

- 4 Dobretsov M, Stimers JR. Neuronal function and alpha3 isoform of the Na/K-ATPase. *Front Biosci* 2005; **10**: 2373–96.
- 5 Dobretsov M, Hastings SL, Sims TJ, Stimers JR, Romanovsky D. Stretch receptor-associated expression of alpha 3 isoform of the Na⁺, K⁺-ATPase in rat peripheral nervous system. *Neuroscience* 2003; **116**: 1069–80.
- 6 Crambert G, Hasler U, Beghah AT, et al. Transport and pharmacological properties of nine different human Na⁺, K⁺-ATPase isoforms. *J Biol Chem* 2000; **275**: 1976–86.
- 7 Senatorov VV, Mooney D, Hu B. The electrogenic effects of Na⁽⁺⁾-K⁽⁺⁾-ATPase in rat auditory thalamus. *J Physiol* 1997; **502**: 375–85.
- 8 Vaillend C, Mason SE, Cuttle MF, Alger BE. Mechanisms of neuronal hyperexcitability caused by partial inhibition of Na⁺/K⁺-ATPases in the rat CA1 hippocampal region. *J Neurophysiol* 2002; **88**: 2963–78.
- 9 Shiiina N, Yamaguchi K, Tokunaga M. RNG105 deficiency impairs the dendritic localization of mRNAs for Na⁺/K⁺ ATPase subunit isoforms and leads to the degeneration of neuronal networks. *J Neurosci* 2010; **30**: 12816–30.
- 10 Blom H, Rönnlund D, Scott L, et al. Spatial distribution of Na⁺-K⁺-ATPase in dendritic spines dissected by nanoscale superresolution STED microscopy. *BMC Neurosci* 2011; **12**: 16.
- 11 Rose CR, Konnerth A. NMDA receptor-mediated Na⁺ signals in spines and dendrites. *J Neurosci* 2001; **21**: 4207–14.
- 12 Reinhard L, Tidow H, Clausen MJ, Nissen P. Na⁺, K⁺-ATPase as a docking station: protein-protein complexes of the Na⁺, K⁺-ATPase. *Cell Mol Life Sci* 2013; **70**: 205–22.
- 13 Brashear A, DeLeon D, Bressman SB, Thyagarajan D, Farlow MR, Dobyns WB. Rapid-onset dystonia-parkinsonism in a second family. *Neurology* 1997; **48**: 1066–69.
- 14 Dobyns WB, Ozelius LJ, Kramer PL, et al. Rapid-onset dystonia-parkinsonism. *Neurology* 1993; **43**: 2596–602.
- 15 Kramer PL, Mineta M, Klein C, et al. Rapid-onset dystonia-parkinsonism: linkage to chromosome 19q13. *Ann Neurol* 1999; **46**: 176–82.
- 16 Pittock SJ, Joyce C, O'Keane V, et al. Rapid-onset dystonia-parkinsonism: a clinical and genetic analysis of a new kindred. *Neurology* 2000; **55**: 991–95.
- 17 Zaremba J, Mierzewska H, Lysiak Z, Kramer P, Ozelius LJ, Brashear A. Rapid-onset dystonia-parkinsonism: a fourth family consistent with linkage to chromosome 19q13. *Mov Disord* 2004; **19**: 1506–10.
- 18 de Carvalho Aguiar P, Sweadner KJ, Penniston JT, et al. Mutations in the Na⁺/K⁺-ATPase alpha3 gene *ATP1A3* are associated with rapid-onset dystonia parkinsonism. *Neuron* 2004; **43**: 169–75.
- 19 Brashear A, Dobyns WB, de Carvalho Aguiar P, et al. The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the *ATP1A3* gene. *Brain* 2007; **130**: 828–35.
- 20 McKeon A, Ozelius LJ, Hardiman O, Greenway MJ, Pittock SJ. Heterogeneity of presentation and outcome in the Irish rapid-onset dystonia-parkinsonism kindred. *Mov Disord* 2007; **22**: 1325–27.
- 21 Barbano RL, Hill DF, Snively BM, et al. New triggers and non-motor findings in a family with rapid-onset dystonia-parkinsonism. *Parkinsonism Relat Disord* 2012; **18**: 737–41.
- 22 Lee JY, Gollamudi S, Ozelius LJ, Kim JY, Jeon BS. *ATP1A3* mutation in the first Asian case of rapid-onset dystonia-parkinsonism. *Mov Disord* 2007; **22**: 1808–09.
- 23 Zanotti-Fregonara P, Vidailhet M, Kas A, et al. [123I]-FP-CIT and [99mTc]-HMPAO single photon emission computed tomography in a new sporadic case of rapid-onset dystonia-parkinsonism. *J Nucl Sci Technol* 2008; **27**: 148–51.
- 24 Blanco-Arias P, Einholm AP, Mamsa H, et al. A C-terminal mutation of *ATP1A3* underscores the crucial role of sodium affinity in the pathophysiology of rapid-onset dystonia-parkinsonism. *Hum Mol Genet* 2009; **18**: 2370–77.
- 25 Anselmi IA, Sweadner KJ, Gollamudi S, Ozelius LJ, Darras BT. Rapid-onset dystonia-parkinsonism in a child with a novel *ATP1A3* gene mutation. *Neurology* 2009; **73**: 400–01.
- 26 Svetel M, Ozelius LJ, Buckley A, et al. Rapid-onset dystonia-parkinsonism: case report. *J Neurol* 2010; **257**: 472–74.
- 27 Kammer C, Fogel W, Wächter T, et al. Novel *ATP1A3* mutation in a sporadic RDP patient with minimal benefit from deep brain stimulation. *Neurology* 2008; **70**: 1501–03.
- 28 Tarsy D, Sweadner KJ, Song PC. Case records of the Massachusetts General Hospital. Case 17-2010 - a 29-year-old woman with flexion of the left hand and foot and difficulty speaking. *N Engl J Med* 2010; **362**: 2213–19.
- 29 Roubergue A, Roze E, Vuillaumier-Barrot S, et al. The multiple faces of the *ATP1A3*-related dystonic movement disorder. *Mov Disord* 2013; **28**: 1457–59.
- 30 Brashear A, Mink JW, Hill DF, et al. *ATP1A3* mutations in infants: a new rapid-onset dystonia-Parkinsonism phenotype characterized by motor delay and ataxia. *Dev Med Child Neurol* 2012; **54**: 1065–67.
- 31 Heinzen EL, Swoboda KJ, Hitomi Y, et al, and the European Alternating Hemiplegia of Childhood (AHC) Genetics Consortium, and the Biobanca e Registro Clinico per l'Emiplegia Alternante (I.B.AHC) Consortium, and the European Network for Research on Alternating Hemiplegia (ENRAH) for Small and Medium-sized Enterprises (SMEs) Consortium. De novo mutations in *ATP1A3* cause alternating hemiplegia of childhood. *Nat Genet* 2012; **44**: 1030–34.
- 32 Rosewich H, Thiele H, Ohlenbusch A, et al. Heterozygous de-novo mutations in *ATP1A3* in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification study. *Lancet Neurol* 2012; **11**: 764–73.
- 33 Ishii A, Saito Y, Mitsui J, et al. Identification of *ATP1A3* mutations by exome sequencing as the cause of alternating hemiplegia of childhood in Japanese patients. *PLoS One* 2013; **8**: e6120.
- 34 Hoei-Hansen CE, Dali CI, Lyngbye TJ, Duno M, Uldall P. Alternating hemiplegia of childhood in Denmark: clinical manifestations and *ATP1A3* mutation status. *Eur J Paediatr Neurol* 2014; **18**: 50–54.
- 35 Kamphuis DJ, Koelman H, Lees AJ, Tijssen MA. Sporadic rapid-onset dystonia-parkinsonism presenting as Parkinson's disease. *Mov Disord* 2006; **21**: 118–19.
- 36 Brashear A, Hill DF, Snively B, Sweadner KJ, Ozelius L. De novo and recurrent mutations in *ATP1A3* are common in rapid-onset dystonia-parkinsonism. *Neurology* 2010; **74** (suppl 2): A204.
- 37 Petrovski S, Wang Q, Heinzen EL, Allen AS, Goldstein DB. Genic intolerance to functional variation and the interpretation of personal genomes. *PLoS Genet* 2013; **9**: e1003709.
- 38 Brashear A, Farlow MR, Butler IJ, Kasarskis EJ, Dobyns WB. Variable phenotype of rapid-onset dystonia-parkinsonism. *Mov Disord* 1996; **11**: 151–56.
- 39 Brashear A, Butler IJ, Ozelius LJ, et al. Rapid-onset dystonia-parkinsonism: a report of clinical, biochemical, and genetic studies in two families. *Adv Neurol* 1998; **78**: 335–39.
- 40 Brashear A, Butler IJ, Hyland K, Farlow MR, Dobyns WB. Cerebrospinal fluid homovanillic acid levels in rapid-onset dystonia-parkinsonism. *Ann Neurol* 1998; **43**: 521–26.
- 41 Brashear A, Cook JF, Hill DF, et al. Psychiatric disorders in rapid-onset dystonia-parkinsonism. *Neurology* 2012; **79**: 1168–73.
- 42 Bourgeois M, Aicardi J, Goutières F. Alternating hemiplegia of childhood. *J Pediatr* 1993; **122**: 673–79.
- 43 Neville BG, Ninan M. The treatment and management of alternating hemiplegia of childhood. *Dev Med Child Neurol* 2007; **49**: 777–80.
- 44 Sweeney MT, Silver K, Gerard-Blanluet M, et al. Alternating hemiplegia of childhood: early characteristics and evolution of a neurodevelopmental syndrome. *Pediatrics* 2009; **123**: e534–41.
- 45 Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. *Neurology* 1993; **43**: 36–41.
- 46 Casae P. Flunarizine in alternating hemiplegia in childhood. An international study in 12 children. *Neuropediatrics* 1987; **18**: 191–95.
- 47 Casae P, Azou M. Flunarizine in alternating hemiplegia in childhood. *Lancet* 1984; **2**: 579.
- 48 Sasaki M, Sakuragawa N, Osawa M. Long-term effect of flunarizine on patients with alternating hemiplegia of childhood in Japan. *Brain Dev* 2001; **23**: 303–05.
- 49 Kanavakis E, Xaidara A, Papathanasiou-Klontza D, Papadimitriou A, Velentza S, Youroukos S. Alternating hemiplegia of childhood: a syndrome inherited with an autosomal dominant trait. *Dev Med Child Neurol* 2003; **45**: 833–36.
- 50 Bassi MT, Bresolin N, Tonelli A, et al. A novel mutation in the *ATP1A2* gene causes alternating hemiplegia of childhood. *J Med Genet* 2004; **41**: 621–28.

- 51 Swoboda KJ, Kanavakis E, Xaidara A, et al. Alternating hemiplegia of childhood or familial hemiplegic migraine? A novel ATP1A2 mutation. *Ann Neurol* 2004; **55**: 884–87.
- 52 Andermann E, Andermann F, Silver K, Levin S, Arnold D. Benign familial nocturnal alternating hemiplegia of childhood. *Neurology* 1994; **44**: 1812–14.
- 53 Wagener-Schimmel LJ, Nicolai J. Child neurology: benign nocturnal alternating hemiplegia of childhood. *Neurology* 2012; **79**: e161–63.
- 54 Mikati MA, Kramer U, Zupanc ML, Shanahan RJ. Alternating hemiplegia of childhood: clinical manifestations and long-term outcome. *Pediatr Neurol* 2000; **23**: 134–41.
- 55 Saito Y, Sakuragawa N, Sasaki M, Sugai K, Hashimoto T. A case of alternating hemiplegia of childhood with cerebellar atrophy. *Pediatr Neurol* 1998; **19**: 65–68.
- 56 Saito Y, Inui T, Sakakibara T, Sugai K, Sakuma H, Sasaki M. Evolution of hemiplegic attacks and epileptic seizures in alternating hemiplegia of childhood. *Epilepsy Res* 2010; **90**: 248–58.
- 57 Dangond F, Garada B, Murawski BJ, Rey-Casserly C, Holman BL, Mikati MA. Focal brain dysfunction in a 41-year old man with familial alternating hemiplegia. *Eur Arch Psychiatry Clin Neurosci* 1997; **247**: 35–41.
- 58 Mikati M. Alternating hemiplegia of childhood. *Pediatr Neurol* 1999; **21**: 764.
- 59 Panagiotakaki E, Gobbi G, Neville B, et al, and the ENRAH Consortium. Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults. *Brain* 2010; **133**: 3598–610.
- 60 Verret S, Steele JC. Alternating hemiplegia in childhood: a report of eight patients with complicated migraine beginning in infancy. *Pediatrics* 1971; **47**: 675–80.
- 61 Krägeloh I, Aicardi J. Alternating hemiplegia in infants: report of five cases. *Dev Med Child Neurol* 1980; **22**: 784–91.
- 62 Mikati MA, Maguire H, Barlow CF, et al. A syndrome of autosomal dominant alternating hemiplegia: clinical presentation mimicking intractable epilepsy; chromosomal studies; and physiologic investigations. *Neurology* 1992; **42**: 2251–57.
- 63 Sasaki M, Ishii A, Saito Y, et al. Genotype-phenotype correlations in alternating hemiplegia of childhood. *Neurology* 2014; **82**: 482–90.
- 64 Di Michele M, Goubau C, Waelkens E, et al. Functional studies and proteomics in platelets and fibroblasts reveal a lysosomal defect with increased cathepsin-dependent apoptosis in ATP1A3 defective alternating hemiplegia of childhood. *J Proteomics* 2013; **86**: 53–69.
- 65 Post RL, Hegyvary C, Kume S. Activation by adenosine triphosphate in the phosphorylation kinetics of sodium and potassium ion transport adenosine triphosphatase. *J Biol Chem* 1972; **247**: 6530–40.
- 66 Toustrup-Jensen MS, Einholm AP, Schack VR, et al. Relationship between intracellular Na⁺ concentration and reduced Na⁺ affinity in Na⁺,K⁺-ATPase mutants causing neurological disease. *J Biol Chem* 2014; **289**: 3186–97.
- 67 Koenderink JB, Geibel S, Grabsch E, De Pont JJ, Bamberg E, Friedrich T. Electrophysiological analysis of the mutated Na⁺,K⁺-ATPase cation binding pocket. *J Biol Chem* 2003; **278**: 51213–22.
- 68 Poulsen H, Khandelia H, Morth JP, et al. Neurological disease mutations compromise a C-terminal ion pathway in the Na⁽⁺⁾/K⁽⁺⁾-ATPase. *Nature* 2010; **467**: 99–102.
- 69 Toustrup-Jensen M, Vilsen B. Importance of Glu(282) in transmembrane segment M3 of the Na⁽⁺⁾,K⁽⁺⁾-ATPase for control of cation interaction and conformational changes. *J Biol Chem* 2002; **277**: 38607–17.
- 70 Rodacker V, Toustrup-Jensen M, Vilsen B. Mutations Phe785Leu and Thr618Met in Na⁺,K⁺-ATPase, associated with familial rapid-onset dystonia parkinsonism, interfere with Na⁺ interaction by distinct mechanisms. *J Biol Chem* 2006; **281**: 18539–48.
- 71 Einholm AP, Toustrup-Jensen MS, Holm R, Andersen JP, Vilsen B. The rapid-onset dystonia parkinsonism mutation D923N of the Na⁺,K⁺-ATPase alpha3 isoform disrupts Na⁺ interaction at the third Na⁺ site. *J Biol Chem* 2010; **285**: 26245–54.
- 72 Ogawa H, Shinoda T, Cornelius F, Toyoshima C. Crystal structure of the sodium-potassium pump (Na⁺,K⁺-ATPase) with bound potassium and ouabain. *Proc Natl Acad Sci USA* 2009; **106**: 13742–47.
- 73 Kirshenbaum GS, Dawson N, Mullins JGL, et al. Alternating hemiplegia of childhood-related neural and behavioural phenotypes in Na⁺,K⁺-ATPase α3 missense mutant mice. *PLoS One* 2013; **8**: e60141.
- 74 Kaneko M, Desai BS, Cook B. Ionic leakage underlies a gain-of-function effect of dominant disease mutations affecting diverse P-type ATPases. *Nat Genet* 2014; **46**: 144–51.
- 75 Clapcote SJ, Duffy S, Xie G, et al. Mutation I810N in the α3 isoform of Na⁺,K⁺-ATPase causes impairments in the sodium pump and hyperexcitability in the CNS. *Proc Natl Acad Sci USA* 2009; **106**: 14085–90.
- 76 Moseley AE, Williams MT, Schaefer TL, et al. Deficiency in Na⁺,K⁺-ATPase α isoform genes alters spatial learning, motor activity, and anxiety in mice. *J Neurosci* 2007; **27**: 616–26.
- 77 DeAndrade MP, Yokoi F, van Groen T, Lingrel JB, Li Y. Characterization of *Atp1a3* mutant mice as a model of rapid-onset dystonia with parkinsonism. *Behav Brain Res* 2011; **216**: 659–65.
- 78 Ikeda K, Satake S, Onaka T, et al. Enhanced inhibitory neurotransmission in the cerebellar cortex of *Atp1a3*-deficient heterozygous mice. *J Physiol* 2013; **591**: 3433–49.
- 79 Ashmore LJ, Hrizo SL, Paul SM, Van Voorhies WA, Beitel GJ, Palladino MJ. Novel mutations affecting the Na⁺,K⁺-ATPase α model complex neurological diseases and implicate the sodium pump in increased longevity. *Hum Genet* 2009; **126**: 431–47.
- 80 Doğanlı C, Beck HC, Ribera AB, Osvig C, Lykke-Hartmann K. α3Na⁺/K⁺-ATPase deficiency causes brain ventricle dilation and abrupt embryonic motility in zebrafish. *J Biol Chem* 2013; **288**: 8862–74.
- 81 Kirshenbaum GS, Clapcote SJ, Duffy S, et al. Mania-like behavior induced by genetic dysfunction of the neuron-specific Na⁺,K⁺-ATPase α3 sodium pump. *Proc Natl Acad Sci USA* 2011; **108**: 18144–49.
- 82 Kirshenbaum GS, Saltzman K, Rose B, Petersen J, Vilsen B, Roder JC. Decreased neuronal Na⁺,K⁺-ATPase activity in *Atp1a3* heterozygous mice increases susceptibility to depression-like endophenotypes by chronic variable stress. *Genes Brain Behav* 2011; **10**: 542–50.
- 83 Ferrari P, Ferrandi M, Valentini G, Bianchi G, Rostauroxin: an ouabain antagonist that corrects renal and vascular Na⁺,K⁺-ATPase alterations in ouabain and adducin-dependent hypertension. *Am J Physiol Regul Integr Comp Physiol* 2006; **290**: R529–35.
- 84 Pizoli CE, Jinnah HA, Billingsley ML, Hess EJ. Abnormal cerebellar signaling induces dystonia in mice. *J Neurosci* 2002; **22**: 7825–33.
- 85 Calderon DP, Fremont R, Kraenzlin F, Khodakhah K. The neural substrates of rapid-onset dystonia-parkinsonism. *Nat Neurosci* 2011; **14**: 357–65.
- 86 Sweadner KJ. Isozymes of the Na⁺/K⁺-ATPase. *Biochim Biophys Acta* 1989; **988**: 185–220.
- 87 Rajarao SJ, Canfield VA, Mohideen MA, et al. The repertoire of Na⁺,K⁺-ATPase α and β subunit genes expressed in the zebrafish, *Danio rerio*. *Genome Res* 2001; **11**: 1211–20.
- 88 Lebovitz RM, Takeyasu K, Fambrough DM. Molecular characterization and expression of the (Na⁺,K⁺)-ATPase α₁ subunit in *Drosophila melanogaster*. *EMBO J* 1989; **8**: 193–202.
- 89 Palladino MJ, Bower JE, Kreber R, Ganetzky B. Neural dysfunction and neurodegeneration in *Drosophila* Na⁺/K⁺-ATPase α subunit mutants. *J Neurosci* 2003; **23**: 1276–86.

委託業務成果報告書への標記について

委託業務に係る成果報告書の表紙裏に、次の標記を行うものとする。

本報告書は、平成26年度厚生労働科学研究委託事業による委託業務として、福岡大学が実施した平成26年度「Dravet(ドラベ)症候群患者由来iPS細胞を用いた認可医薬品スクリーニングによる革新的な医薬品開発のシーズ探索研究の成果を取りまとめたものです。

