

SLC1A3 variant associated with hemiplegic migraine and acetazolamide-responsive MRS changes

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Familial hemiplegic migraine (FHM) is a group of rare familial disorders caused, in most cases, by mutations in *CACNA1A* and *ATP1A2*.¹ Heterozygous mutations in solute carrier family 1 member 3 (*SLC1A3*), encoding glial glutamate transporter, are associated with episodic ataxia type 6 (EA6).^{2–5} In addition to episodic ataxia (EA), alternating hemiplegia and hemiplegic migraine have been reported twice in patients with EA6.^{2,4} Mutations in *SLC1A3* are very rare; screenings in cohorts of EA and alternating hemiplegia have yielded either negative results^{3,6–8} or variants of unclear significance.^{e-1–e-3} Herein, we characterize a patient featuring sporadic hemiplegic migraine (SHM) responsive to acetazolamide (ACZ) and mild cerebellar atrophy associated with a new variant in *SLC1A3*. We also report the utility of proton magnetic resonance spectroscopy (MRS) for this condition.

Methods

The index case and her mother (figure e-1, doi:10.5061/dryad.v41ns1rsd) were evaluated after providing oral and written consent for this study, which was approved by the Regional Ethics Committee of Stockholm. Patients underwent clinical evaluation, structural imaging with MRI, and genotyping. The index case underwent neurophysiologic tests and proton MRS before and after treatment with ACZ. MRS was also performed in 20 healthy controls (data available from Dryad [appendix, doi:10.5061/dryad.v41ns1rsd]).

Results

Patient II:1

The index case is a female 24-year-old medical student with roots in the Middle East and born to consanguineous parents. She was diagnosed with polycystic ovarian syndrome. She was affected by recurrent episodes of left-side hemiplegic spells triggered often by menstruation but also by stress and preceded by a sensorimotor march. Only occasionally these spells affected the right side. Onset was at age 18 years; those episodes occurred twice per year and lasted for up to 2 hours. On one occasion, she had hemiparesis for 9 hours; migraine without aura preceded the hemiplegia spells by 1 to 2 days. The patient did not have any visual complaints during the attacks either; she reported numbness in the hemiparetic side during the entire hemiplegic episode. Examination during 1 episode that motivated admission demonstrated left-sided hemiparesis but normal visual fields and absence of ataxia. The patient did not have any visual complaints during the attacks either; however, any visual aura may well have disappeared by the time she came to the hospital. Interictally, the patient had gaze-evoked nystagmus (GEN), and EEG and electroneurography

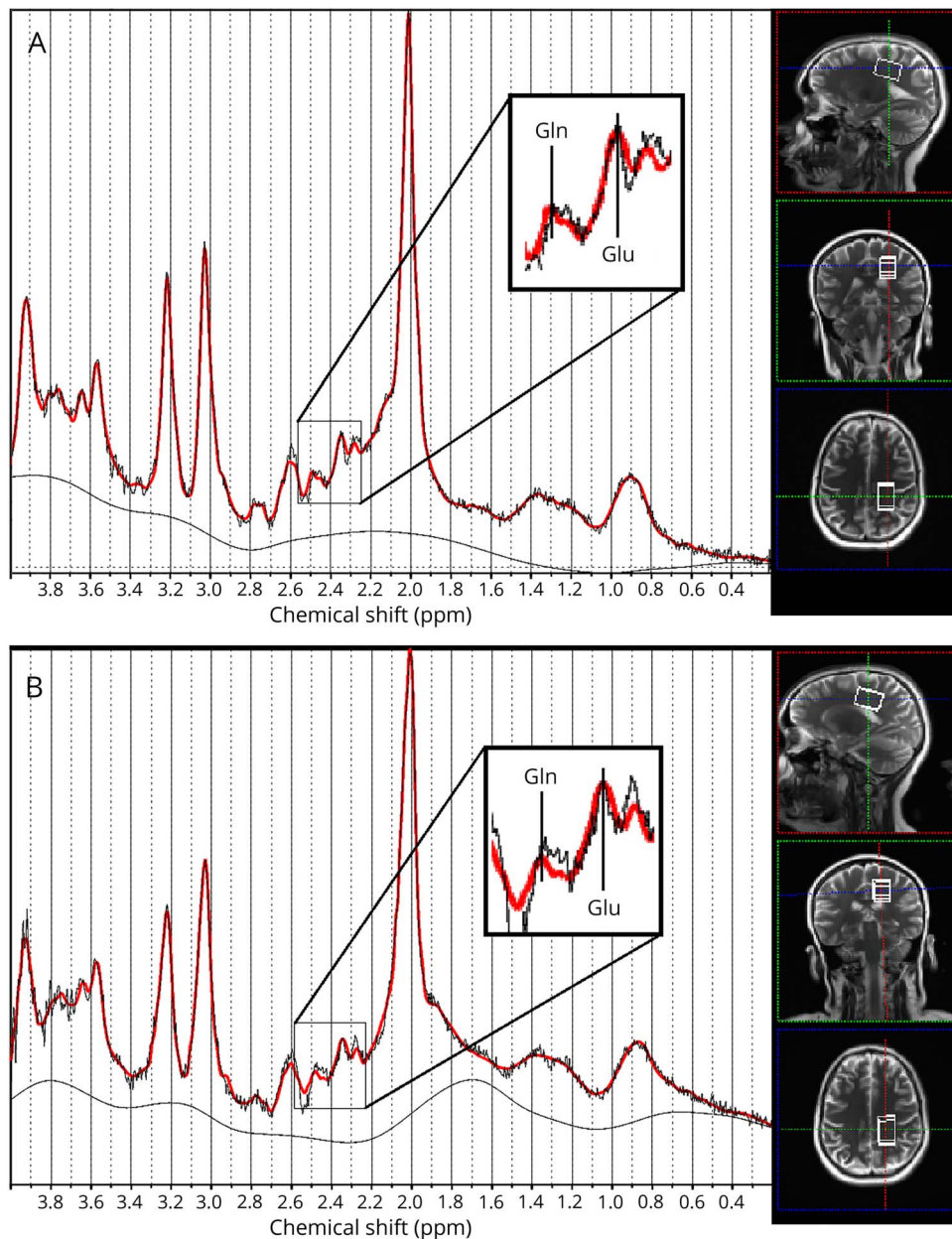
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Figure 1 Spectroscopy of the index case before (A) and after treatment (B)



The T2-weighted images to the right show the location of a 30 × 20 × 20 mm volume of interest in a mid-sagittal, coronal, and transverse plane. The described voxel was averaged 200 times, and the resulting ¹H-MR spectrum is displayed to the left where the main peaks for glutamine and glutamate have been highlighted. In the first measurement, A, the Glx concentration was measured to 3.865 mmol/kg (SD 10%) in the left frontoparietal region. In the second measurement, B, Glx concentration was measured to 4.580 mmol/kg (SD 11%).

were normal. Pathologic CAG expansions in *CACNA1A* and conventional mutations in *CACNA1A*, *ATPIA2*, and *SCN1A* were ruled out. A targeted analysis revealed the novel variant c379_383del in *SLC1A3*. This sequence variant leads to a truncating protein (p.Tyr127Aspfs*60) and is absent in databases (The Genome Aggregation Database [gnomAD], ClinVar, and The Human Gene Mutation Database). Other sequence variants leading to haploinsufficiency are otherwise rare in the normal population (gnomAD). Treatment with ACZ (250 mg twice daily) prevented hemiplegic spells and interictal GEN receded. This therapeutic benefit has lasted for more than 1.5 years, and the patient decided to interrupt this treatment to avoid polypharmacy. MRI of her brain demonstrated mild

vermian atrophy (figure e-2, doi:10.5061/dryad.v41ns1rsd). The index case went through MRS during an interictal period before and after treatment with ACZ (figure 1). MRS demonstrated low Glx (combined glutamate and glutamine) peak (3.865 mmol/kg, SD 10%) and nominally higher levels (4.580 mmol/kg, SD 11%) in the parietal lobe after treatment with ACZ was initiated (data available from Dryad: doi:10.5061/dryad.v41ns1rsd [table e-2, doi:10.5061/dryad.v41ns1rsd]). At age 23 years, the proband developed Cushing syndrome due to an adrenocortical carcinoma, which motivated a right-side nephrectomy and adrenalectomy. Further investigation revealed 2 lung metastases that were resected; recently, one of these metastases has relapsed.

Patient I:1

This patient is a 50-year-old woman who meets the criteria for migraine with visual aura^{e-4} but denies hemiplegic and ataxia episodes. Her examination and brain MRI were normal; she declined MRS and neurophysiologic tests (table e-1, doi:10.5061/dryad.v41ns1rsd).

Discussion

Hemiplegic migraine in association with a *SLC1A3* variant has not been reported before to the best of our knowledge. Despite mild cerebellar atrophy, only interictal nystagmus was found in the index case. Of note, penetrance was reduced in our family; the parent carrying the variant has migraine, which was also reported for the variants p.Cys186Ser and p.Trp387Pro.^{3,4} The long latency between onset of SHM and Cushing syndrome strongly argues against a paraneoplastic syndrome. A correlation between the degree of glutamate reuptake and clinical severity has been suggested,³ but the theoretical haploinsufficiency in our family challenges that hypothesis. A dominant negative effect has been demonstrated for the variants p.Pro290Arg, whereas a clear loss of function was described for p.Trp387Pro.^{2,4} Similar to our case, large deletions in *CACNA1A* cause EA 2 possibly by means of haploinsufficiency.^{e-5} De Fusco et al. proposed a similar mechanism in FHM2.^{e-6} Two reported *SLC1A3* variants^{e-1-e-3} are likely benign considering their frequency in the normal population (gnomAD). Factors modulating variable expressivity and reduced penetrance of *SLC1A3* variants are unknown. *SLC1A3* is highly expressed in the cerebellum and brainstem,² and the sequence variants described in patients are thus far spread in different domains of the protein. Taken together, our findings demonstrate that *SLC1A3* variants are associated with a spectrum of disorders similar to those seen in *CACNA1A* mutations. Our work expands the spectrum of *SLC1A3* mutations beyond EA, illustrates the benefit of ACZ for hemiplegic migraine, and the utility of MRS as a biomarker for altered glutamate transport. An increase in Glx by 22% using MRS was found after treatment, with an acceptable SD for both measurements. Our findings are in contrast with the results reported by Zielman et al. among patients with migraine without aura.^{e-7} These authors found elevated interictal glutamate levels in the visual cortex. In another study by the same group, 7 T¹H-MRS was used for the first time in a group of 18 patients with FHM1 and FHM2.^{e-8} This study revealed reduced total N-acetylaspartate and total creatine in the cerebellum, but Glx/total creatine in the occipital lobe was not significantly altered. MRS studies on other patients harboring *SLC1A3* variants are needed to evaluate whether a specific pattern of metabolite alterations exists for the disease spectrum associated with this gene.

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Name	Location	Contribution
Martin Paucar, MD, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm	Revision of the manuscript; study concept and design; analysis and interpretation of data; and study supervision and coordination
Tobias Granberg, MD, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm	Acquisition and interpretation of neuroimaging data and revision of the manuscript
Kristina Lagerstedt-Robinson, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm	Acquisition and interpretation of genetic data and revision of the manuscript
Elisabet Waldenlind, MD, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm	Interpretation of clinical data and revision of the manuscript
Sven Petersson, PhD	Karolinska University Hospital, Stockholm	Acquisition and interpretation of MRS data and revision of the manuscript
Love Nordin, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm	Acquisition and interpretation of MRS data and revision of the manuscript
Per Svenningsson, MD, PhD	Karolinska University Hospital and Karolinska Institute, Stockholm	Revision of the manuscript; analysis and interpretation of data; study supervision and coordination; and obtaining funding

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References e-1 to e-8 can be accessed via <http://doi:10.5061/dryad.v41ns1rsd>.