

A Case Report of Hemiplegic Migraine with Mutation in the ATP1A2 Gene

Dong-Mei Guan^{1,*}, Yuan-Zhuang Shan^{1,*}, Hao-Tian Zhao², Ying Meng², Zhong-Rui Yan², Hai-Lin Zhang²

¹Shandong University of Tradition Chinese Medicine, Jinan, Shandong, People's Republic of China; ²Department of Neurology, Jining No.1 People's Hospital, Jining, Shandong, People's Republic of China

*These authors contributed equally to this study

Correspondence: Hai-Lin Zhang, Department of Neurology, Jining No.1 People's Hospital, No. 6 of Healthy Road, Rencheng District, Jining, Shandong, 272000, People's Republic of China, Tel +86 176 6130 0365, Email zhanghailin_zhl@126.com

Background: Hemiplegic migraine, a less common variant of migraine, is the focus of this paper. Within the scope of this study, we present a case of hemiplegic migraine that bears the potential for misdiagnosis, particularly as encephalitis.

Brief introduction to the Disease: The patient developed a right-sided headache a day prior to admission, accompanied by fever, nausea, vomiting, and left-sided limb weakness. On the fourth day, the patient experienced a grand mal epilepsy, marked by unconsciousness, leftward deviation of both eyes, limb convulsions, and foaming at the mouth. Cerebrospinal fluid analysis revealed no apparent abnormalities, Electroencephalography showed abnormal slow waves, imaging studies indicated swelling and meningeal thickening in the right cortex, and genetic testing identified a heterozygous mutation in the ATP1A2 gene. The diagnosis was hemiplegic migraine, and the patient received symptomatic supportive treatment, leading to improvement and subsequent discharge. Flunarizine and sodium valproate were prescribed post-discharge, and the patient achieved complete recovery after a one-month follow-up.

Conclusion: Apart from experiencing headaches, patients with hemiplegic migraine may exhibit additional symptoms like fever, epilepsy, and hemiplegia. These manifestations warrant clinical attention, and if deemed necessary, genetic testing should be conducted, and this is an autosomal dominant pattern.

Keywords: ATP1A2 gene mutation, encephalitis, migraine, hemiplegic migraine, swelling of the cortex

Introduction

Migraine is a prevalent neurological disorder marked by recurrent, throbbing, and one-sided headaches that significantly impact patients' work and daily lives. Hemiplegic migraine, a rare subtype characterized by reversible motor aura, is inadequately explored, with an estimated prevalence of 1 in 10,000, as initially reported in Denmark.¹ As per the criteria outlined in the 3rd Edition International Classification of Headache Disorders (ICHD-3),² patients fall into either sporadic hemiplegic migraine (SHM) or familial hemiplegic migraine (FHM) categories, depending on whether their first- or second-degree relatives have a confirmed diagnosis or similar symptoms. The International Classification of Headache Disorders, 3rd edition (ICHD-3), provides specific diagnostic criteria for hemiplegic migraine, a rare subtype of migraine characterized by reversible motor aura. To diagnose hemiplegic migraine, there must be at least two attacks that meet the criteria for migraine with aura. The aura must consist of fully reversible motor weakness along with fully reversible visual, sensory, and/or speech/language symptoms. According to the ICHD-3, the diagnosis of migraine with aura is supported by the following criteria: A. At least two attacks that fulfill criteria B and C. B. One or more of the following aura symptoms that are reversible: visual, retinal, sensory, brainstem, motor, speech, or language. C. At least three of the following six characteristics: At least one aura symptom that spreads gradually over greater than 5 minutes. Two or more symptoms in succession. At least one unilateral aura symptom. At least one positive aura symptom. Each aura symptom lasting 5 to 60 minutes. Aura accompanied by or followed by headache within 60 minutes. D. No other

ICHD-3 diagnosis accounting for the symptoms. This study focuses on the clinical data of a patient with hemiplegic migraine carrying an ATP1A2 gene mutation, initially misdiagnosed as encephalitis (Table S1). The findings aim to contribute to a more comprehensive understanding of hemiplegic migraine among healthcare practitioners through a thorough literature review.

Clinical Data

The patient, a 17-year-old female, was admitted to the hospital on February 19, 2023, with symptoms of fever, headache, and left limb weakness over the course of one day. The onset of headache, primarily on the right side, preceded admission, accompanied by a fever peaking at 39.0 °C, as well as nausea, vomiting, and left limb weakness. Vomiting consisted of non-coffee-colored stomach contents. The initial diagnosis at the local hospital was encephalitis. Various diagnostic tests, including cranial magnetic resonance imaging (MRI), blood routine examination, myocardial enzymes, blood glucose, liver function, renal function, blood lipids, blood homocysteine, coagulation function (five items), glycosylated hemoglobin, myocardial infarction markers (three items), procalcitonin, and pro B type natriuretic peptide (proBNP), revealed no significant abnormalities. The patient had a history of unexplained fever and left limb weakness following startling incidents. Upon admission, the physical examination indicated a blood pressure of 110/65 mmHg, drowsiness, unresponsiveness, unclear speech, and incomplete lateral deviation to the right side in both eyes without noticeable nystagmus. Pupillary responses were isocoric and light reflexes were sensitive, with symmetrical bilateral frontal lines and nasolabial folds. Gross measurements revealed grade 0 muscle strength in the left upper limb, grade 3 muscle strength in the left lower limb, and grade 5 muscle strength in the right limbs. Subsequently, a Babinski sign (+) on the left side, and neck resistance was noted (+).

Following admission, a lumbar puncture was conducted, and an array of diagnostic tests were performed on cerebrospinal fluid, including routine examination, detection of *Cryptococcus neoformans* capsular antigen, ink staining, assessment of immunoglobulin levels, TORCH-IgM/IgG, Brucella antibody detection, Brucella agglutination test, antineutrophil antibody detection, qualitative detection of antinuclear antibodies, antinuclear antibody spectrum, human immunodeficiency virus (HIV) and syphilis antibodies, thyroid function, erythrocyte sedimentation rate, and C-reactive protein (CRP). Results revealed no evident abnormalities. Cranial MRI indicated localized meningeal thickening in bilateral cerebral hemispheres with enhanced signals, suggestive of potential inflammation (Figure 1). The provisional diagnosis upon admission was to exclude central nervous system infection. Symptomatic treatments, including analgesics, antivirals, antipyretics, and rehydration, were administered.

On the fourth day, the patient experienced grand mal epilepsy, characterized by unconsciousness, leftward eye deviation, mouth twitching, limb convulsions, unresponsiveness, foaming at the mouth, increased heart rate, and decreased blood oxygen saturation. After three consecutive episodes, the patient was transferred to the neurological intensive care unit. Cerebral non-contrast scanning revealed swelling of the right cerebral hemisphere cortex, raising the possibility of inflammatory diseases, particularly meningoencephalitis (Figure 1). Anti-epileptic therapy with sodium valproate, anti-infection therapy with ceftriaxone, antiviral therapy with ganciclovir, and dehydration treatments were initiated.

By the 10th day post-admission, the patient's condition improved. Further inquiry into the medical history revealed a history of right-sided headache and left-sided limb weakness lasting 4 to 6 hours, which was spontaneously relieved. Considering the clinical manifestations and medical history, hemiplegic migraine was considered, leading to the prescription of flunarizine for prevention, and a gradual reduction in sodium valproate dosage. After one month of follow-up, the patient fully recovered. Genetic testing revealed a nucleotide change (exon number) c.2998 (exon22) G>A, amino acid change p.E1000K (p.Glu1000Lys) at chromosome position chr1:160109738, and this is an autosomal dominant pattern. Due to the patient being an adoptee with no available family history or samples, it was challenging to clearly differentiate between familial hemiplegic migraine (FHM) and sporadic hemiplegic migraine (SHM).

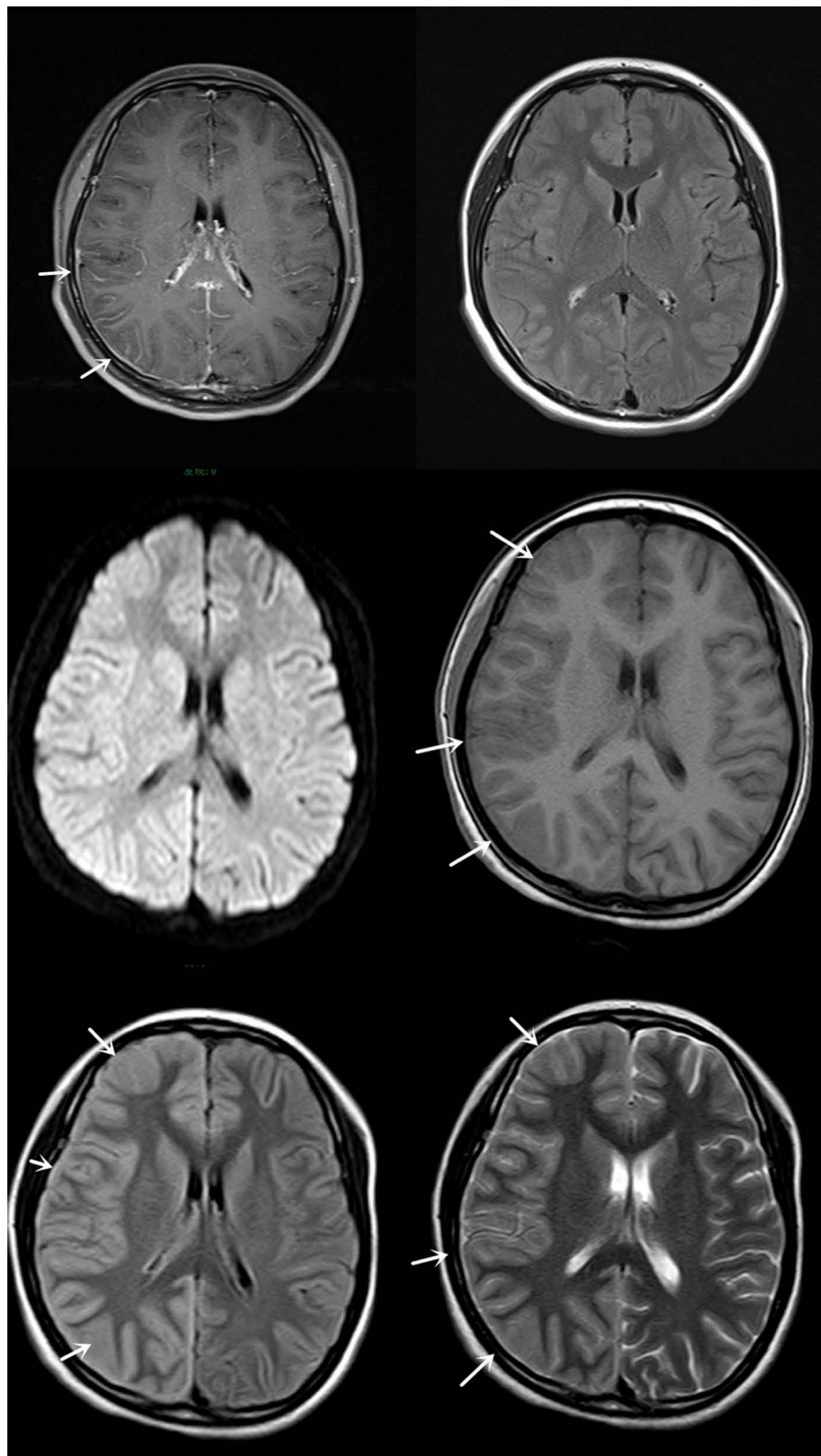


Figure 1 Cranial MRI at the time of admission and reviewed after the symptoms worsened. (The arrow indicates the swollen area).

Discussion

Premonitory manifestations of hemiplegic migraine typically manifest as fully reversible hemi-limb weakness, accompanied by at least one premonitory symptom such as paresthesia, visual deficits, or dysarthria. The sequence of onset for premonitory symptoms and the migraine itself varies, with instances of simultaneous occurrence.³ In this case, the patient exhibited persistent premonitory symptoms without a known family history, followed by severe encephalitis-like attacks. According to pertinent literature, the limb weakness associated with this condition is typically hemi-lateral, predominantly affecting the right side, and progresses from distal to proximal. Alternating paralysis of both limbs may also be observed, although simultaneous involvement of both left and right limbs is uncommon. Generally, premonitory symptoms tend to subside within 20 to 60 minutes or up to three days. However, in some cases, symptoms may persist for weeks or even months.⁴ During the early stages of the disease, mild hemi-headache may be present, often localized to one side or both sides with varying severity. The side experiencing the headache may be ipsilateral or contralateral to the affected limb, and in 2% of cases, no headache is reported.⁵ The clinical spectrum of the disease ranges from simple migraine and hemi-myasthenia to severe conditions that may include additional symptoms such as epilepsy, cognitive impairment, fever, posterior circulation-related defects, coma, and even permanent brain damage, including infarction, cerebellar defects, cerebral atrophy, and death.⁶

Common triggers for hemiplegic migraine encompass bright light exposure, physical and emotional stress, sleep deprivation, mild head trauma, and viral infections. These triggers can precipitate severe hemiplegic migraine attacks, with digital subtraction angiography (DSA) testing also posing a potential trigger.^{4,7} In this case, further inquiry into the medical history revealed episodes of right-sided headache and left limb weakness following head trauma, consistent with common triggers.

The ATP1A2 gene associated with hemiplegic migraine is situated within the 0.9 Mb region at 1q23, comprising 23 exons spanning approximately 20 bases and encoding the alpha-2 subunit of glial Na⁺/K⁺-ATPase.⁸ Heterozygous pathogenic variants in this gene commonly result in type 2 FHM, type 1 alternating hemiplegia in children, type 98 developmental and epileptic encephalopathy, fetal movement disorders, respiratory insufficiency, microcephalus, polygyria malformation, and facial deformity. Over 90 mutations, primarily missense mutations, have been identified in ATP1A2, but there is no clear genotype-phenotype correlation.^{9,10}

In a cohort of 14 Chinese patients with severe hemiplegic migraine involving ATP1A2 (p.P782R,¹¹ p.G855E,¹² p.G715R,¹³ p.T378I,¹⁴ p.E825K,¹⁵ p.G825L¹⁵), CACNA1A gene (p.R1352Q,¹⁶ p.P225H,¹⁷ p.T666M,¹⁸ p.F1502D,¹⁹ p.S218I,¹⁹ p.V358M,¹⁹ p.TS1048I,¹⁹ p.L194Q¹⁹), 14 exhibited impaired consciousness, 7 had fever reaching up to 39 °C, and 6 experienced epilepsy attacks, a severe symptom. The affected individuals were predominantly children, with adults being relatively less affected, possibly linked to a decreasing frequency and severity of episodes with age.²⁰

During the disease onset and interictal phases, electroencephalography (EEG) may reveal abnormal slow waves in one cerebral hemisphere in some patients. In cases with epilepsy, EEG may exhibit epileptiform discharges, potentially making it more accurate and earlier than MRI in revealing impaired brain function. Although cranial imaging is typically normal during or after a hemiplegic migraine attack, severe attacks may affect both cerebral hemispheres, with MRI occasionally indicating cerebral edema and diffusion limitation on the contralateral side of hemiplegia. Most cases show a return to normal imaging after symptom relief, with hemispheric atrophy or cortical lamellar necrosis being rare after severe attacks.²¹

Wang et al¹⁴ reported a patient with negative results on apparent diffusion coefficient (ADC), diffusion-weighted imaging (DWI), and T2-weighted imaging (T2WI), where only fluid-attenuated inversion recovery (FLAIR) revealed increased cortical sulcus in the left hemisphere. The patient exhibited unilateral cortical lesions, demonstrating a lace sign on DWI with slightly higher signals and slightly lower signals on ADC. Contrast-enhanced imaging indicated dural enhancement, increased blood vessels on the brain surface, and enhanced signals on FLAIR. Symptoms such as migraine slowly propagate in the cerebral cortex due to neuronal and glial depolarization, distinguishing it from other conditions through imaging examinations, EEG, and laboratory testing.^{6,22} Distinctive attention is required to differentiate the disease from autoimmune encephalitis, neuronal intranuclear inclusion disease (NIID), and mitochondrial encephalopathy.^{22,23}

Paralysis is an infrequent manifestation in bacterial encephalitis, with MRI typically revealing leptomeningeal enhancement rather than enhancement of the gyri themselves. Herpes simplex virus encephalitis tends to manifest in the anterior temporal lobe, hippocampus, insular lobe, and base of the frontal lobe, potentially affecting both hemispheres in severe cases. However, in this instance, the lesions were strictly confined to one hemisphere, presenting as diffuse lesions across the entire gyrus unilaterally. The typical imaging manifestations of mitochondrial encephalopathy include migratory cortical lesions with pronounced cortical restriction. In this case, the patient exhibited normal lactate level at rest, with no multisystem damage and exercise intolerance, and imaging showed atypical restricted diffusion. The subcortical ribbon sign is predominantly observed in the imaging of NIID, with hemisphere edematous lesions occasionally present. Brain atrophy may develop in later stages of the disease progression. Cerebral hypoperfusion linked to hemiplegic migraine may result in eosinophilic inclusion body accumulation. Hence, accurate differentiation of these diseases is crucial.

HM can be misdiagnosed as epilepsy, stroke, or other neurological disorders, particularly in cases where headaches are not associated with the episode. The clinical features of HM include reversible unilateral limb weakness, visual, sensory, or language impairments. HM has genetic aspects, especially when it presents as a familial condition, often inheriting in an autosomal dominant pattern. Mutations in genes related to HM include CACNA1A, ATP1A2, and SCN1A. Notably, the SCN1A gene is frequently associated with epilepsy, and epileptic seizures are commonly observed in patients with familial Hemiplegic Migraine.²⁴ At present, no specific therapy has been established for hemiplegic migraine, with symptomatic approaches being the primary course of action. Early initiation of preventive medication may prove efficacious in diminishing the frequency of disease episodes. However, due to the limited patient population and absence of randomized controlled trials, conducting clinical investigations to ascertain effective treatments during the acute phase remains unfeasible. Currently, low-dose hormone therapy is advocated in clinical settings, showing potential effectiveness. A case study documented the successful treatment of a severely afflicted child with glucocorticoids and hypertonic saline, while memantine and butylphthalide have demonstrated potential for shortening the disease duration.²⁵ Notably, caution is warranted when considering medications for prevention or acute management such as β -blockers, triptans, and ergotamine derivatives, as they may exacerbate symptoms through vasoconstriction.

Conclusion

In brief, apart from headache, hemiplegic migraine may manifest with clinical symptoms such as fever, altered consciousness, seizures, and hemiplegia. Imaging studies may reveal features resembling those of meningoencephalitis. It is crucial to meticulously collect medical history during clinical assessments, remain vigilant for potential hereditary conditions, and consider genetic testing when warranted.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Jining No.1 People's Hospital. A written informed consent was obtained from the patient's legal guardians.

Our institutional approved to publish the case details.

Consent for Publication

Consent for publication was obtained from the patient's legal guardians.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Thomsen LL, Eriksen MK, Roemer SF, Andersen I, Olesen J, Russell MB. A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. *Brain*. 2002;125(Pt 6):1379–1391. doi:10.1093/brain/awf132

2. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1–211. doi:10.1177/0333102417738202
3. Jen JC, Klein A, Boltshauser E, et al. Prolonged hemiplegic episodes in children due to mutations in ATP1A2. *J Neurol Neurosurg Psych*. 2007;78(5):523–526. doi:10.1136/jnnp.2006.103267
4. Kumar A, Samanta D, Emmady PD, Arora R. Hemiplegic Migraine. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2023.
5. Russell MB, Ducros A. Sporadic and familial hemiplegic migraine: pathophysiological mechanisms, clinical characteristics, diagnosis, and management. *Lancet Neurol*. 2011;10(5):457–470. doi:10.1016/S1474-4422(11)70048-5
6. Di Stefano V, Rispoli MG, Pellegrino N, et al. Diagnostic and therapeutic aspects of hemiplegic migraine. *J. Neurol Neurosurg Psych*. 2020;91(7):764–771. doi:10.1136/jnnp-2020-322850
7. Grangeon L, Lange KS, Waliszewska-Prosół M, et al. Genetics of migraine: where are we now? *J Headache Pain*. 2023;24(1):12. doi:10.1186/s10194-023-01547-8
8. Shull MM, Pugh DG, Lingrel JB. Characterization of the human Na, K-ATPase alpha 2 gene and identification of intragenic restriction fragment length polymorphisms. *J Biol Chem*. 1989;264(29):17532–17543.
9. Oda I, Danno D, Saigoh K, et al. Hemiplegic migraine type 2 with new mutation of the ATP1A2 gene in Japanese cases. *Neurosci Res*. 2022;180:83–89. doi:10.1016/j.neures.2022.03.002
10. Li Y, Tang W, Kang L, et al. Functional correlation of ATP1A2 mutations with phenotypic spectrum: from pure hemiplegic migraine to its variant forms. *J Headache Pain*. 2021;22(1):92. doi:10.1186/s10194-021-01309-4
11. Hu XY, Tang JH, Xi XJ, et al. Hemiplegic migraine with episodic disturbance of consciousness as the main clinical phenotype (a case report and literature review). *Chinese Clin Neurosci*. 2020;28(06):649–654.
12. Dai L, Ding C, Tian X, et al. The clinical spectrum associated with ATP1A2 variants in Chinese pediatric patients. *Brain Dev*. 2023;45(8):422–431. doi:10.1016/j.braindev.2023.04.003
13. Chen H, Sun X, Wang R, et al. A case report of atypical hemiplegic migraine with nonheadache onset in a Chinese child. *BMC Neurol*. 2021;21(1):267. doi:10.1186/s12883-021-02302-9
14. Wang P, Yang YR, Zhang HB, Wang JH, Wang Y. Cognitive dysfunction in a patient with migraine and APT1A2 mutation: a case report. *Neurol Sci*. 2021;42(12):5425–5431. doi:10.1007/s10072-021-05284-1
15. Du Y, Li C, Duan FJ, Zhao C, Zhang W. <atl>Early Treatment in Acute Severe Encephalopathy Caused by ATP1A2 Mutation of Familial Hemiplegic Migraine Type 2. *Neuropediatrics*. 2020;51(3):215–220. doi:10.1055/s-0039-3400986
16. Zhang LX, Shi KL, Yang YS, et al. Hemiplegic migraine in children with congenital ataxia: a case study and literature review [J]. *Chinese Med Clinic*. 2019;19(07):1145–1148.
17. Xiang Y, Li F, Song Z, et al. Two pediatric patients with hemiplegic migraine presenting as acute encephalopathy: case reports and a literature review. *Front Pediatr*. 2023;11:1214837. doi:10.3389/fped.2023.1214837
18. Li M, Zheng X, Zhong R, et al. Familial Hemiplegic Migraine With Progressive Cerebellar Ataxia Caused by a p.Thr666Met CACNA1A Gene Mutation in a Chinese Family. *Front Neurol*. 2019;10:1221. doi:10.3389/fneur.2019.01221
19. Zhuo XW, Ren SS, Gong S, et al. Clinical and genetic analysis of 5 pediatric patients with hemiplegic migraine presenting as acute encephalopathy. *Zhonghua Er Ke Za Zhi*. 2021;59(4):316–321. doi:10.3760/cma.j.cn112140-20201015-00946
20. Bonemazzi I, Brunello F, Pin JN, et al. Hemiplegic Migraine in Children and Adolescents. *J Clin Med*. 2023;12(11):3783. doi:10.3390/jcm12113783
21. Ryan DJ, Coughlan S, McSweeney N, Dineen J, Fanning N. Hemiplegic Migraine as a Stroke Mimic. *Imagi Electroencep Findi Stroke*. 2023;54(7):e306–e309. doi:10.1161/STROKEAHA.122.041369
22. Wang R, Nie X, Xu S, Zhang M, Dong Z, Yu S. Interrelated Pathogenesis? Neuronal Intranuclear Inclusion Disease Combining With Hemiplegic Migraine. *Headache*. 2020;60(2):382–395. doi:10.1111/head.13687
23. Gosalia H, Karsan N, Goadsby PJ. Genetic Mechanisms of Migraine: insights from Monogenic Migraine Mutations. *Int J Mol Sci*. 2023;24(16):12697. doi:10.3390/ijms241612697
24. Bosak M, Słowik A, Domitrz I. EEG changes during left- and right-sided weakness in patient with sporadic hemiplegic migraine. *Neurol Neurochir Pol*. 2022;56(6):508–510.
25. Moya-Mendez ME, Mueller DM, Pratt M, et al. Early onset severe ATP1A2 epileptic encephalopathy: clinical characteristics and underlying mutations. *Epilepsy Behav*. 2021;116:107732. doi:10.1016/j.yebeh.2020.107732

Pharmacogenomics and Personalized Medicine

Dovepress

Publish your work in this journal

Pharmacogenomics and Personalized Medicine is an international, peer-reviewed, open access journal characterizing the influence of genotype on pharmacology leading to the development of personalized treatment programs and individualized drug selection for improved safety, efficacy and sustainability. This journal is indexed on the American Chemical Society's Chemical Abstracts Service (CAS). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/pharmacogenomics-and-personalized-medicine-journal>