

contributed to the design and conceptualization of the study, interpretation of the data, draft and revision of the manuscript for intellectual content.

ACKNOWLEDGMENT

The authors thank the Stanley Medical Research Institute Brain Collection for providing the SMRI specimens, the contributors (listed on the *Neurology*® Web site at www.neurology.org) for providing patient samples and clinical records, and Ms. Kiyomi Noyama and Ms. Aya Shoda for technical assistance.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

M. Shinohara reports no disclosures. M. Saitoh is funded by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science No. 22591176. D. Nishizawa and K. Ikeda report no disclosures. S. Hirose is funded by a by a Grant-in-Aid for Nervous and Mental Disorder Grant 24-7 and H24-Nanji-Ippan-29 from the Ministry of Health, Labour and Welfare, Japan. J. Takanashi is funded by a Grant-in-Aid for research on Measures for Intractable Diseases H23-Nanji-Ippan-78 from the Ministry of Health, Labour and Welfare, Japan. J. Takita and K. Kikuchi report no disclosures. M. Kubota is funded by a Grant-in-Aid for research on Measures for Intractable Diseases H23-Nanji-Ippan-78 from the Ministry of Health, Labour and Welfare, Japan. G. Yamanaka, T. Shiihara, A. Kumakura, M. Kikuchi, M. Toyoshima, T. Goto, and H. Yamanouchi report no disclosures. M. Mizuguchi is funded by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science No. 20390293 and by a Grant-in-Aid for research on Measures for Intractable Diseases H23-Nanji-Ippan-78 from the Ministry of Health, Labour and Welfare, Japan. Go to Neurology.org for full disclosures.

Received September 13, 2012. Accepted in final form January 10, 2013.

REFERENCES

1. Nabhout R, Vezzani A, Dulac O, Chiron C. Acute encephalopathy with inflammation-mediated status epilepticus. *Lancet Neurol* 2011;10:99–108.
2. Takanashi J, Oba H, Barkovich AJ, et al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. *Neurology* 2006;66:1304–1309.
3. Hoshino A, Saitoh M, Oka A, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. *Brain Dev* 2012;34:337–343.
4. Mizuguchi M, Yannanouchi H, Ichiyama T, Shiomi M. Acute encephalopathy associated with influenza and other viral infections. *Acta Neurol Scand* 2007;115:45–56.
5. Takanashi J, Tada H, Terada H, Barkovich AJ. Excitotoxicity in acute encephalopathy with biphasic seizures and late reduced diffusion. *AJNR Am J Neuroradiol* 2009;30:132–135.
6. Takanashi J. Two newly proposed infectious encephalitis/encephalopathy syndromes. *Brain Dev* 2009;31:521–528.
7. Shinohara M, Saitoh M, Takanashi J, et al. Carnitine palmitoyl transferase II polymorphism is associated with multiple syndromes of acute encephalopathy with various infectious diseases. *Brain Dev* 2011;33:512–517.
8. Yu LQ, Frith MC, Suzuki Y, et al. Characterization of genomic organization of the adenosine A2A receptor gene by molecular and bioinformatics analyses. *Brain Res* 2004;1000:156–173.
9. Olah ME, Stiles GL. Adenosine receptor subtypes: characterization and therapeutic regulation. *Annu Rev Pharmacol Toxicol* 1995;35:581–606.
10. Huang S, Apasov S, Koshiha M, Sitkovsky M. Role of A2a extracellular adenosine receptor-mediated signaling in

adenosine-mediated inhibition of T-cell activation and expansion. *Blood* 1997;90:1600–1610.

11. Fredholm BB, Chen JF, Cunha RA, Svenningsson P, Vaugeois JM. Adenosine and brain function. *Int Rev Neurobiol* 2005;63:191–270.
12. Dragunow M. Adenosine: the brain's natural anticonvulsant. *Trends Pharmacol Sci* 1986;7:128–130.
13. Avsar E, Empson RM. Adenosine acting via A1 receptors, controls the transition to status epilepticus-like behaviour in an in vitro model of epilepsy. *Neuropharmacology* 2004;47:427–437.
14. Zeraati M, Mirnajafi-Zadeh J, Fathollahi Y, Namvar S, Rezvani ME. Adenosine A1 and A2A receptors of hippocampal CA1 region have opposite effects on piriform cortex kindled seizures in rats. *Seizure* 2006;15:41–48.
15. El Yacoubi M, Ledent C, Parmentier M, et al. Absence of the adenosine A2A receptor or its chronic blockade decrease ethanol withdrawal-induced seizures in mice. *Neuropharmacology* 2001;40:424–432.
16. Fukuda M, Suzuki Y, Hino H, Morimoto T, Ishii E. Activation of central adenosine A2A receptors lowers the seizure threshold of hyperthermia-induced seizure in childhood rats. *Seizure* 2011;20:156–159.
17. Rogers PJ, Hohoff C, Heatherley SV, et al. Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. *Neuropsychopharmacology* 2010;35:1973–1983.
18. Childs E, Hohoff C, Deckert J, Xu K, Badner J, de Wit H. Association between ADORA2A and DRD2 polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology* 2008;33:2791–2800.
19. Alsene K, Deckert J, Sand P, de Wit H. Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology* 2003;28:1694–1702.
20. King DC, Taylor J, Elnitski L, Chiaromonte F, Miller W, Hardison RC. Evaluation of regulatory potential and conservation scores for detecting cis-regulatory modules in aligned mammalian genome sequences. *Genome Res* 2005;15:1051–1060.
21. Conde L, Vaquerizas JM, Dopazo H, et al. PupaSuite: finding functional single nucleotide polymorphisms for large-scale genotyping purposes. *Nucleic Acids Res* 2006;34:W621–W625.
22. Higley MJ, Sabatini BL. Competitive regulation of synaptic Ca²⁺ influx by D2 dopamine and A2A adenosine receptors. *Nat Neurosci* 2010;13:958–977.
23. Skeberdis VA, Chevaleyre V, Lau CG, et al. Protein kinase A regulates calcium permeability of NMDA receptors. *Nat Neurosci* 2006;9:501–510.
24. Cunha RA. Adenosine as a neuromodulator and as a homeostatic regulator in the nervous system: different roles, different sources and different receptors. *Neurochem Int* 2001;38:107–125.
25. Fredholm BB, Chern Y, Franco R, Sitkovsky M. Aspects of the general biology of adenosine A2A signaling. *Prog Neurobiol* 2007;83:263–276.
26. O'Regan MH, Simpson RE, Perkins LM, Phillis JW. The selective adenosine A2 receptor agonist CGS 21680 enhances excitatory transmitter amino acid release from the ischemic rat cerebral cortex. *Neurosci Lett* 1992;138:169–172.
27. Jones PA, Smith RA, Stone TW. Protection against hippocampal kainate excitotoxicity by intracerebral administration of an adenosine A2A receptor antagonist. *Brain Res* 1998;800:328–335.

***ADORA2A* polymorphism predisposes children to encephalopathy with febrile status epilepticus**

Mayu Shinohara, Makiko Saitoh, Daisuke Nishizawa, et al.
Neurology 2013;80;1571; Published online before print March 27, 2013;
DOI 10.1212/WNL.0b013e31828f18d8

This information is current as of May 6, 2013

Updated Information & Services	including high resolution figures, can be found at: http://www.neurology.org/content/80/17/1571.full.html
Supplementary Material	Supplementary material can be found at: http://www.neurology.org/content/suppl/2013/03/27/WNL.0b013e31828f18d8.DC1.html http://www.neurology.org/content/suppl/2013/03/27/WNL.0b013e31828f18d8.DC2.html
References	This article cites 27 articles, 5 of which can be accessed free at: http://www.neurology.org/content/80/17/1571.full.html#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Pediatric http://www.neurology.org/cgi/collection/all_pediatric Association studies in genetics http://www.neurology.org/cgi/collection/association_studies_in_genetics Gene expression studies http://www.neurology.org/cgi/collection/gene_expression_studies Status epilepticus http://www.neurology.org/cgi/collection/status_epilepticus
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://www.neurology.org/misc/addir.xhtml#reprintsus



