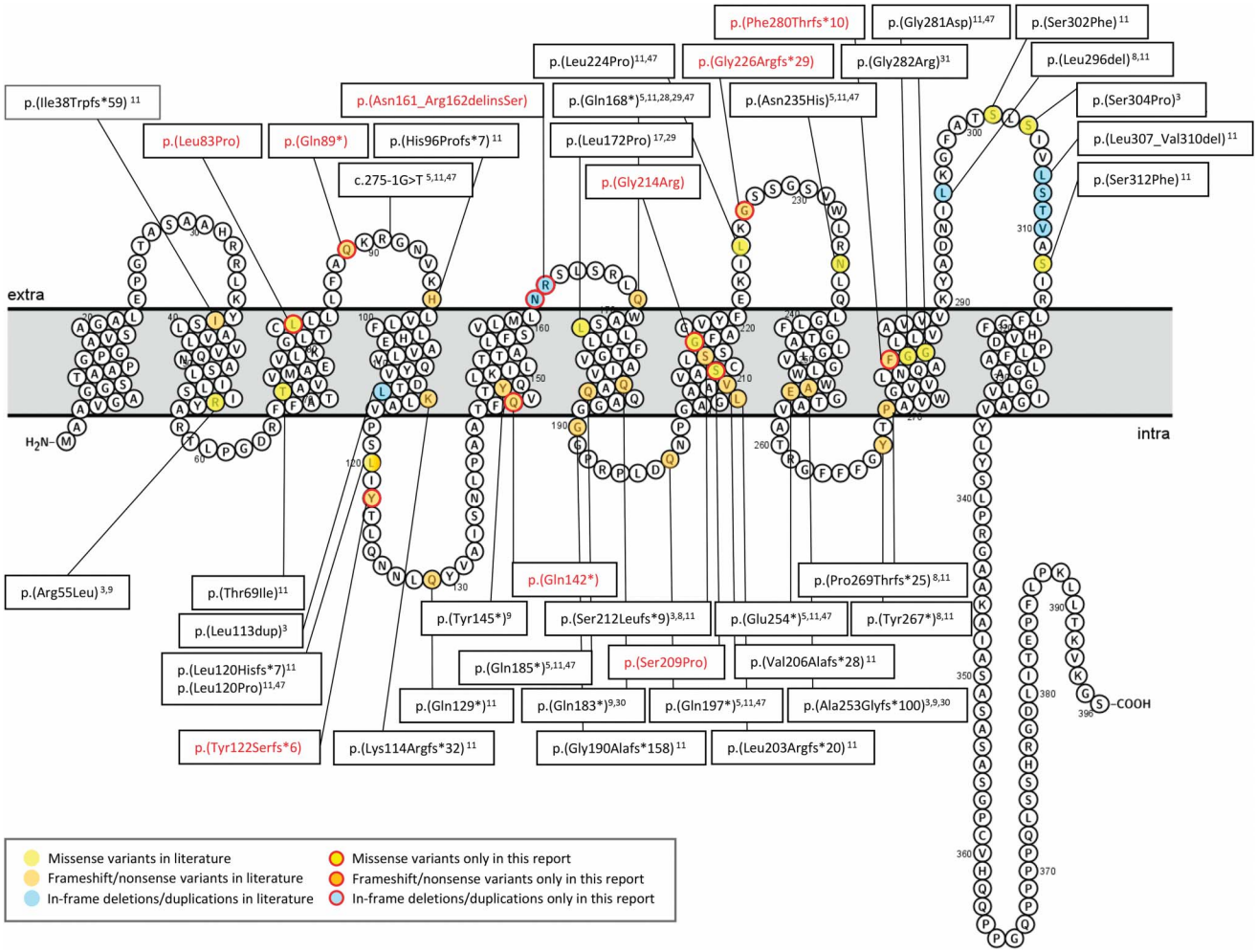
(A) Five-year-old girl. Axial FLAIR-weighted 3T MRI showing cortical thickening and blurring of the white matter and gray matter–white matter junction in the right frontal lobe (arrows). (B and C) Five-year-old girl. Axial FLAIR-weighted 3T MRI showing cortical thickening and white matter blurring in the left frontobasal area (B) and blurring of the gray matter–white matter junction in the left frontal anterior area (C) (arrows). (D) Thirty-two-year-old woman. Coronal FLAIR-weighted 3T MRI showing extended white matter blurring involving the right frontopolar area (arrow). (E) Three-year-old boy. Axial FLAIR-weighted 3T MRI showing extended white matter blurring (arrows) and mesial simplified gyral pattern (asterisk) involving the left occipito-temporal area. (F) Two-year-old boy. Axial FLAIR-weighted 3T MRI showing cortical thickening, abnormal folding, and white matter blurring in the right frontoparietal area (arrows). (G) Two-year-old girl. Axial FLAIR-weighted 1.5 T MRI showing increased subcortical white matter signal in the left frontomesial area (asterisks). (H) Seven-month-old girl. Axial FLAIR-weighted 1.5 T MRI showing increased subcortical white matter signal in the left frontomesial area (asterisks). (I) Six-year-old girl. Axial FLAIR-weighted 3T MRI showing extended white matter blurring involving the right orbital area (arrowhead). (J and K) Two-year-old girl. Axial (J) and coronal FLAIR-weighted (K) 3T MRI showing left frontal abnormal folding (see arrow) and left hemispheric white matter blurring (asterisk). (L) Two-year-old boy. Axial T2-weighted 1.5 T MRI showing increased and laminar subcortical white matter signal in the right frontal lobe (arrows). (M) Fifty-eight-year-old woman. Axial FLAIR-weighted 3T MRI showing a small white matter blurring involving the R frontolateral blurring (arrowhead).

In patients with EE, interictal EEG showed slow and/or disorganized background activity and/or absent differentiation between, or poor representation of sleep stages and diffuse or multifocal epileptiform abnormalities. In patients with DR-FE, interictal EEG showed focal or multifocal but lateralized epileptiform abnormalities and normal or nearly normal background activity. Invasive recordings were performed to better define the area to be removed in 12 (25.5%) patients (10 stereoelectroencephalography [SEEG], 1 subdural grid, and 1 depth electrode). We could not identify any specific interictal or ictal scalp or invasive EEG pattern (eTable 1, links.lww.com/WNL/C456).

Brain MRIs revealed abnormalities in 43 (91.5%) of 47 patients. Specifically, brain MRI was abnormal in all patients with EE and in 50% of those with DR-FE. Neuroimaging findings were centrally reviewed in 38 patients (80.8%) (examples are presented in Figure 2, and details are summarized in eTable 2, links.lww.com/WNL/C456). The location of the brain abnormalities was frontal in 31 (72%) patients and multilobar in 17 (39.5%). In 2 patients, we observed a small nodule of periventricular heterotopia, unrelated to the seizure onset zone and surgery. Preoperative cognitive assessment (IQ/DS) was available in 44 patients and revealed normal scores in 6 patients (12.8%), borderline functioning in 4 (8.5%), mild ID in 14 (31.8%), moderate ID in 9 (20.4%), and severe ID in 11 (25%). Patients with DR-FE had normal (6) or borderline (2) cognitive functioning. However, all patients with normal IQ scores exhibited neuropsychological deficits related to executive, visuospatial, or memory functions One of the patients with EE and borderline IQ experienced electrical status epilepticus during sleep with atonic absences, tonic seizures, and cognitive deterioration, whereas the remaining patient experienced late-onset (>3 years old) epileptic spasms.

The following types of surgery were performed: 33 (70.2%) lobectomies, 7 (6.4%) hemispherotomies, 4 (8.5%)

Figure 3 Membrane Topology Modeling of *SLC35A2*



Schematic representation of variants included in this study. Novel variants are written in red; variants already described are written in black. Membrane topology was predicted using the Protter online tool[46] (P78381-SLC35A2_HUMAN).

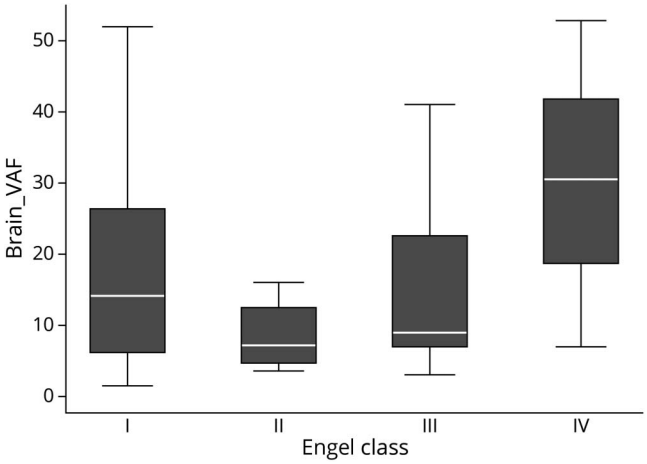
lesionectomies or lesionectomies plus corticectomies, and 3 (7.1%) corticectomies. Eight patients (17%) underwent multiple surgeries (from 2 to 4). The resection at last surgery was considered complete based on postoperative brain MRI in 30 patients (63.8%). Reassessment of histopathology through consensus (44 patients, 95.6%) or centralized review (2 patients) revealed MOGHE in 44 patients (Figure 1) and was nonconclusive in 2 as their tissue specimens were too small; the remaining case was unavailable for review.

At last follow-up, 30 patients (63.8%) were in Engel Class I, of which 26 (55.3%) were in Class IA, with a mean duration of follow-up of 35.5 ± 21.5 months. Complete seizure freedom was achieved in 61.5% of patients with EE and in 37.5% of those with DR-FE. ASMs were withdrawn in 8 patients (17.0%). Information on postsurgical developmental outcome was available in 33 (70.2%) patients. Cognitive function remained unchanged in 25 (75.8%) patients, worsened in 5 (15.1%), and improved in 3 (9.0%). Postoperative EEG, available in 45 patients (95.7%), was abnormal but improved in 31 patients (68.9%), unchanged in 10 (22.2%), and normal in 4 (8.9%) (see eTable1 for details, links.lww.com/WNL/C456.).

Genetic Analysis

The 47 patients included in the study harbored 42 distinct *SLC35A2* variants (Tables 1 and 2 and Figure 3). These 42 variants included 14 (33.3%) missense, 13 (30.9%) frameshift, 10 (23.8%) nonsense, 4 (9.5%) in-frame deletions/duplications, and 1 (2.4%) splice-affecting variant. Five variants, p.(Leu120Hisfs*7), p.(Gln129*), p.(Ser212Leufs*9), p.(Ser302Phe), and p.(Ser312Phe), were identified in more than 1 patient, with different mosaic fractions. Overall, 9 (21.4%) variants were novel. Among the 32 previously reported variants, the p.(Gln168*),[28] p.(Leu172Pro),[29] p.(Gln183*),[30] and p.(Ala253Glyfs*100)[30] variants were described as de novo heterozygous events in association with a congenital disorder of glycosylation,[28-30] whereas the *p*.Gly282Arg[31] variant was present in a patient with infantile spasms who carried a different nucleotide substitution leading to the same amino acid change (c.844G>C instead of c.844G>A).

Figure 4 Brain VAF (%) by Seizure Outcome (Engel Class)



The median of brain VAF in patients with Engel Class I was 14.5% (IQR 6%–26.5%), whereas the median of brain VAF in patients with Engel Class IV was 30.5% (IQR 18.5%–41.8%). VAF = variant allele frequency.

All variants were observed in brain samples in a mosaic state, with VAFs ranging from 1.4% to 52.6% (mean VAF: 17.3 ± 13.5%, median VAF: 14%). Allelic fraction ranged from 2% to 33% (mean VAF: 10.4%, median VAF: 7%) in females, meaning that between 0.8% and 66% of brain cells carry the variant, and from 1.4% to 52.6% (mean VAF: 21.6%, median VAF: 22.6%) in males, reflecting an equal number of brain cells harboring the variant allele. Identified somatic variants were absent from peripheral blood samples of all the 27 (64.3%) patients in whom this matched analysis could be performed.

None of the variants was present in the gnomAD database (gnomAD v3.1 accessed July 2022). We considered frameshift, nonsense, and splicing variants as pathogenic. We assessed missense variants based on 4 different pathogenicity prediction tools and 1 conservation score. All these variants were predicted to have a damaging effect on the protein product (Table 2) and occurred in conserved (GERP >2)[32] or highly conserved (GERP >5) nucleotides. We classified missense variants as likely pathogenic or pathogenic according to the ACMG criteria.

We did not identify additional somatic or constitutional variants in the patients included in this cohort. Assessing the distribution of the percentage of mosaicism toward seizure outcome, we found that the median was 14.5% (IQR 6%–26.5%) in patients in Engel Class I and 30.5% (IQR 18.5%–41.8%) in those in Engel Class IV (Figure 4).

Statistical Analysis

Analysis of Associations

First, we assessed that no significant associations emerged between the selected preoperative clinical variables (cognitive level, type of epilepsy, age at seizure onset, neuroimaging, and interictal EEG) and the genetic variables (VAF and type of variant; eTable3, links.lww.com/WNL/C456).

Then, we evaluated through univariate analysis whether any of the variables of interest may represent a predictor of seizure outcome, thereby revealing the following significant associations:

1. Patients with Engel Class IA outcome had a shorter duration of epilepsy (4.23 vs 8.98 years, $p = 0.018$) and a younger age at last surgery (6.35 vs 13.14 years, $p = 0.033$) than those with Engel Class IB-IV.
2. Patients with Engel Class I outcome had a shorter duration of epilepsy (4.22 vs 10.11 years, $p = 0.004$) and younger age at last surgery (6.43 vs 14.59 years, $p = 0.013$) than those with Engel Class II-IV outcome.
Duration of epilepsy and age at last surgery were highly correlated (correlation coefficient was 0.93).
3. Patients who underwent a complete resection had a higher propensity to achieve Engel Class IA outcome than those with incomplete resection (76.9% vs 47.6%, $p = 0.038$).
4. Patients with normal or improved postoperative EEG at last FU had a higher propensity to achieve Engel Class IA outcome than those whose postoperative EEG remained unchanged (100% and 61.3% vs 10%, $p = 0.002$).
5. Patients with normal or improved postoperative EEG at last follow-up had higher propensity to achieve Engel Class I outcome than those whose postoperative EEG remained unchanged (100% and 70.97% vs 20%, $p = 0.003$) and to withdraw from ASM at last follow-up rather than to persist with them (75% and 12.9% vs 0%, $p = 0.010$).
6. Patients with improved cognitive outcome had a higher propensity to show brain VAF lower than the median value of 14% than those with unchanged or worsened cognitive performances (100% vs 40% and 66.7%, $p = 0.033$).

There was no correlation between Engel Class I outcome and postoperative cognitive functioning ($p = 0.48$).

Regression Analyses

For the regression models, we used the exact methods. Also, for collinearity issues, we decided to use the duration of epilepsy instead of the age at last surgery. Age at seizure onset was considered a possible confounder.

The probability of achieving Engel Class IA outcome, adjusted by age at seizure onset, was lower when the duration of epilepsy increased (OR = 0.79, $p = 0.016$) and higher when postoperative EEG was normal (vs EEG unchanged OR = 26.76, $p = 0.007$) or improved (vs EEG unchanged OR = 13.80, $p = 0.015$). The probability of achieving Engel Class I outcome, adjusted by age at seizure onset, was lower when the duration of epilepsy increased (OR = 0.75, $p = 0.008$) and higher when postoperative EEG improved

(vs EEG unchanged OR = 10.42, $p = 0.023$) or was normal (vs EEG unchanged OR = 18.96, $p = 0.020$).

Finally, the withdrawal of ASM, adjusted by age at seizure onset, was lower when postoperative EEG was normal (vs EEG unchanged OR = 0.08, $p = 0.044$) or improved (vs EEG unchanged OR = 0.56, $p = 0.063$). None of the variables of interest had a significant effect on cognitive outcome.

Discussion

We identified EE, associated with epileptic spasms in most patients, and DR-FE, with or without focal to bilateral tonic-clonic seizures as being the 2 main phenotypes associated with *SLC35A2* somatic variants. EE with spasms was the most frequent presentation (39 of 47 patients) and was characterized in all patients by early-onset seizures (range 3 months–3.5 years), moderate to severe ID, and brain MRI abnormalities with preferential frontal lobe involvement. DR-FE was characterized by seizure onset between adolescence and adulthood and normal/borderline cognitive level with selective neuropsychological deficits mainly affecting executive and memory functions. In addition, in DR-FE, brain MRI was unrevealing in 50% of patients. We cannot exclude that epileptic spasms in patients with early-onset EE represent an age-related variable since spasms usually begin between 3 months and 1 year of age, irrespective of etiology. However, some of our patients manifested epileptic spasms after 1 year of age and spasms persisted in older patients not cured by surgery.

Complete seizure freedom was achieved in 61.5% of patients with EE and in 37.5% of those with DR-FE. The less common occurrence of the DR-FE phenotype in this cohort might reflect the predominance of pediatric hospitals among the participating centers. In addition, nonlesional epilepsies represent a minority of all surgeries owing to complexities in defining the area to be removed and overall worse surgical prognosis.[33,34]

We found no clear histopathologic or genetic differences between these 2 clinical subgroups, despite they differed in age at onset and associated cognitive performances. Specifically, in the group with EE, mosaicism rates ranged between 2% and 52%, whereas in the DR-FE group, they varied between 2.4% and 40.2%. The percentage of truncating variants was higher in the EE than in the DR-FE group (73% vs 50%), but this difference was not significant.

Brain MRI, analyzed in 38 patients, revealed features in line with previous descriptions in patients with MOGHE,[15,16] with an association of both cortical and white matter abnormalities and a preferential frontal lobe location or multilobar involvement. We confirm laminar subcortical hyperintensities in FLAIR and T2 sequences to be a highly specific pattern in MOGHE, especially in the younger age group.[15] MRI-visible cortical abnormalities in this malformation may be related to increased density of oligodendrocyte and heterotopic neuron precursors.[16] Some of the white matter abnormalities associated with *SLC35A2* somatic variants are rather subtle, and in some patients, they were identified when seizure and EEG localization prompted a closer inspection in the search for regional or lobar abnormalities. Not surprisingly, the white matter abnormalities are reminiscent of those associated with constitutional *SLC35A2* variant–associated congenital disorders of glycosylation (CDG) in girls.[30] In addition, we observed a small periventricular heterotopia in 2 patients, of which 1 has already been described[3] and not related with the site of the seizure onset zone and surgery. It is impossible to clarify whether the small heterotopia had occurred purely by chance or causative role for *SLC35A2* gene variants should be considered.

In this study, a review of histopathologic features[12] identified MOGHE in 44 of 47 patients, 29 of which had been diagnosed as FCD type I or mMCD or nonlesional at first assessment.[3,5,8] Histopathology in the remaining 3 patients was inconclusive. Our data confirm and expand those of a recent study[11] in which *SLC35A2* gene variants could be demonstrated in 70% of patients with MOGHE. The predominance of MOGHE in our cohort defined by *SLC35A2* brain somatic variants is notable. Some of the previous surgical series, including those we have cited and from where many of the cases presented here are derived, did not include MOGHE in their classifications. In fact, only very recently has MOGHE been included as a new category in the updated FCD classification.[14] This near-uniform association between mosaic *SLC35A2* in the brain and the MOGHE pattern raises the question of how, or if, the MOGHE histopathologic substrate relates directly to epileptogenesis. Recently, 2 different hypotheses have been proposed to explain epileptogenesis in MOGHE.[12] In the first scenario, subgranular cortical layers, compromised by oligodendroglial hyperplasia, would directly contribute to aberrant neuronal activity. The second proposed mechanism suggests that epileptic activity might directly trigger oligodendrogliogenesis. In either case, to what extent oligodendroglial hyperplasia and/or hypomyelination contributes to epileptogenesis remains unclear. A further element of complexity is related to the allelic fraction gradient in the brain as the molecular analysis on a resected sample may not be fully representative of the whole 3-dimensional variant gradient.

In our cohort, the rate of seizure freedom after a mean follow-up of 35 ± 22 months was in line with previous reports in patients exhibiting epileptic spasms.[35,36] or with MOGHE[8,11,16,17] associated or not with *SLC35A2* gene variants. The rate of ASM withdrawal was low, even after long follow-up periods, possibly due to physicians' reluctance to stop medication in patients with complex clinical pictures, i.e., EE and DR-FE, and persistence of EEG abnormalities after surgery.

While assessing possible predictors of seizure outcome, we found no significant correlation between seizure outcome and genetic findings (e.g., brain VAF and type of variant). In a recent series,[11] no differences in surgery outcome were apparent between *SLC35A2* variant–positive and panel-negative MOGHE patients. However, in our study, the median of the

percentage of the mutant allele in patients with Engel Class I was lower than in those with Engel Class IV outcome (14.5% vs 30.5%). In a previous single-case observation,[6] average spikes per minute during intracranial recordings correlated with the proportions of *SLC35A2* variant allele in 12 different brain specimens, with the highest rate of IEDs being associated with the highest VAF. Given that all the patients reported here, regardless of VAF, had refractory epilepsy, including many with epileptic spasms, it is clear that even a small number of genetically abnormal cells can lead to profoundly abnormal network activity. The fraction of variant-positive cells in the resected tissue represents the center of an abnormal network, as determined by presurgical studies, but VAF rates in the adjacent nonresected region(s) and their residual capability of organizing an epileptogenic network remain unknown. Further studies including larger cohorts and molecular neuropathology study of large brain specimens are needed to clarify possible correlations between genetic findings and surgical results.

In this study, shorter duration of epilepsy and normal or improved postoperative EEG were the main predictors of favorable seizure outcome in regression analyses. Duration of epilepsy has been associated with seizure outcome in several studies on epilepsy surgery at large.[37,38] An improved postoperative EEG was associated with better seizure outcome in previous small surgical series on epileptic encephalopathies.[39,40] A recent series,[17] including 20 patients with MOGHE, reported 12 patients who were seizure-free after surgery, of whom 5 with normal postoperative EEG and 7 still exhibiting interictal abnormalities, leaving the predictive value of this variable uncertain in that cohort.

Using univariate analyses, we identified 2 additional weak favorable prognostic factors of seizure freedom (i.e., completeness of resection and younger age at surgery), which are well-known predictors of surgical outcome.[34,41,42] We cannot exclude that MRI-visible epileptogenic lesions, whose detection is associated with better outcomes,[43] in 91.5% of patients, might have favored earlier age at surgery.

Cognitive performances were unchanged in most patients after surgery, irrespective of seizure freedom and EEG improvement, and even worsened in some. Maintaining ASM in most patients might have influenced this finding.[44] Cognitive deterioration observed in a few patients might also be related to the persistence/recurrence of seizures/epileptiform discharges. We found a weak association between improved postoperative cognitive outcome and lower brain VAF, but this finding was not confirmed in regression analyses, possibly due to the small sample size.[8,11,17]

The consequences of this study are limited by its retrospective nature, although all patients had been registered prospectively in each center's database. We evaluated only clinical reports of preoperative and postoperative EEGs. However, all centers involved in the study have a high level of expertise in epilepsy and EEG interpretation, with regular training and adoption of international recommendations.[22,25,27,45] Finally, there was no standardization in timing and methods of cognitive assessment between centers, which might have partly influenced the evaluation of the postoperative changes.

MOGHE was revealed in all our patients with brain somatic variants in the *SLC35A2* gene and a definite histopathologic diagnosis. This recently identified histopathologic entity is probably underdiagnosed, especially if small tissue fragments are available or possible artifacts related to previous SEEG occur. The specificity of the somatic *SLC35A2* variant–MOGHE association should lead to ascertain this histopathologic diagnosis whenever an *SLC35A2* variant is found and, vice versa, prompt a search for the *SLC35A2* gene when histopathology suggests MOGHE.[13] A clinical phenotype of early-onset EE with epileptic spasms and moderate-to-severe cognitive delay, together with peculiar and, in younger patients, specific neuroimaging features, is highly suggestive of *SLC35A2* gene-related MOGHE. The *SLC35A2* gene–related MOGHE is also a possible etiology for drug-resistant lesional or nonlesional focal epilepsy, especially with frontal lobe involvement and onset in adolescence or young adulthood, as in most of our patients with DR-FE.

We studied drug-resistant patients. However, based on current knowledge, it cannot be excluded that brain somatic *SLC35A2* pathogenic variants may cause other clinical phenotypes, including patients who are more responsive to antiseizure medications. In general, *SLC35A2* gene–related MOGHE might represent a model for integrative phenotype-genotype-neuroimaging correlations aiming at guiding the surgical strategy and helping patients' counseling on postoperative seizure and cognitive outcome.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix 1 Authors

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Carmen Barba, MD, PhD	IRCCS Meyer Children's Hospital, Florence, Italy; University of Florence, Florence, Italy	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Ingmar Blumcke, MD	University Hospital Erlangen, Erlangen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; additional contributions: central review of histopathology
Melodie R. Winawer, MD, MS	Columbia University, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Till Hartlieb, MD	Neurorehabilitation and Epileptology, Vogtareuth, Germany; PMU Salzburg, Salzburg, Austria	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; additional contributions: central review of neuroimaging
Hoon-Chul Kang, MD	Yonsei University College of Medicine, Seoul, Republic of Korea	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Laura Grisotto, PhD	University of Florence, Florence, Italy	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; additional contributions: statistical analysis
Mathilde Chipaux, MD, PhD	Rothschild Foundation Hospital, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
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Barbora Heřmanovská, MD	Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
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Valentina Cetica, PhD	IRCCS Meyer Children's Hospital, Florence, Italy	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; additional contributions: central review of genetic data
Friedrich G. Woermann, MD	Society of Epilepsy Research, Bielefeld, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
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Ludovico D'Incerti, MD	IRCCS Meyer Children's Hospital, Florence, Italy	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; additional contributions: central review of neuroimaging
Sara Baldassari, PhD	Sorbonne University, Paris Brain Institute (ICM), INSERM, CNRS, AP-HP, Pitié-Salpêtrière Hospital, France	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Edward Yang, MD, PhD	Boston Children's Hospital and Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
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Appendix 1 *(continued)*

Name	Location	Contribution
Hannes Vogel, MD	Stanford University, School of Medicine Stanford, CA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Barbora Straka, MD, PhD	Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Letizia Macconi, MD	IRCCS Meyer Children's Hospital, Florence, Italy	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; additional contributions: central review of neuroimaging
Tilman Polster, MD	Krankenhaus Mara, Bielefeld University, Medical School, Bielefeld, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Gerald A. Grant, MD	Lucile Packard Children's Hospital at Stanford University, School of Medicine Stanford, CA	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Lenka Krsková, MD, PhD	Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Hui Jin Shin, MD	Yonsei University College of Medicine, Seoul, Republic of Korea	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Ara Ko, MD	Korea Advanced Institute of Science and Technology, Daejeon, South Korea	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Peter B. Crino, MD, PhD	University of Maryland School of Medicine, Baltimore, MD, USA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Pavel Krsek, MD, PhD	Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Jeong Ho Lee, MD, PhD	Korea Advanced Institute of Science and Technology, Daejeon, South Korea	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Dennis Lal, PhD	Broad Institute of Harvard and M.I.T, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data

Appendix 1 *(continued)*

Name	Location	Contribution
Stéphanie Baulac, PhD	Sorbonne University, Paris Brain Institute (ICM), INSERM, CNRS, AP-HP, Pitié-Salpêtrière Hospital, France	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Annapurna Poduri, MD	Boston Children's Hospital and Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Renzo Guerrini MD, FRCP	IRCCS Meyer Children's Hospital, University of Florence, Florence, Italy	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Annamaria Buccoliero, MD	IRCCS Meyer Children's Hospital, Florence, Italy	Head of the Pathology Unit	Coordinated histopathologic analysis for site
Valerio Conti, PhD	IRCCS Meyer Children's Hospital, Florence, Italy	Site investigator	Performed genetic data analysis
Flavio Giordano, MD	IRCCS Meyer Children's Hospital, Florence, Italy; University of Florence, Florence, Italy	Site investigator	Performed neurosurgical data analysis for site
James Goldman, MD	Columbia University Medical Center, New York, NY.	Site investigator	Performed histopathologic analysis for site
Erin L Heinzen, PharmD, PhD	University of North Carolina at Chapel Hill, Chapel Hill, NC.	Site investigator	Coordinated clinical and genetic data for site
Miroslav Koblížek, MD	Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic	Site investigator	Performed histopathologic analysis for site
Audrey LI, BS	Columbia University, New York, NY	Study coordinator	Coordinated communication among investigators for site
Claudia Mandorlini, MS	Meyer Children's Hospital, Florence, Italy	Site investigator	Performed molecular analysis on brain tissues for site and genetic data analysis
Francesco Mari, MD	Meyer Children's Hospital, Florence, Italy	Site investigator	Collected clinical data for site

Continued

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Davide Mei, MS	Meyer Children's Hospital, Florence, Italy	Site investigator	Performed genetic data analysis
Sara Minghetti, MD	Meyer Children's Hospital, Florence, Italy	Site investigator	Collected clinical data for site
Lucio Parmeggiani, MD	Bolzano Hospital, Bolzano, Italy	Site investigator	Collected clinical data for site
Josef Zámečník, MD	Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic	Site investigator	Performed histopathologic analysis for site

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