

# **ANÀLISI GENÈTICA I MOLECULAR DE LES MIGRANYES HEREDITÀRIES**

memòria presentada per:  
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Aquest treball ha estat realitzat sota la direcció del **Dr. Alfons Macaya Ruiz** i el **Dr. Bru Cormand Rifà**, al Laboratori de Neurologia Infantil i Psiquiatria Genètica de la Unitat de Neurologia Infantil de l'Hospital Universitari Vall d'Hebron i al Departament de Genètica de la Universitat de Barcelona.

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## **BIBLIOGRAFIA**

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## BIBLIOGRAFIA

Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain.  
Headache Classification Committee of the International Headache Society.  
*Cephalgia* 8 Suppl 7 (1988) 1-96.

The World Health Report: Mental Health: New Understanding, New Hope, 2001.

The International Classification of Headache Disorders: 2nd edition. *Cephalgia* 24 Suppl 1 (2004) 9-160.

- A**breu, P.C., Greenberg, D.A. and Hodge, S.E.: Direct power comparisons between simple LOD scores and NPL scores for linkage analysis in complex diseases. *Am J Hum Genet* 65 (1999) 847-57.
- Abu-Arefeh, I. and Russell, G.: Prevalence of headache and migraine in schoolchildren. *Br J Med* 309 (1994) 765-9.
- Ackerman, M.J. and Clapham, D.E.: Ion channels--basic science and clinical disease. *N Engl J Med* 336 (1997) 1575-86.
- Akerman, S., Williamson, D.J. and Goadsby, P.J.: Voltage-dependent calcium channels are involved in neurogenic dural vasodilatation via a presynaptic transmitter release mechanism. *Br J Pharmacol* 140 (2003) 558-66.
- Almasy, L. and Blangero, J.: Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet* 62 (1998) 1198-211.
- Alonso, I., Barros, J., Tuna, A., Coelho, J., Sequeiros, J., Silveira, I. and Coutinho, P.: Phenotypes of spinocerebellar ataxia type 6 and familial hemiplegic migraine caused by a unique CACNA1A missense mutation in patients from a large family. *Arch Neurol* 60 (2003) 610-4.
- Altmuller, J., Palmer, L.J., Fischer, G., Scherb, H. and Wjst, M.: Genomewide scans of complex human diseases: true linkage is hard to find. *Am J Hum Genet* 69 (2001) 936-50.
- Ambrosini, A. and Schoenen, J.: The electrophysiology of migraine. *Curr Opin Neurol* 16 (2003) 327-31.
- Anttila, V., Kallela, M., Os swell, G., Kaunisto, M.A., Nyholt, D.R., Hamalainen, E., Havanka, H., Ilmavirta, M., Terwilliger, J., Sobel, E., Peltonen, L., Kaprio, J., Farkkila, M., Wessman, M. and Palotie, A.: Trait components provide tools to dissect the genetic susceptibility of migraine. *Am J Hum Genet* 79 (2006) 85-99.
- Armstrong, C.M. and Hille, B.: Voltage-gated ion channels and electrical excitability. *Neuron* 20 (1998) 371-80.
- Augustine, G.J., Santamaria, F. and Tanaka, K.: Local calcium signaling in neurons. *Neuron* 40 (2003) 331-46.
- Ayata, C., Shimizu-Sasamata, M., Lo, E.H., Noebels, J.L. and Moskowitz, M.A.: Impaired neurotransmitter release and elevated threshold for cortical spreading depression in mice with mutations in the alpha1A subunit of P/Q type calcium channels. *Neuroscience* 95 (2000) 639-45.

- B**adia, X., Magaz, S., Gutierrez, L. and Galvan, J.: The burden of migraine in Spain: beyond direct costs. *Pharmacoeconomics* 22 (2004) 591-603.
- Baker, K.E. and Parker, R.: Nonsense-mediated mRNA decay: terminating erroneous gene expression. *Curr Opin Cell Biol* 16 (2004) 293-9.

- Baloh, R.W., Yue, Q., Furman, J.M. and Nelson, S.F.: Familial episodic ataxia: clinical heterogeneity in four families linked to chromosome 19p. *Ann Neurol* 41 (1997) 8-16.
- Barrett, C.F., Cao, Y.Q. and Tsien, R.W.: Gating deficiency in a familial hemiplegic migraine type 1 mutant P/Q-type calcium channel. *J Biol Chem* 280 (2005) 24064-71.
- Bartsch, T., Knight, Y.E. and Goadsby, P.J.: Activation of 5-HT(1B/1D) receptor in the periaqueductal gray inhibits nociception. *Ann Neurol* 56 (2004) 371-81.
- Bassi, M.T., Bresolin, N., Tonelli, A., Nazos, K., Crippa, F., Baschirotto, C., Zucca, C., Bersano, A., Dolcetta, D., Boneschi, F.M., Barone, V. and Casari, G.: A novel mutation in the ATP1A2 gene causes alternating hemiplegia of childhood. *J Med Genet* 41 (2004) 621-8.
- Battistini, S., Stenirri, S., Piatti, M., Gelfi, C., Righetti, P.G., Rocchi, R., Giannini, F., Battistini, N., Guazzi, G.C., Ferrari, M. and Carrera, P.: A new CACNA1A gene mutation in acetazolamide-responsive familial hemiplegic migraine and ataxia. *Neurology* 53 (1999) 38-43.
- Bearden, C.E., Reus, V.I. and Freimer, N.B.: Why genetic investigation of psychiatric disorders is so difficult. *Curr Opin Genet Dev* 14 (2004) 280-6.
- Berridge, M.J., Lipp, P. and Bootman, M.D.: The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol* 1 (2000) 11-21.
- Bezprozvanny, I., Scheller, R.H. and Tsien, R.W.: Functional impact of syntaxin on gating of N-type and Q-type calcium channels. *Nature* 378 (1995) 623-6.
- Bjornsson, A., Gudmundsson, G., Gudfinnsson, E., Hrafnssdottir, M., Benedikz, J., Skuladottir, S., Kristjansson, K., Frigge, M.L., Kong, A., Stefansson, K. and Gulcher, J.R.: Localization of a gene for migraine without aura to chromosome 4q21. *Am J Hum Genet* 73 (2003) 986-93.
- Bolay, H., Reuter, U., Dunn, A.K., Huang, Z., Boas, D.A. and Moskowitz, M.A.: Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med* 8 (2002) 136-42.
- Boomsma, D., Busjahn, A. and Peltonen, L.: Classical twin studies and beyond. *Nat Rev Genet* 3 (2002) 872-82.
- Bousser, M.G.: Estrogens, migraine, and stroke. *Stroke* 35 (2004) 2652-6.
- Bowyer, S.M., Aurora, K.S., Moran, J.E., Tepley, N. and Welch, K.M.: Magnetoencephalographic fields from patients with spontaneous and induced migraine aura. *Ann Neurol* 50 (2001) 582-7.
- Breslau, N. and Rasmussen, B.K.: The impact of migraine: Epidemiology, risk factors, and comorbidities. *Neurology* 56 (2001) S4-12.
- Brugnoni, R., Leone, M., Rigamonti, A., Moranduzzo, E., Cornelio, F., Mantegazza, R. and Bussone, G.: Is the CACNA1A gene involved in familial migraine with aura? *Neurol Sci* 23 (2002) 1-5.
- Bulman, D.E.: Phenotype variation and newcomers in ion channel disorders. *Hum Mol Genet* 6 (1997) 1679-85.
- Burgess, D.L., Jones, J.M., Meisler, M.H. and Noebels, J.L.: Mutation of the Ca<sup>2+</sup> channel beta subunit gene Cchb4 is associated with ataxia and seizures in the lethargic (lh) mouse. *Cell* 88 (1997) 385-92.
- Burstein, R., Yarnitsky, D., Goor-Aryeh, I., Ransil, B.J. and Bajwa, Z.H.: An association between migraine and cutaneous allodynia. *Ann Neurol* 47 (2000) 614-24.

**C**addick, S.J., Wang, C., Fletcher, C.F., Jenkins, N.A., Copeland, N.G. and Hosford, D.A.: Excitatory but not inhibitory synaptic transmission is reduced in lethargic (Cacnb4(lh)) and tottering (Cacna1atg) mouse thalamus. *J Neurophysiol* 81 (1999) 2066-74.

- Cader, Z.M., Noble-Topham, S., Dyment, D.A., Cherny, S.S., Brown, J.D., Rice, G.P. and Ebers, G.C.: Significant linkage to migraine with aura on chromosome 11q24. *Hum Mol Genet* 12 (2003) 2511-7.
- Canti, C., Page, K.M., Stephens, G.J. and Dolphin, A.C.: Identification of residues in the N terminus of alpha<sub>1</sub>B critical for inhibition of the voltage-dependent calcium channel by Gbeta gamma. *J Neurosci* 19 (1999) 6855-64.
- Cao, Y., Welch, K.M., Aurora, S. and Vikingstad, E.M.: Functional MRI-BOLD of visually triggered headache in patients with migraine. *Arch Neurol* 56 (1999) 548-54.
- Cao, Y.Q., Piedras-Renteria, E.S., Smith, G.B., Chen, G., Harata, N.C. and Tsien, R.W.: Presynaptic Ca<sub>2+</sub> channels compete for channel type-preferring slots in altered neurotransmission arising from Ca<sub>2+</sub> channelopathy. *Neuron* 43 (2004) 387-400.
- Cao, Y.Q. and Tsien, R.W.: Effects of familial hemiplegic migraine type 1 mutations on neuronal P/Q-type Ca<sub>2+</sub> channel activity and inhibitory synaptic transmission. *Proc Natl Acad Sci U S A* 102 (2005) 2590-5.
- Cardon, L.R. and Bell, J.I.: Association study designs for complex diseases. *Nat Rev Genet* 2 (2001) 91-9.
- Cargill, M., Altshuler, D., Ireland, J., Sklar, P., Ardlie, K., Patil, N., Shaw, N., Lane, C.R., Lim, E.P., Kalyanaraman, N., Nemesh, J., Ziaugra, L., Friedland, L., Rolfe, A., Warrington, J., Lipshutz, R., Daley, G.Q. and Lander, E.S.: Characterization of single-nucleotide polymorphisms in coding regions of human genes. *Nat Genet* 22 (1999) 231-8.
- Carlsson, A., Forsgren, L., Nylander, P.O., Hellman, U., Forsman-Semb, K., Holmgren, G., Holmberg, D. and Holmberg, M.: Identification of a susceptibility locus for migraine with and without aura on 6p12.2-p21.1. *Neurology* 59 (2002) 1804-7.
- Carrera, P., Piatti, M., Stenirri, S., Grimaldi, L.M., Marchionni, E., Curcio, M., Righetti, P.G., Ferrari, M. and Gelfi, C.: Genetic heterogeneity in Italian families with familial hemiplegic migraine. *Neurology* 53 (1999) 26-33.
- Castro, M.J., Stam, A.H., Lemos, C., Barros, J., Gouveia, R.G., Martins, I.P., Koenderink, J.B., Vanmolkot, K.R., Mendes, A.P., Frants, R.R., Ferrari, M.D., Sequeiros, J., Pereira-Monteiro, J.M. and van den Maagdenberg, A.M.: Recurrent ATP<sub>1</sub>A<sub>2</sub> mutations in Portuguese families with familial hemiplegic migraine. *J Hum Genet* (2007).
- Catterall, W.A.: Structure and function of voltage-gated ion channels. *Annu Rev Biochem* 64 (1995) 493-531.
- Catterall, W.A.: Structure and function of neuronal Ca<sub>2+</sub> channels and their role in neurotransmitter release. *Cell Calcium* 24 (1998) 307-23.
- Catterall, W.A.: From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron* 26 (2000) 13-25.
- Cevoli, S., Pierangeli, G., Monari, L., Valentino, M.L., Bernardoni, P., Mochi, M., Cortelli, P. and Montagna, P.: Familial hemiplegic migraine: clinical features and probable linkage to chromosome 1 in an Italian family. *Neurol Sci* 23 (2002) 7-10.
- Chang, C.L., Donaghay, M. and Poulter, N.: Migraine and stroke in young women: case-control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Bmj* 318 (1999) 13-8.
- Chioza, B., Wilkie, H., Nashef, L., Blower, J., McCormick, D., Sham, P., Asherson, P. and Makoff, A.J.: Association between the alpha(1a) calcium channel gene CACNA1A and idiopathic generalized epilepsy. *Neurology* 56 (2001) 1245-6.
- Choudhuri, R., Cui, L., Yong, C., Bowyer, S., Klein, R.M., Welch, K.M. and Berman, N.E.: Cortical spreading depression and gene regulation: relevance to migraine. *Ann Neurol* 51 (2002) 499-506.
- Chronicle, E. and Mulleners, W.: Anticonvulsant drugs for migraine prophylaxis. *Cochrane Database Syst Rev* (2004) CD003226.

- Clark, V.J. and Dean, M.: Haplotype structure and linkage disequilibrium in chemokine and chemokine receptor genes. *Hum Genomics* 1 (2004) 255-73.
- Colson, N.J., Lea, R.A., Quinlan, S., MacMillan, J. and Griffiths, L.R.: The estrogen receptor 1 G594A polymorphism is associated with migraine susceptibility in two independent case/control groups. *Neurogenetics* 5 (2004) 129-33.
- Colson, N.J., Lea, R.A., Quinlan, S., MacMillan, J. and Griffiths, L.R.: Investigation of hormone receptor genes in migraine. *Neurogenetics* 6 (2005) 17-23.
- Cordell, H.J.: Epistasis: what it means, what it doesn't mean, and statistical methods to detect it in humans. *Hum Mol Genet* 11 (2002) 2463-8.
- Cricchi, F., Di Lorenzo, C., Grieco, G.S., Rengo, C., Cardinale, A., Racaniello, M., Santorelli, F.M., Nappi, G., Pierelli, F. and Casali, C.: Early-onset progressive ataxia associated with the first CACNA1A mutation identified within the I-II loop. *J Neurol Sci* 254 (2007) 69-71.
- Cuenca-León, E., Corominas, R., Fernández-Castillo, N., Volpini, V., del Toro, M., Roig, M., Macaya, A., Cormand, B.: Genetic analysis of 27 Spanish patients with hemiplegic migraine, basilar-type migraine and childhood periodic syndromes. *Cephalgia* (in press) (2008).
- Curtain, R., Tajouri, L., Lea, R., MacMillan, J. and Griffiths, L.: No mutations detected in the INSR gene in a chromosome 19p13 linked migraine pedigree. *Eur J Med Genet* 49 (2006) 57-62.
- Curtain, R.P., Lea, R.A., Tajouri, L., Haupt, L.M., Ovcaric, M., MacMillan, J. and Griffiths, L.R.: Analysis of chromosome 1 microsatellite markers and the FHM2-ATP1A2 gene mutations in migraine pedigrees. *Neurol Res* 27 (2005) 647-52.
- Cutrer, F.M., Sorenson, A.G., Weisskoff, R.M., Ostergaard, L., Sanchez del Rio, M., Lee, E.J., Rosen, B.R. and Moskowitz, M.A.: Perfusion-weighted imaging defects during spontaneous migrainous aura. *Ann Neurol* 43 (1998) 25-31.

Dagleish, R.: The human type I collagen mutation database. *Nucleic Acids Res* 25 (1997) 181-7.

De Fusco, M., Marconi, R., Silvestri, L., Atorino, L., Rampoldi, L., Morgante, L., Ballabio, A., Aridon, P. and Casari, G.: Haploinsufficiency of ATP1A2 encoding the Na<sup>+</sup>/K<sup>+</sup> pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nat Genet* 33 (2003) 192-6.

De Simone, R., Ranieri, A., Marano, E., Beneduce, L., Ripa, P., Bilo, L., Meo, R. and Bonavita, V.: Migraine and epilepsy: clinical and pathophysiological relations. *Neurol Sci* 28 Suppl 2 (2007) S150-5.

De Waard, M., Liu, H., Walker, D., Scott, V.E., Gurnett, C.A. and Campbell, K.P.: Direct binding of G-protein betagamma complex to voltage-dependent calcium channels. *Nature* 385 (1997) 446-50.

Denier, C., Ducros, A., Vahedi, K., Joutel, A., Thierry, P., Ritz, A., Castelnovo, G., Deonna, T., Gerard, P., Devoize, J.L., Gayou, A., Perroud, B., Soisson, T., Autret, A., Warter, J.M., Vighetto, A., Van Bogaert, P., Alamowitch, S., Roullet, E. and Tournier-Lasserve, E.: High prevalence of CACNA1A truncations and broader clinical spectrum in episodic ataxia type 2. *Neurology* 52 (1999) 1816-21.

Dent, W., Spiss, H., Helbok, R., Matuja, W., Scheunemann, S. and Schmutzhard, E.: Prevalence of migraine in a rural area in South Tanzania: a door-to-door survey. *Cephalgia* 24 (2004) 960-6.

Dermitsakis, E.T., Reymond, A. and Antonarakis, S.E.: Conserved non-genic sequences - an unexpected feature of mammalian genomes. *Nat Rev Genet* 6 (2005) 151-7.

Dib, C., Faure, S., Fizames, C., Samson, D., Drouot, N., Vignal, A., Millasseau, P., Marc, S., Hazan, J., Seboun, E., Lathrop, M., Gyapay, G., Morissette, J. and Weissenbach, J.: A

- comprehensive genetic map of the human genome based on 5,264 microsatellites. *Nature* 380 (1996) 152-4.
- Dichgans, M., Freilinger, T., Eckstein, G., Babini, E., Lorenz-Depiereux, B., Biskup, S., Ferrari, M.D., Herzog, J., van den Maagdenberg, A.M., Pusch, M. and Strom, T.M.: Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. *Lancet* 366 (2005a) 371-7.
- Dichgans, M., Herzog, J., Freilinger, T., Wilke, M. and Auer, D.P.:  $^1\text{H}$ -MRS alterations in the cerebellum of patients with familial hemiplegic migraine type 1. *Neurology* 64 (2005b) 608-13.
- Ducros, A., Denier, C., Joutel, A., Cecillon, M., Lescoat, C., Vahedi, K., Darcel, F., Vicaut, E., Bousser, M.G. and Tournier-Lasserre, E.: The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *N Engl J Med* 345 (2001) 17-24.
- Ducros, A., Denier, C., Joutel, A., Vahedi, K., Michel, A., Darcel, F., Madigand, M., Guerouaou, D., Tison, F., Julien, J., Hirsch, E., Chedru, F., Bisgard, C., Lucotte, G., Despres, P., Billard, C., Barthez, M.A., Ponsot, G., Bousser, M.G. and Tournier-Lasserre, E.: Recurrence of the T666M calcium channel CACNA1A gene mutation in familial hemiplegic migraine with progressive cerebellar ataxia. *Am J Hum Genet* 64 (1999) 89-98.
- Ducros, A., Joutel, A., Vahedi, K., Cecillon, M., Ferreira, A., Bernard, E., Verier, A., Echenne, B., Lopez de Munain, A., Bousser, M.G. and Tournier-Lasserre, E.: Mapping of a second locus for familial hemiplegic migraine to 1q21-q23 and evidence of further heterogeneity. *Ann Neurol* 42 (1997) 885-90.

**E**nattah, N.S., Sahi, T., Savilahti, E., Terwilliger, J.D., Peltonen, L. and Jarvela, I.: Identification of a variant associated with adult-type hypolactasia. *Nat Genet* 30 (2002) 233-7.

Ertel, E.A., Campbell, K.P., Harpold, M.M., Hofmann, F., Mori, Y., Perez-Reyes, E., Schwartz, A., Snutch, T.P., Tanabe, T., Birnbaumer, L., Tsien, R.W. and Catterall, W.A.: Nomenclature of voltage-gated calcium channels. *Neuron* 25 (2000) 533-5.

Etminan, M., Takkouche, B., Isorna, F.C. and Samii, A.: Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *Bmj* 330 (2005) 63.

Eunson, L.H., Graves, T.D. and Hanna, M.G.: New calcium channel mutations predict aberrant RNA splicing in episodic ataxia. *Neurology* 65 (2005) 308-10.

Ewens, W.J. and Spielman, R.S.: Locating genes by linkage and association. *Theor Popul Biol* 60 (2001) 135-9.

**F**elix, R.: Channelopathies: ion channel defects linked to heritable clinical disorders. *J Med Genet* 37 (2000) 729-40.

Fenichel: Migraine as a cause of benign paroxysmal vertigo of childhood. *Journal of Pediatrics* 71 (1967) 114-5.

Fernandez, F., Lea, R.A., Colson, N.J., Bellis, C., Quinlan, S. and Griffiths, L.R.: Association between a 19 bp deletion polymorphism at the dopamine beta-hydroxylase (DBH) locus and migraine with aura. *J Neurol Sci* 251 (2006) 118-23.

Ferrari, M.D.: Migraine. *Lancet* 351 (1998) 1043-51.

Fletcher, C.F., Lutz, C.M., O'Sullivan, T.N., Shaughnessy, J.D., Jr., Hawkes, R., Frankel, W.N., Copeland, N.G. and Jenkins, N.A.: Absence epilepsy in tottering mutant mice is associated with calcium channel defects. *Cell* 87 (1996) 607-17.

Fletcher, C.F., Tottene, A., Lennon, V.A., Wilson, S.M., Dubel, S.J., Paylor, R., Hosford, D.A., Tessarollo, L., McEnergy, M.W., Pietrobon, D., Copeland, N.G. and Jenkins, N.A.:

- Dystonia and cerebellar atrophy in *Cacna1a* null mice lacking P/Q calcium channel activity. *Faseb J* 15 (2001) 1288-90.
- Friend, K.L., Crimmins, D., Phan, T.G., Sue, C.M., Colley, A., Fung, V.S., Morris, J.G., Sutherland, G.R. and Richards, R.I.: Detection of a novel missense mutation and second recurrent mutation in the *CACNA1A* gene in individuals with EA-2 and FHM. *Hum Genet* 105 (1999) 261-5.
- Frontali, M.: Spinocerebellar ataxia type 6: channelopathy or glutamine repeat disorder? *Brain Res Bull* 56 (2001) 227-31.
- Furukawa, T., Miura, R., Mori, Y., Strobeck, M., Suzuki, K., Ogihara, Y., Asano, T., Morishita, R., Hashii, M., Higashida, H., Yoshii, M. and Nukada, T.: Differential interactions of the C terminus and the cytoplasmic I-II loop of neuronal Ca<sub>2+</sub> channels with G-protein alpha and beta gamma subunits. II. Evidence for direct binding. *J Biol Chem* 273 (1998) 17595-603.

- G**ardner, K., Barmada, M.M., Ptacek, L.J. and Hoffman, E.P.: A new locus for hemiplegic migraine maps to chromosome 1q31. *Neurology* 49 (1997) 1231-8.
- Gargus, J.J. and Tournay, A.: Novel Mutation Confirms Seizure Locus SCN1A is Also Familial Hemiplegic Migraine Locus FHM3. *Pediatr Neurol* 37 (2007) 407-10.
- Gervil, M., Ulrich, V., Kyvik, K.O., Olesen, J. and Russell, M.B.: Migraine without aura: a population-based twin study. *Ann Neurol* 46 (1999) 606-11.
- Giffin, N.J., Benton, S. and Goadsby, P.J.: Benign paroxysmal torticollis of infancy: four new cases and linkage to *CACNA1A* mutation. *Dev Med Child Neurol* 44 (2002) 490-3.
- Glazier, A.M., Nadeau, J.H. and Aitman, T.J.: Finding genes that underlie complex traits. *Science* 298 (2002) 2345-9.
- Goring, H.H. and Terwilliger, J.D.: Linkage analysis in the presence of errors IV: joint pseudomarker analysis of linkage and/or linkage disequilibrium on a mixture of pedigrees and singletons when the mode of inheritance cannot be accurately specified. *Am J Hum Genet* 66 (2000) 1310-27.
- Greenberg, R.A. and Rittichier, K.K.: Pediatric nonenvironmental hypothermia presenting to the emergency department: Episodic spontaneous hypothermia with hyperhidrosis. *Pediatr Emerg Care* 19 (2003) 32-4.
- Gudbjartsson, D.F., Jonasson, K., Frigge, M.L. and Kong, A.: Allegro, a new computer program for multipoint linkage analysis. *Nat Genet* 25 (2000) 12-3.
- Guida, S., Trettel, F., Pagnutti, S., Mantuano, E., Tottene, A., Veneziano, L., Fellin, T., Spadaro, M., Stauderman, K., Williams, M., Volsen, S., Ophoff, R., Frants, R., Jodice, C., Frontali, M. and Pietrobon, D.: Complete loss of P/Q calcium channel activity caused by a *CACNA1A* missense mutation carried by patients with episodic ataxia type 2. *Am J Hum Genet* 68 (2001) 759-64.
- Gulcher, J.R., Kong, A. and Stefansson, K.: The role of linkage studies for common diseases. *Curr Opin Genet Dev* 11 (2001) 264-7.
- Gurnett, C.A. and Campbell, K.P.: Transmembrane auxiliary subunits of voltage-dependent ion channels. *J Biol Chem* 271 (1996) 27975-8.
- Gyapay, G., Morissette, J., Vignal, A., Dib, C., Fizames, C., Millasseau, P., Marc, S., Bernardi, G., Lathrop, M. and Weissenbach, J.: The 1993-94 Genethon human genetic linkage map. *Nat Genet* 7 (1994) 246-339.

- H**adjikhani, N., Sanchez Del Rio, M., Wu, O., Schwartz, D., Bakker, D., Fischl, B., Kwong, K.K., Cutrer, F.M., Rosen, B.R., Tootell, R.B., Sorensen, A.G. and Moskowitz, M.A.: Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci U S A* 98 (2001) 4687-92.

- Hans, M., Luvisetto, S., Williams, M.E., Spagnolo, M., Urrutia, A., Tottene, A., Brust, P.F., Johnson, E.C., Harpold, M.M., Stauderman, K.A. and Pietrobon, D.: Functional consequences of mutations in the human alpha<sub>1A</sub> calcium channel subunit linked to familial hemiplegic migraine. *J Neurosci* 19 (1999) 1610-9.
- Hastbacka, J., de la Chapelle, A., Mahtani, M.M., Clines, G., Reeve-Daly, M.P., Daly, M., Hamilton, B.A., Kusumi, K., Trivedi, B., Weaver, A. and et al.: The diastrophic dysplasia gene encodes a novel sulfate transporter: positional cloning by fine-structure linkage disequilibrium mapping. *Cell* 78 (1994) 1073-87.
- Hirschhorn, J.N. and Daly, M.J.: Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet* 6 (2005) 95-108.
- Hodge, S.E.: Model-free vs. model-based linkage analysis: a false dichotomy? *Am J Med Genet* 105 (2001) 62-4.
- Hofmann, F., Lacinova, L. and Klugbauer, N.: Voltage-dependent calcium channels: from structure to function. *Rev Physiol Biochem Pharmacol* 139 (1999) 33-87.
- Hubner, C.A. and Jentsch, T.J.: Ion channel diseases. *Hum Mol Genet* 11 (2002) 2435-45.
- I**adecola, C.: From CSD to headache: a long and winding road. *Nat Med* 8 (2002) 110-2.
- Ikeda, K., Onaka, T., Yamakado, M., Nakai, J., Ishikawa, T.O., Taketo, M.M. and Kawakami, K.: Degeneration of the amygdala/piriform cortex and enhanced fear/anxiety behaviors in sodium pump alpha<sub>2</sub> subunit (Atp1a2)-deficient mice. *J Neurosci* 23 (2003) 4667-76.
- Imbrici, P., Jaffe, S.L., Eunson, L.H., Davies, N.P., Herd, C., Robertson, R., Kullmann, D.M. and Hanna, M.G.: Dysfunction of the brain calcium channel CaV2.1 in absence epilepsy and episodic ataxia. *Brain* 127 (2004) 2682-92.
- Ioannidis, J.P., Ntzani, E.E. and Trikalinos, T.A.: 'Racial' differences in genetic effects for complex diseases. *Nat Genet* 36 (2004) 1312-8.
- Ioannidis, J.P., Ntzani, E.E., Trikalinos, T.A. and Contopoulos-Ioannidis, D.G.: Replication validity of genetic association studies. *Nat Genet* 29 (2001) 306-9.
- J**en, J., Kim, G.W. and Baloh, R.W.: Clinical spectrum of episodic ataxia type 2. *Neurology* 62 (2004a) 17-22.
- Jen, J., Wan, J., Graves, M., Yu, H., Mock, A.F., Coulin, C.J., Kim, G., Yue, Q., Papazian, D.M. and Baloh, R.W.: Loss-of-function EA2 mutations are associated with impaired neuromuscular transmission. *Neurology* 57 (2001) 1843-8.
- Jen, J.C., Graves, T.D., Hess, E.J., Hanna, M.G., Griggs, R.C. and Baloh, R.W.: Primary episodic ataxias: diagnosis, pathogenesis and treatment. *Brain* 130 (2007) 2484-93.
- Jen, J.C., Kim, G.W., Dudding, K.A. and Baloh, R.W.: No mutations in CACNA1A and ATP1A2 in probands with common types of migraine. *Arch Neurol* 61 (2004b) 926-8.
- Jodice, C., Mantuano, E., Veneziano, L., Trettel, F., Sabbadini, G., Calandriello, L., Francia, A., Spadaro, M., Pierelli, F., Salvi, F., Ophoff, R.A., Frants, R.R. and Frontali, M.: Episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) due to CAG repeat expansion in the CACNA1A gene on chromosome 19p. *Hum Mol Genet* 6 (1997) 1973-8.
- Johnson, M.P., Lea, R.A., Curtain, R.P., MacMillan, J.C. and Griffiths, L.R.: An investigation of the 5-HT<sub>2C</sub> receptor gene as a migraine candidate gene. *Am J Med Genet B Neuropsychiatr Genet* 117 (2003) 86-9.
- Jones, K.W., Ehm, M.G., Pericak-Vance, M.A., Haines, J.L., Boyd, P.R. and Peroutka, S.J.: Migraine with aura susceptibility locus on chromosome 19p13 is distinct from the familial hemiplegic migraine locus. *Genomics* 78 (2001) 150-4.

- Joutel, A., Bousser, M.G., Bioussé, V., Labauge, P., Chabriat, H., Nibbio, A., Maciazeck, J., Meyer, B., Bach, M.A., Weissenbach, J. and et al.: A gene for familial hemiplegic migraine maps to chromosome 19. *Nat Genet* 5 (1993) 40-5.
- Jouvenceau, A., Eunson, L.H., Spauschus, A., Ramesh, V., Zuberi, S.M., Kullmann, D.M. and Hanna, M.G.: Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. *Lancet* 358 (2001) 801-7.
- Jun, K., Piedras-Renteria, E.S., Smith, S.M., Wheeler, D.B., Lee, S.B., Lee, T.G., Chin, H., Adams, M.E., Scheller, R.H., Tsien, R.W. and Shin, H.S.: Ablation of P/Q-type Ca(2+) channel currents, altered synaptic transmission, and progressive ataxia in mice lacking the alpha(1A)-subunit. *Proc Natl Acad Sci U S A* 96 (1999) 15245-50.
- Jurkat-Rott, K., Freilinger, T., Dreier, J.P., Herzog, J., Gobel, H., Petzold, G.C., Montagna, P., Gasser, T., Lehmann-Horn, F. and Dichgans, M.: Variability of familial hemiplegic migraine with novel A<sub>1</sub>A<sub>2</sub> Na<sup>+</sup>/K<sup>+</sup>-ATPase variants. *Neurology* 62 (2004) 1857-61.

- K**allela, M., Wessman, M., Havanka, H., Palotie, A. and Farkkila, M.: Familial migraine with and without aura: clinical characteristics and co-occurrence. *Eur J Neurol* 8 (2001) 441-9.
- Kaniecki R, L.S.: Standards of care for headache diagnosis and treatment. Chicago (IL): National Headache Foundation, 2004.
- Kaplan, J.H.: Biochemistry of Na,K-ATPase. *Annu Rev Biochem* 71 (2002) 511-35.
- Kaprio, J.: Science, medicine, and the future. Genetic epidemiology. *Bmj* 320 (2000) 1257-9.
- Kara, I., Sazci, A., Ergul, E., Kaya, G. and Kilic, G.: Association of the C677T and A1298C polymorphisms in the 5,10 methylenetetrahydrofolate reductase gene in patients with migraine risk. *Brain Res Mol Brain Res* 111 (2003) 84-90.
- Kaunisto, M.A., Harno, H., Kallela, M., Somer, H., Sallinen, R., Hamalainen, E., Miettinen, P.J., Vesa, J., Orpana, A., Palotie, A., Farkkila, M. and Wessman, M.: Novel splice site CACNA1A mutation causing episodic ataxia type 2. *Neurogenetics* 5 (2004) 69-73.
- Kaunisto, M.A., Kallela, M., Hamalainen, E., Kilpikari, R., Havanka, H., Harno, H., Nissila, M., Sako, E., Ilmavirta, M., Liukkonen, J., Teirmaa, H., Tornwall, O., Jussila, M., Terwilliger, J., Farkkila, M., Kaprio, J., Palotie, A. and Wessman, M.: Testing of variants of the MTHFR and ESR1 genes in 1798 Finnish individuals fails to confirm the association with migraine with aura. *Cephalgia* 26 (2006) 1462-72.
- Kaunisto, M.A., Tikka, P.J., Kallela, M., Leal, S.M., Papp, J.C., Korhonen, A., Hamalainen, E., Harno, H., Havanka, H., Nissila, M., Sako, E., Ilmavirta, M., Kaprio, J., Farkkila, M., Ophoff, R.A., Palotie, A. and Wessman, M.: Chromosome 19p13 loci in Finnish migraine with aura families. *Am J Med Genet B Neuropsychiatr Genet* 132 (2005) 85-9.
- Kawaguchi, Y., Okamoto, T., Taniwaki, M., Aizawa, M., Inoue, M., Katayama, S., Kawakami, H., Nakamura, S., Nishimura, M., Akiguchi, I. and et al.: CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. *Nat Genet* 8 (1994) 221-8.
- Kelman, L.: The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. *Headache* 44 (2004) 865-72.
- Kim, J.S., Yue, Q., Jen, J.C., Nelson, S.F. and Baloh, R.W.: Familial migraine with vertigo: no mutations found in CACNA1A. *Am J Med Genet* 79 (1998) 148-51.
- Kloos, R.T.: Spontaneous periodic hypothermia. *Medicine (Baltimore)* 74 (1995) 268-80.
- Knight, Y.E., Bartsch, T., Kaube, H. and Goadsby, P.J.: P/Q-type calcium-channel blockade in the periaqueductal gray facilitates trigeminal nociception: a functional genetic link for migraine? *J Neurosci* 22 (2002) RC213.
- Knight, Y.E. and Goadsby, P.J.: The periaqueductal grey matter modulates trigeminovascular input: a role in migraine? *Neuroscience* 106 (2001) 793-800.
- Kong, A. and Cox, N.J.: Allele-sharing models: LOD scores and accurate linkage tests. *Am J Hum Genet* 61 (1997) 1179-88.

- Kong, A., Gudbjartsson, D.F., Sainz, J., Jonsdottir, G.M., Gudjonsson, S.A., Richardsson, B., Sigurdardottir, S., Barnard, J., Hallbeck, B., Masson, G., Shlien, A., Palsson, S.T., Frigge, M.L., Thorgeirsson, T.E., Gulcher, J.R. and Stefansson, K.: A high-resolution recombination map of the human genome. *Nat Genet* 31 (2002) 241-7.
- Kors, E.E., Haan, J., Giffin, N.J., Pazdera, L., Schnittger, C., Lennox, G.G., Terwindt, G.M., Vermeulen, F.L., Van den Maagdenberg, A.M., Frants, R.R. and Ferrari, M.D.: Expanding the phenotypic spectrum of the CACNA1A gene T666M mutation: a description of 5 families with familial hemiplegic migraine. *Arch Neurol* 60 (2003) 684-8.
- Kors, E.E., Melberg, A., Vanmolkot, K.R., Kumlien, E., Haan, J., Raininko, R., Flink, R., Ginjaar, H.B., Frants, R.R., Ferrari, M.D. and van den Maagdenberg, A.M.: Childhood epilepsy, familial hemiplegic migraine, cerebellar ataxia, and a new CACNA1A mutation. *Neurology* 63 (2004) 1136-7.
- Kowa, H., Yasui, K., Takeshima, T., Urakami, K., Sakai, F. and Nakashima, K.: The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. *Am J Med Genet* 96 (2000) 762-4.
- Kramer, P.L., Yue, Q., Gancher, S.T., Nutt, J.G., Baloh, R., Smith, E., Browne, D., Bussey, K., Lovrien, E., Nelson, S. and et al.: A locus for the nystagmus-associated form of episodic ataxia maps to an 11-cM region on chromosome 19p. *Am J Hum Genet* 57 (1995) 182-5.
- Kraus, R.L., Sinnegger, M.J., Glossmann, H., Hering, S. and Striessnig, J.: Familial hemiplegic migraine mutations change alpha<sub>1</sub>A Ca<sup>2+</sup> channel kinetics. *J Biol Chem* 273 (1998) 5586-90.
- Kraus, R.L., Sinnegger, M.J., Koschak, A., Glossmann, H., Stenirri, S., Carrera, P. and Striessnig, J.: Three new familial hemiplegic migraine mutants affect P/Q-type Ca(2+) channel kinetics. *J Biol Chem* 275 (2000) 9239-43.
- Kruglyak, L.: The use of a genetic map of biallelic markers in linkage studies. *Nat Genet* 17 (1997) 21-4.
- Kruglyak, L., Daly, M.J., Reeve-Daly, M.P. and Lander, E.S.: Parametric and nonparametric linkage analysis: a unified multipoint approach. *Am J Hum Genet* 58 (1996) 1347-63.
- Kruglyak, L. and Lander, E.S.: High-resolution genetic mapping of complex traits. *Am J Hum Genet* 56 (1995) 1212-23.
- Kuivaniemi, H., Tromp, G. and Prockop, D.J.: Mutations in collagen genes: causes of rare and some common diseases in humans. *Faseb J* 5 (1991) 2052-60.
- Kullmann, D.M. and Hanna, M.G.: Neurological disorders caused by inherited ion-channel mutations. *Lancet Neurol* 1 (2002) 157-66.
- Lander, E. and Kruglyak, L.: Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet* 11 (1995) 241-7.
- Lander, E.S.: The new genomics: global views of biology. *Science* 274 (1996) 536-9.
- Lashley, K.: Patterns of cerebral integration indicated by the scotomas of migraine. *Arch Neurol Psych* 46 (1941) 333-339.
- Launer, L.J., Terwindt, G.M. and Ferrari, M.D.: The prevalence and characteristics of migraine in a population-based cohort: the GEM study. *Neurology* 53 (1999) 537-42.
- Lauritzen, M.: Pathophysiology of the migraine aura. The spreading depression theory. *Brain* 117 (Pt 1) (1994) 199-210.
- Lea, R.A., Curtain, R.P., Hutchins, C., Brimage, P.J. and Griffiths, L.R.: Investigation of the CACNA1A gene as a candidate for typical migraine susceptibility. *Am J Med Genet* 105 (2001) 707-12.

- Lea, R.A., Nyholt, D.R., Curtain, R.P., Ovcaric, M., Sciascia, R., Bellis, C., Macmillan, J., Quinlan, S., Gibson, R.A., McCarthy, L.C., Riley, J.H., Smithies, Y.J., Kinrade, S. and Griffiths, L.R.: A genome-wide scan provides evidence for loci influencing a severe heritable form of common migraine. *Neurogenetics* 6 (2005a) 67-72.
- Lea, R.A., Ovcaric, M., Sundholm, J., MacMillan, J. and Griffiths, L.R.: The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura. *BMC Med* 2 (2004) 3.
- Lea, R.A., Ovcaric, M., Sundholm, J., Solyom, L., Macmillan, J. and Griffiths, L.R.: Genetic variants of angiotensin converting enzyme and methylenetetrahydrofolate reductase may act in combination to increase migraine susceptibility. *Brain Res Mol Brain Res* 136 (2005b) 112-7.
- Lea, R.A., Shepherd, A.G., Curtain, R.P., Nyholt, D.R., Quinlan, S., Brimage, P.J. and Griffiths, L.R.: A typical migraine susceptibility region localizes to chromosome 1q31. *Neurogenetics* 4 (2002) 17-22.
- Leao, A.: Spreading depression of activity in cerebral cortex. *J Neurophysiol* 7 (1944) 379-390.
- Lee, A., Scheuer, T. and Catterall, W.A.: Ca<sup>2+</sup>/calmodulin-dependent facilitation and inactivation of P/Q-type Ca<sup>2+</sup> channels. *J Neurosci* 20 (2000) 6830-8.
- Lee, A., Wong, S.T., Gallagher, D., Li, B., Storm, D.R., Scheuer, T. and Catterall, W.A.: Ca<sup>2+</sup>/calmodulin binds to and modulates P/Q-type calcium channels. *Nature* 399 (1999) 155-9.
- Lennon, V.A., Kryzer, T.J., Griesmann, G.E., O'Suilleabhain, P.E., Windebank, A.J., Woppmann, A., Miljanich, G.P. and Lambert, E.H.: Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. *N Engl J Med* 332 (1995) 1467-74.
- Levy, D., Jakubowski, M. and Burstein, R.: Disruption of communication between peripheral and central trigeminovascular neurons mediates the antimigraine action of 5HT<sub>1B/1D</sub> receptor agonists. *Proc Natl Acad Sci U S A* 101 (2004) 4274-9.
- Lingrel, J., Moseley, A., Dostanic, I., Cougnon, M., He, S., James, P., Woo, A., O'Connor, K. and Neumann, J.: Functional roles of the alpha isoforms of the Na,K-ATPase. *Ann NY Acad Sci* 986 (2003) 354-9.
- Lohmueller, K.E., Pearce, C.L., Pike, M., Lander, E.S. and Hirschhorn, J.N.: Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet* 33 (2003) 177-82.

**M**acGregor, E.A.: Oestrogen and attacks of migraine with and without aura. *Lancet Neurol* 3 (2004) 354-61.

Mantuano, E., Veneziano, L., Spadaro, M., Giunti, P., Guida, S., Leggio, M.G., Verriello, L., Wood, N., Jodice, C. and Frontali, M.: Clusters of non-truncating mutations of P/Q type Ca<sup>2+</sup> channel subunit Ca(v)2.1 causing episodic ataxia 2. *J Med Genet* 41 (2004) e82.

Marconi, R., De Fusco, M., Aridon, P., Plewnia, K., Rossi, M., Carapelli, S., Ballabio, A., Morgante, L., Musolino, R., Epifanio, A., Micieli, G., De Michele, G. and Casari, G.: Familial hemiplegic migraine type 2 is linked to 0.9Mb region on chromosome 1q23. *Ann Neurol* 53 (2003) 376-81.

Markowitz, S., Saito, K. and Moskowitz, M.A.: Neurogenically mediated leakage of plasma protein occurs from blood vessels in dura mater but not brain. *J Neurosci* 7 (1987) 4129-36.

Mattsson, P., Bjelfman, C., Lundberg, P.O. and Rane, A.: Cytochrome P450 2D6 and glutathione S-transferase M1 genotypes and migraine. *Eur J Clin Invest* 30 (2000) 367-71.

- May, A., Ophoff, R.A., Terwindt, G.M., Urban, C., van Eijk, R., Haan, J., Diener, H.C., Lindhout, D., Frants, R.R., Sandkuijl, L.A. and et al.: Familial hemiplegic migraine locus on 19p13 is involved in the common forms of migraine with and without aura. *Hum Genet* 96 (1995) 604-8.
- Mazaheri, S., Hajilooi, M. and Rafiei, A.: The G-308A promoter variant of the tumor necrosis factor-alpha gene is associated with migraine without aura. *J Neurol* 253 (2006) 1589-93.
- McCarthy, L.C., Hosford, D.A., Riley, J.H., Bird, M.I., White, N.J., Hewett, D.R., Peroutka, S.J., Griffiths, L.R., Boyd, P.R., Lea, R.A., Bhatti, S.M., Hosking, L.K., Hood, C.M., Jones, K.W., Handley, A.R., Rallan, R., Lewis, K.F., Yeo, A.J., Williams, P.M., Priest, R.C., Khan, P., Donnelly, C., Lumsden, S.M., O'Sullivan, J., See, C.G., Smart, D.H., Shaw-Hawkins, S., Patel, J., Langrish, T.C., Feniuk, W., Knowles, R.G., Thomas, M., Libri, V., Montgomery, D.S., Manasco, P.K., Xu, C.F., Dykes, C., Humphrey, P.P., Roses, A.D. and Purvis, I.J.: Single-nucleotide polymorphism alleles in the insulin receptor gene are associated with typical migraine. *Genomics* 78 (2001) 135-49.
- McClatchey, A.I., Van den Bergh, P., Pericak-Vance, M.A., Raskind, W., Verellen, C., McKenna-Yasek, D., Rao, K., Haines, J.L., Bird, T., Brown, R.H., Jr. and et al.: Temperature-sensitive mutations in the III-IV cytoplasmic loop region of the skeletal muscle sodium channel gene in paramyotonia congenita. *Cell* 68 (1992) 769-74.
- Melliti, K., Grabner, M. and Seabrook, G.R.: The familial hemiplegic migraine mutation R192Q reduces G-protein-mediated inhibition of P/Q-type (Ca(V)2.1) calcium channels expressed in human embryonic kidney cells. *J Physiol* 546 (2003) 337-47.
- Merikangas, K.R.: Genetics of migraine and other headache. *Curr Opin Neurol* 9 (1996) 202-5.
- Miyazaki, T., Hashimoto, K., Shin, H.S., Kano, M. and Watanabe, M.: P/Q-type Ca<sup>2+</sup> channel alpha1A regulates synaptic competition on developing cerebellar Purkinje cells. *J Neurosci* 24 (2004) 1734-43.
- Mochi, M., Cevoli, S., Cortelli, P., Pierangeli, G., Scapoli, C., Soriani, S. and Montagna, P.: Investigation of an LDLR gene polymorphism (19p13.2) in susceptibility to migraine without aura. *J Neurol Sci* 213 (2003) 7-10.
- Mochida, S., Sheng, Z.H., Baker, C., Kobayashi, H. and Catterall, W.A.: Inhibition of neurotransmission by peptides containing the synaptic protein interaction site of N-type Ca<sup>2+</sup> channels. *Neuron* 17 (1996) 781-8.
- Mori, Y., Wakamori, M., Oda, S., Fletcher, C.F., Sekiguchi, N., Mori, E., Copeland, N.G., Jenkins, N.A., Matsushita, K., Matsuyama, Z. and Imoto, K.: Reduced voltage sensitivity of activation of P/Q-type Ca<sup>2+</sup> channels is associated with the ataxic mouse mutation rolling Nagoya (tg(rol)). *J Neurosci* 20 (2000) 5654-62.
- Morris, R.W. and Kaplan, N.L.: On the advantage of haplotype analysis in the presence of multiple disease susceptibility alleles. *Genet Epidemiol* 23 (2002) 221-33.
- Morton, N.E.: LODs past and present. *Genetics* 140 (1995) 7-12.
- Moseley, A.E., Lieske, S.P., Wetzel, R.K., James, P.F., He, S., Shelly, D.A., Paul, R.J., Boivin, G.P., Witte, D.P., Ramirez, J.M., Sweadner, K.J. and Lingrel, J.B.: The Na,K-ATPase alpha 2 isoform is expressed in neurons, and its absence disrupts neuronal activity in newborn mice. *J Biol Chem* 278 (2003) 5317-24.
- Moskowitz, M.A., Bolay, H. and Dalkara, T.: Deciphering migraine mechanisms: clues from familial hemiplegic migraine genotypes. *Ann Neurol* 55 (2004) 276-80.
- Moskowitz, M.A. and Macfarlane, R.: Neurovascular and molecular mechanisms in migraine headaches. *Cerebrovasc Brain Metab Rev* 5 (1993) 159-77.
- Mulder, E.J., Van Baal, C., Gaist, D., Kallela, M., Kaprio, J., Svensson, D.A., Nyholt, D.R., Martin, N.G., MacGregor, A.J., Cherkas, L.F., Boomsma, D.I. and Palotie, A.: Genetic and environmental influences on migraine: a twin study across six countries. *Twin Res* 6 (2003) 422-31.

- Mullner, C., Broos, L.A., van den Maagdenberg, A.M. and Striessnig, J.: Familial hemiplegic migraine type 1 mutations K1336E, W1684R, and V1696I alter Cav2.1 Ca<sup>2+</sup> channel gating: evidence for beta-subunit isoform-specific effects. *J Biol Chem* 279 (2004) 51844-50.
- Muth, J.N., Varadi, G. and Schwartz, A.: Use of transgenic mice to study voltage-dependent Ca<sup>2+</sup> channels. *Trends Pharmacol Sci* 22 (2001) 526-32.

**N**yholt, D.R.: Genetic case-control association studies--correcting for multiple testing. *Hum Genet* 109 (2001) 564-7.

Nyholt, D.R., Curtain, R.P. and Griffiths, L.R.: Familial typical migraine: significant linkage and localization of a gene to Xq24-28. *Hum Genet* 107 (2000) 18-23.

Nyholt, D.R., Dawkins, J.L., Brimage, P.J., Goadsby, P.J., Nicholson, G.A. and Griffiths, L.R.: Evidence for an X-linked genetic component in familial typical migraine. *Hum Mol Genet* 7 (1998a) 459-63.

Nyholt, D.R., Gillespie, N.G., Heath, A.C., Merikangas, K.R., Duffy, D.L. and Martin, N.G.: Latent class and genetic analysis does not support migraine with aura and migraine without aura as separate entities. *Genet Epidemiol* 26 (2004) 231-44.

Nyholt, D.R., Lea, R.A., Goadsby, P.J., Brimage, P.J. and Griffiths, L.R.: Familial typical migraine: linkage to chromosome 19p13 and evidence for genetic heterogeneity. *Neurology* 50 (1998b) 1428-32.

Nyholt, D.R., Morley, K.I., Ferreira, M.A., Medland, S.E., Boomsma, D.I., Heath, A.C., Merikangas, K.R., Montgomery, G.W. and Martin, N.G.: Genomewide significant linkage to migrainous headache on chromosome 5q21. *Am J Hum Genet* 77 (2005) 500-12.

**O**lesen, J., Friberg, L., Olsen, T.S., Iversen, H.K., Lassen, N.A., Andersen, A.R. and Karle, A.: Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. *Ann Neurol* 28 (1990) 791-8.

Ophoff, R.A., Escamilla, M.A., Service, S.K., Spesny, M., Meshi, D.B., Poon, W., Molina, J., Fournier, E., Gallegos, A., Mathews, C., Neylan, T., Batki, S.L., Roche, E., Ramirez, M., Silva, S., De Mille, M.C., Dong, P., Leon, P.E., Reus, V.I., Sandkuijl, L.A. and Freimer, N.B.: Genomewide linkage disequilibrium mapping of severe bipolar disorder in a population isolate. *Am J Hum Genet* 71 (2002) 565-74.

Ophoff, R.A., Terwindt, G.M., Vergouwe, M.N., van Eijk, R., Oefner, P.J., Hoffman, S.M., Lamerdin, J.E., Mohrenweiser, H.W., Bulman, D.E., Ferrari, M., Haan, J., Lindhout, D., van Ommen, G.J., Hofker, M.H., Ferrari, M.D. and Frants, R.R.: Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca<sup>2+</sup> channel gene CACNL1A4. *Cell* 87 (1996) 543-52.

Ophoff, R.A., van Eijk, R., Sandkuijl, L.A., Terwindt, G.M., Grubben, C.P., Haan, J., Lindhout, D., Ferrari, M.D. and Frants, R.R.: Genetic heterogeneity of familial hemiplegic migraine. *Genomics* 22 (1994) 21-6.

Orlowski, J. and Lingrel, J.B.: Tissue-specific and developmental regulation of rat Na,K-ATPase catalytic alpha isoform and beta subunit mRNAs. *J Biol Chem* 263 (1988) 10436-42.

Oterino, A., Pascual, J., Ruiz de Alegria, C., Valle, N., Castillo, J., Bravo, Y., Gonzalez, F., Sanchez-Velasco, P., Cayon, A., Leyva-Cobian, F., Alonso-Arranz, A. and Munoz, P.: Association of migraine and ESR1 G325C polymorphism. *Neuroreport* 17 (2006) 61-4.

Oterino, A., Ruiz-Alegria, C., Castillo, J., Valle, N., Bravo, Y., Cayon, A., Alonso, A., Tejera, P., Ruiz-Lavilla, N., Munoz, P. and Pascual, J.: GNAS1 T393C polymorphism is associated with migraine. *Cephalgia* 27 (2007) 429-34.

- Oterino, A., Valle, N., Bravo, Y., Munoz, P., Sanchez-Velasco, P., Ruiz-Alegria, C., Castillo, J., Leyva-Cobian, F., Vadillo, A. and Pascual, J.: MTHFR T677 homozygosity influences the presence of aura in migraineurs. *Cephalalgia* 24 (2004) 491-4.
- Ott, J.: Computer-simulation methods in human linkage analysis. *Proc Natl Acad Sci U S A* 86 (1989) 4175-8.
- Overeem, S., van Vliet, J.A., Lammers, G.J., Zitman, F.G., Swaab, D.F. and Ferrari, M.D.: The hypothalamus in episodic brain disorders. *Lancet Neurol* 1 (2002) 437-44.

- P**age, K.M., Heblich, F., Davies, A., Butcher, A.J., Leroy, J., Bertaso, F., Pratt, W.S. and Dolphin, A.C.: Dominant-negative calcium channel suppression by truncated constructs involves a kinase implicated in the unfolded protein response. *J Neurosci* 24 (2004) 5400-9.
- Pajukanta, P., Lilja, H.E., Sinsheimer, J.S., Cantor, R.M., Lusis, A.J., Gentile, M., Duan, X.J., Soro-Paavonen, A., Naukkarinen, J., Saarela, J., Laakso, M., Ehnholm, C., Taskinen, M.R. and Peltonen, L.: Familial combined hyperlipidemia is associated with upstream transcription factor 1 (USF1). *Nat Genet* 36 (2004) 371-6.
- Parker, H.L.: Periodic ataxia. In: Saunders, P.W.B. (Ed.), *Collected Papers of the Mayo Clinic, Philadelphia*, 1946, pp. 642-645.
- Paterna, S., Di Pasquale, P., D'Angelo, A., Seidita, G., Tuttolomondo, A., Cardinale, A., Maniscalchi, T., Follone, G., Giubilato, A., Tarantello, M. and Licata, G.: Angiotensin-converting enzyme gene deletion polymorphism determines an increase in frequency of migraine attacks in patients suffering from migraine without aura. *Eur Neurol* 43 (2000) 133-6.
- Paulson, H.L.: Dominantly inherited ataxias: lessons learned from Machado-Joseph disease/spinocerebellar ataxia type 3. *Semin Neurol* 27 (2007) 133-42.
- Peltonen, L.: GenomEUtwin: a strategy to identify genetic influences on health and disease. *Twin Res* 6 (2003) 354-60.
- Peltonen, L., Palotie, A. and Lange, K.: Use of population isolates for mapping complex traits. *Nat Rev Genet* 1 (2000) 182-90.
- Perez-Reyes, E., Cribbs, L.L., Daud, A., Lacerda, A.E., Barclay, J., Williamson, M.P., Fox, M., Rees, M. and Lee, J.H.: Molecular characterization of a neuronal low-voltage-activated T-type calcium channel. *Nature* 391 (1998) 896-900.
- Pierelli, F., Grieco, G.S., Pauri, F., Pirro, C., Fiermonte, G., Ambrosini, A., Costa, A., Buzzi, M.G., Valoppi, M., Caltagirone, C., Nappi, G. and Santorelli, F.M.: A novel ATP<sub>1</sub>A<sub>2</sub> mutation in a family with FHM type II. *Cephalalgia* 26 (2006) 324-8.
- Pietrobon, D.: Calcium channels and channelopathies of the central nervous system. *Mol Neurobiol* 25 (2002) 31-50.
- Pietrobon, D.: Function and dysfunction of synaptic calcium channels: insights from mouse models. *Curr Opin Neurobiol* 15 (2005) 257-65.
- Pietrobon, D.: Familial hemiplegic migraine. *Neurotherapeutics* 4 (2007) 274-84.
- Pietrobon, D. and Striessnig, J.: Neurobiology of migraine. *Nat Rev Neurosci* 4 (2003) 386-98.
- Pineda, J.C., Waters, R.S. and Foehring, R.C.: Specificity in the interaction of HVA Ca<sub>2+</sub> channel types with Ca<sub>2+</sub>-dependent AHPs and firing behavior in neocortical pyramidal neurons. *J Neurophysiol* 79 (1998) 2522-34.
- Plomp, J.J., Vergouwe, M.N., Van den Maagdenberg, A.M., Ferrari, M.D., Frants, R.R. and Molenaar, P.C.: Abnormal transmitter release at neuromuscular junctions of mice carrying the tottering alpha(1A) Ca(2+) channel mutation. *Brain* 123 Pt 3 (2000) 463-71.
- Pryse-Phillips, W.E., Dodick, D.W., Edmeads, J.G., Gawel, M.J., Nelson, R.F., Purdy, R.A., Robinson, G., Stirling, D. and Worthington, I.: Guidelines for the diagnosis and

- management of migraine in clinical practice. Canadian Headache Society. Cmaj 156 (1997) 1273-87.
- Ptacek, L.J.: The place of migraine as a channelopathy. Curr Opin Neurol 11 (1998) 217-26.
- Ptacek, L.J. and Fu, Y.H.: Channels and disease: past, present, and future. Arch Neurol 61 (2004) 1665-8.
- Ptacek, L.J., George, A.L., Jr., Griggs, R.C., Tawil, R., Kallen, R.G., Barchi, R.L., Robertson, M. and Leppert, M.F.: Identification of a mutation in the gene causing hyperkalemic periodic paralysis. Cell 67 (1991) 1021-7.
- Purves D, A.G., Fitzpatrick D, Katz LC, LaMantia A-S and McNamara JO: Neuroscience. Sunderland, Sinauer Associates, 1997.

**Q**uin, N., Platano, D., Olcese, R., Stefani, E. and Birnbaumer, L.: Direct interaction of gbetagamma with a C-terminal gbetagamma-binding domain of the Ca<sup>2+</sup> channel alpha1 subunit is responsible for channel inhibition by G protein-coupled receptors. Proc Natl Acad Sci U S A 94 (1997) 8866-71.

**R**ainero, I., Fasano, E., Rubino, E., Rivoiro, C., Valfre, W., Gallone, S., Savi, L., Gentile, S., Lo Giudice, R., De Martino, P., Dall'Ombo, A.M. and Pinessi, L.: Association between migraine and HLA-DRB1 gene polymorphisms. J Headache Pain 6 (2005) 185-7.

Rainero, I., Grimaldi, L.M., Salani, G., Valfre, W., Rivoiro, C., Savi, L. and Pinessi, L.: Association between the tumor necrosis factor-alpha -308 G/A gene polymorphism and migraine. Neurology 62 (2004) 141-3.

Reich, D.E. and Lander, E.S.: On the allelic spectrum of human disease. Trends Genet 17 (2001) 502-10.

Rettig, J., Sheng, Z.H., Kim, D.K., Hodson, C.D., Snutch, T.P. and Catterall, W.A.: Isoform-specific interaction of the alpha1A subunits of brain Ca<sup>2+</sup> channels with the presynaptic proteins syntaxin and SNAP-25. Proc Natl Acad Sci U S A 93 (1996) 7363-8.

Riant, F., De Fusco, M., Aridon, P., Ducros, A., Ploton, C., Marchelli, F., Maciazeck, J., Bousser, M.G., Casari, G. and Tournier-Lasserve, E.: ATP1A2 mutations in 11 families with familial hemiplegic migraine. Hum Mutat 26 (2005) 281.

Rindskopf, D. and Rindskopf, W.: The value of latent class analysis in medical diagnosis. Stat Med 5 (1986) 21-7.

Risch, N. and Merikangas, K.: The future of genetic studies of complex human diseases. Science 273 (1996) 1516-7.

Risch, N.J.: Searching for genetic determinants in the new millennium. Nature 405 (2000) 847-56.

Ruiz, C., Gener, B., Garaizar, C. and Prats, J.M.: Episodic spontaneous hypothermia: a periodic childhood syndrome. Pediatr Neurol 28 (2003) 304-6.

Russell, M.B., Hilden, J., Sorensen, S.A. and Olesen, J.: Familial occurrence of migraine without aura and migraine with aura. Neurology 43 (1993) 1369-73.

Russell, M.B., Iselius, L. and Olesen, J.: Inheritance of migraine investigated by complex segregation analysis. Hum Genet 96 (1995a) 726-30.

Russell, M.B. and Olesen, J.: The genetics of migraine without aura and migraine with aura. Cephalgia 13 (1993) 245-8.

Russell, M.B. and Olesen, J.: Increased familial risk and evidence of genetic factor in migraine. Bmj 311 (1995) 541-4.

Russell, M.B. and Olesen, J.: A nosographic analysis of the migraine aura in a general population. Brain 119 (Pt 2) (1996) 355-61.

Russell, M.B., Rasmussen, B.K., Thorvaldsen, P. and Olesen, J.: Prevalence and sex-ratio of the subtypes of migraine. Int J Epidemiol 24 (1995b) 612-8.

Russo, L., Mariotti, P., Sangiorgi, E., Giordano, T., Ricci, I., Lupi, F., Chiera, R., Guzzetta, F., Neri, G. and Gurrieri, F.: A new susceptibility locus for migraine with aura in the 15q11-q13 genomic region containing three GABA-A receptor genes. *Am J Hum Genet* 76 (2005) 327-33.

- S**achidanandam, R., Weissman, D., Schmidt, S.C., Kakol, J.M., Stein, L.D., Marth, G., Sherry, S., Mullikin, J.C., Mortimore, B.J., Willey, D.L., Hunt, S.E., Cole, C.G., Coggill, P.C., Rice, C.M., Ning, Z., Rogers, J., Bentley, D.R., Kwok, P.Y., Mardis, E.R., Yeh, R.T., Schultz, B., Cook, L., Davenport, R., Dante, M., Fulton, L., Hillier, L., Waterston, R.H., McPherson, J.D., Gilman, B., Schaffner, S., Van Etten, W.J., Reich, D., Higgins, J., Daly, M.J., Blumenstiel, B., Baldwin, J., Stange-Thomann, N., Zody, M.C., Linton, L., Lander, E.S. and Altshuler, D.: A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* 409 (2001) 928-33.
- Sander, T., Toliat, M.R., Heils, A., Becker, C. and Nurnberg, P.: Failure to replicate an allelic association between an exon 8 polymorphism of the human alpha(1A) calcium channel gene and common syndromes of idiopathic generalized epilepsy. *Epilepsy Res* 49 (2002) 173-7.
- Sawcer, S.J., Maranian, M., Singlehurst, S., Yeo, T., Compston, A., Daly, M.J., De Jager, P.L., Gabriel, S., Hafler, D.A., Ivinston, A.J., Lander, E.S., Rioux, J.D., Walsh, E., Gregory, S.G., Schmidt, S., Pericak-Vance, M.A., Barcellos, L., Hauser, S.L., Oksenberg, J.R., Kenealy, S.J. and Haines, J.L.: Enhancing linkage analysis of complex disorders: an evaluation of high-density genotyping. *Hum Mol Genet* 13 (2004) 1943-9.
- Scher, A.I., Terwindt, G.M., Verschuren, W.M., Kruit, M.C., Blom, H.J., Kowa, H., Frants, R.R., van den Maagdenberg, A.M., van Buchem, M., Ferrari, M.D. and Launer, L.J.: Migraine and MTHFR C677T genotype in a population-based sample. *Ann Neurol* 59 (2006) 372-5.
- Schols, L., Bauer, P., Schmidt, T., Schulte, T. and Riess, O.: Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. *Lancet Neurol* 3 (2004) 291-304.
- Segall, L., Mezzetti, A., Scanzano, R., Gargus, J.J., Purisima, E. and Blostein, R.: Alterations in the alpha<sub>2</sub> isoform of Na,K-ATPase associated with familial hemiplegic migraine type 2. *Proc Natl Acad Sci U S A* 102 (2005) 11106-11.
- Segall, L., Scanzano, R., Kaunisto, M.A., Weissman, M., Palotie, A., Gargus, J.J. and Blostein, R.: Kinetic alterations due to a missense mutation in the Na,K-ATPase alpha<sub>2</sub> subunit cause familial hemiplegic migraine type 2. *J Biol Chem* 279 (2004) 43692-6.
- Sheffield, V.C., Stone, E.M. and Carmi, R.: Use of isolated inbred human populations for identification of disease genes. *Trends Genet* 14 (1998) 391-6.
- Shull, M.M., Pugh, D.G. and Lingrel, J.B.: Characterization of the human Na,K-ATPase alpha 2 gene and identification of intragenic restriction fragment length polymorphisms. *J Biol Chem* 264 (1989) 17532-43.
- Silberstein S, L.R., Goadby PJ: Headache in Clinical Practice. Oxford, Isis Medical Media, 1998.
- Slager, S.L., Huang, J. and Vieland, V.J.: Effect of allelic heterogeneity on the power of the transmission disequilibrium test. *Genet Epidemiol* 18 (2000) 143-56.
- Snow, V., Weiss, K., Wall, E.M. and Mottur-Pilson, C.: Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med* 137 (2002) 840-9.
- Soragna, D., Vettori, A., Carraro, G., Marchioni, E., Vazza, G., Bellini, S., Tupler, R., Savoldi, F. and Mostacciolo, M.L.: A locus for migraine without aura maps on chromosome 14q21.2-q22.3. *Am J Hum Genet* 72 (2003) 161-7.

- Spacey, S.D., Hildebrand, M.E., Materek, L.A., Bird, T.D. and Snutch, T.P.: Functional implications of a novel EA2 mutation in the P/Q-type calcium channel. *Ann Neurol* 56 (2004) 213-20.
- Spadaro, M., Ursu, S., Lehmann-Horn, F., Liana, V., Giovanni, A., Paola, G., Frontali, M. and Jurkat-Rott, K.: A G301R Na<sup>+</sup>/K<sup>+</sup>-ATPase mutation causes familial hemiplegic migraine type 2 with cerebellar signs. *Neurogenetics* 5 (2004) 177-85.
- Splawski, I., Timothy, K.W., Sharpe, L.M., Decher, N., Kumar, P., Bloise, R., Napolitano, C., Schwartz, P.J., Joseph, R.M., Condouris, K., Tager-Flusberg, H., Priori, S.G., Sanguinetti, M.C. and Keating, M.T.: Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* 119 (2004) 19-31.
- Steinlein, O.K.: Genetic mechanisms that underlie epilepsy. *Nat Rev Neurosci* 5 (2004) 400-8.
- Stotz, S.C. and Zamponi, G.W.: Structural determinants of fast inactivation of high voltage-activated Ca(2+) channels. *Trends Neurosci* 24 (2001) 176-81.
- Stovner, L.J., Zwart, J.A., Hagen, K., Terwindt, G.M. and Pascual, J.: Epidemiology of headache in Europe. *Eur J Neurol* 13 (2006) 333-45.
- Strachan, R.: Human Molecular Genetics. Oxford, BIOS Scientific Publishers Limited, 1996.
- Strassman, A.M., Raymond, S.A. and Burstein, R.: Sensitization of meningeal sensory neurons and the origin of headaches. *Nature* 384 (1996) 560-4.
- Strupp, M., Zwergal, A. and Brandt, T.: Episodic ataxia type 2. *Neurotherapeutics* 4 (2007) 267-73.
- Sutton, K.G., McRory, J.E., Guthrie, H., Murphy, T.H. and Snutch, T.P.: P/Q-type calcium channels mediate the activity-dependent feedback of syntaxin-1A. *Nature* 401 (1999) 800-4.
- Swoboda, K.J., Kanavakis, E., Xaidara, A., Johnson, J.E., Leppert, M.F., Schlesinger-Massart, M.B., Ptacek, L.J., Silver, K. and Youroukos, S.: Alternating hemiplegia of childhood or familial hemiplegic migraine? A novel ATP1A2 mutation. *Ann Neurol* 55 (2004) 884-7.
- Syvanen, A.C.: Accessing genetic variation: genotyping single nucleotide polymorphisms. *Nat Rev Genet* 2 (2001) 930-42.

**T**abor, H.K., Risch, N.J. and Myers, R.M.: Candidate-gene approaches for studying complex genetic traits: practical considerations. *Nat Rev Genet* 3 (2002) 391-7.

Takahashi, T., Igarashi, S., Kimura, T., Hozumi, I., Kawachi, I., Onodera, O., Takano, H., Saito, M. and Tsuji, S.: Japanese cases of familial hemiplegic migraine with cerebellar ataxia carrying a T666M mutation in the CACNA1A gene. *J Neurol Neurosurg Psychiatry* 72 (2002) 676-7.

Takeshima, T., Kusumi, M., Fukuwara, Y., Kowa, H., Adachi, Y. and Nakashima, K.: [An update on the familial headache syndromes]. *Rinsho Shinkeigaku* 44 (2004) 944-7.

Tanabe, T., Takeshima, H., Mikami, A., Flockerzi, V., Takahashi, H., Kangawa, K., Kojima, M., Matsuo, H., Hirose, T. and Numa, S.: Primary structure of the receptor for calcium channel blockers from skeletal muscle. *Nature* 328 (1987) 313-8.

Teh, B.T., Silburn, P., Lindblad, K., Betz, R., Boyle, R., Schalling, M. and Larsson, C.: Familial periodic cerebellar ataxia without myokymia maps to a 19-cM region on 19p13. *Am J Hum Genet* 56 (1995) 1443-9.

Terwilliger, J. and Ott, J.: Handbook of human genetic linkage, 1st ed. ed. The Johns Hopkins University Press, Baltimore, 1994.

Terwilliger, J.D. and Weiss, K.M.: Linkage disequilibrium mapping of complex disease: fantasy or reality? *Curr Opin Biotechnol* 9 (1998) 578-94.

Terwindt, G., Kors, E., Haan, J., Vermeulen, F., Van den Maagdenberg, A., Frants, R. and Ferrari, M.: Mutation analysis of the CACNA1A calcium channel subunit gene in 27 patients with sporadic hemiplegic migraine. *Arch Neurol* 59 (2002) 1016-8.

- Terwindt, G.M., Ophoff, R.A., Haan, J., Vergouwe, M.N., van Eijk, R., Frants, R.R. and Ferrari, M.D.: Variable clinical expression of mutations in the P/Q-type calcium channel gene in familial hemiplegic migraine. Dutch Migraine Genetics Research Group. *Neurology* 50 (1998) 1105-10.
- Terwindt, G.M., Ophoff, R.A., van Eijk, R., Vergouwe, M.N., Haan, J., Frants, R.R., Sandkuijl, L.A. and Ferrari, M.D.: Involvement of the CACNA1A gene containing region on 19p13 in migraine with and without aura. *Neurology* 56 (2001) 1028-32.
- Thomas, P.D. and Kejariwal, A.: Coding single-nucleotide polymorphisms associated with complex vs. Mendelian disease: evolutionary evidence for differences in molecular effects. *Proc Natl Acad Sci U S A* 101 (2004) 15398-403.
- Thomsen, L.L., Eriksen, M.K., Roemer, S.F., Andersen, I., Olesen, J. and Russell, M.B.: A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. *Brain* 125 (2002) 1379-91.
- Thomsen, L.L., Kirchmann, M., Bjornsson, A., Stefansson, H., Jensen, R.M., Fasquel, A.C., Petursson, H., Stefansson, M., Frigge, M.L., Kong, A., Gulcher, J., Stefansson, K. and Olesen, J.: The genetic spectrum of a population-based sample of familial hemiplegic migraine. *Brain* 130 (2007) 346-56.
- Thomsen, L.L., Olesen, J. and Russell, M.B.: Increased risk of migraine with typical aura in probands with familial hemiplegic migraine and their relatives. *Eur J Neurol* 10 (2003) 421-7.
- Thornton-Wells, T.A., Moore, J.H. and Haines, J.L.: Genetics, statistics and human disease: analytical retooling for complexity. *Trends Genet* 20 (2004) 640-7.
- Todt, U., Dichgans, M., Jurkat-Rott, K., Heinze, A., Zifarelli, G., Koenderink, J.B., Goebel, I., Zumbroich, V., Stiller, A., Ramirez, A., Friedrich, T., Gobel, H. and Kubisch, C.: Rare missense variants in ATP1A2 in families with clustering of common forms of migraine. *Hum Mutat* 26 (2005) 315-21.
- Toru, S., Murakoshi, T., Ishikawa, K., Saegusa, H., Fujigasaki, H., Uchihara, T., Nagayama, S., Osanai, M., Mizusawa, H. and Tanabe, T.: Spinocerebellar ataxia type 6 mutation alters P-type calcium channel function. *J Biol Chem* 275 (2000) 10893-8.
- Tottene, A., Fellin, T., Pagnutti, S., Luvisetto, S., Striessnig, J., Fletcher, C. and Pietrobon, D.: Familial hemiplegic migraine mutations increase Ca(2+) influx through single human CaV2.1 channels and decrease maximal CaV2.1 current density in neurons. *Proc Natl Acad Sci U S A* 99 (2002) 13284-9.
- Tottene, A., Pivotto, F., Fellin, T., Cesetti, T., van den Maagdenberg, A.M. and Pietrobon, D.: Specific kinetic alterations of human CaV2.1 calcium channels produced by mutation S218L causing familial hemiplegic migraine and delayed cerebral edema and coma after minor head trauma. *J Biol Chem* 280 (2005) 17678-86.
- Turner, T.J., Adams, M.E. and Dunlap, K.: Calcium channels coupled to glutamate release identified by omega-Aga-IVA. *Science* 258 (1992) 310-3.
- Tzourio, C., Iglesias, S., Hubert, J.B., Visy, J.M., Alperovitch, A., Tehindrazanarivelo, A., Biousse, V., Woimant, F. and Bousser, M.G.: Migraine and risk of ischaemic stroke: a case-control study. *Bmj* 307 (1993) 289-92.
- Tzourio, C., Tehindrazanarivelo, A., Iglesias, S., Alperovitch, A., Chedru, F., d'Anglejan-Chatillon, J. and Bousser, M.G.: Case-control study of migraine and risk of ischaemic stroke in young women. *Bmj* 310 (1995) 830-3.

**U**rich, V., Gervil, M., Fenger, K., Olesen, J. and Russell, M.B.: The prevalence and characteristics of migraine in twins from the general population. *Headache* 39 (1999a) 173-80.

Ulrich, V., Gervil, M., Kyvik, K.O., Olesen, J. and Russell, M.B.: Evidence of a genetic factor in migraine with aura: a population-based Danish twin study. *Ann Neurol* 45 (1999b) 242-6.

Ulrich, V., Russell, M.B., Ostergaard, S. and Olesen, J.: Analysis of 31 families with an apparently autosomal-dominant transmission of migraine with aura in the nuclear family. *Am J Med Genet* 74 (1997) 395-7.

**V**ahedi, K., Joutel, A., Van Bogaert, P., Ducros, A., Maciazeck, J., Bach, J.F., Bousser, M.G. and Tournier-Lasserre, E.: A gene for hereditary paroxysmal cerebellar ataxia maps to chromosome 19p. *Ann Neurol* 37 (1995) 289-93.

van den Maagdenberg, A.M., Pietrobon, D., Pizzorusso, T., Kaja, S., Broos, L.A., Cesetti, T., van de Ven, R.C., Tottene, A., van der Kaa, J., Plomp, J.J., Frants, R.R. and Ferrari, M.D.: A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. *Neuron* 41 (2004) 701-10.

Van den Maagdenberg, K., Claeys, E., Stinckens, A., Buys, N. and De Smet, S.: Differences in proteolytic enzyme activities during growth of the pig with different IGF-II genotypes. *Commun Agric Appl Biol Sci* 69 (2004) 297-300.

Vanmolkot, K.R., Babini, E., de Vries, B., Stam, A.H., Freilinger, T., Terwindt, G.M., Norris, L., Haan, J., Frants, R.R., Ramadan, N.M., Ferrari, M.D., Pusch, M., van den Maagdenberg, A.M. and Dichgans, M.: The novel p.L1649Q mutation in the SCN1A epilepsy gene is associated with familial hemiplegic migraine: genetic and functional studies. *Mutation in brief #957. Online. Hum Mutat* 28 (2007) 522.

Vanmolkot, K.R., Kors, E.E., Hottenga, J.J., Terwindt, G.M., Haan, J., Hoefnagels, W.A., Black, D.F., Sandkuijl, L.A., Frants, R.R., Ferrari, M.D. and van den Maagdenberg, A.M.: Novel mutations in the Na<sup>+</sup>, K<sup>+</sup>-ATPase pump gene ATP1A2 associated with familial hemiplegic migraine and benign familial infantile convulsions. *Ann Neurol* 54 (2003a) 360-6.

Vanmolkot, K.R., Kors, E.E., Turk, U., Turkdogan, D., Keyser, A., Broos, L.A., Kia, S.K., van den Heuvel, J.J., Black, D.F., Haan, J., Frants, R.R., Barone, V., Ferrari, M.D., Casari, G., Koenderink, J.B. and van den Maagdenberg, A.M.: Two de novo mutations in the Na,K-ATPase gene ATP1A2 associated with pure familial hemiplegic migraine. *Eur J Hum Genet* 14 (2006a) 555-60.

Vanmolkot, K.R., Stroink, H., Koenderink, J.B., Kors, E.E., van den Heuvel, J.J., van den Boogerd, E.H., Stam, A.H., Haan, J., De Vries, B.B., Terwindt, G.M., Frants, R.R., Ferrari, M.D. and van den Maagdenberg, A.M.: Severe episodic neurological deficits and permanent mental retardation in a child with a novel FHM2 ATP1A2 mutation. *Ann Neurol* 59 (2006b) 310-4.

Vanmolkot, K.R., van den Maagdenberg, A.M., Haan, J. and Ferrari, M.D.: New discoveries about the second gene for familial hemiplegic migraine, ATP1A2. *Lancet Neurol* 2 (2003b) 721.

Vincent, M. and Hadjikhani, N.: The cerebellum and migraine. *Headache* 47 (2007) 820-33.

von Brederlow, B., Hahn, A.F., Koopman, W.J., Ebers, G.C. and Bulman, D.E.: Mapping the gene for acetazolamide responsive hereditary paroxysmal cerebellar ataxia to chromosome 19p. *Hum Mol Genet* 4 (1995) 279-84.

**W**ada, T., Kobayashi, N., Takahashi, Y., Aoki, T., Watanabe, T. and Saitoh, S.: Wide clinical variability in a family with a CACNA1A T666m mutation: hemiplegic migraine, coma, and progressive ataxia. *Pediatr Neurol* 26 (2002) 47-50.

Wakamori, M., Yamazaki, K., Matsunodaira, H., Teramoto, T., Tanaka, I., Niidome, T., Sawada, K., Nishizawa, Y., Sekiguchi, N., Mori, E., Mori, Y. and Imoto, K.: Single

- tottering mutations responsible for the neuropathic phenotype of the P-type calcium channel. *J Biol Chem* 273 (1998) 34857-67.
- Wan, J., Carr, J.R., Baloh, R.W. and Jen, J.C.: Nonconsensus intronic mutations cause episodic ataxia. *Ann Neurol* 57 (2005a) 131-5.
- Wan, J., Khanna, R., Sandusky, M., Papazian, D.M., Jen, J.C. and Baloh, R.W.: CACNA1A mutations causing episodic and progressive ataxia alter channel trafficking and kinetics. *Neurology* 64 (2005b) 2090-7.
- Wang, Q., Li, L. and Ye, Y.: Regulation of retrotranslocation by p97-associated deubiquitinating enzyme ataxin-3. *J Cell Biol* 174 (2006) 963-71.
- Wappl, E., Koschak, A., Poteser, M., Sinnegger, M.J., Walter, D., Eberhart, A., Groschner, K., Glossmann, H., Kraus, R.L., Grabner, M. and Striessnig, J.: Functional consequences of P/Q-type Ca<sub>2+</sub> channel Cav2.1 missense mutations associated with episodic ataxia type 2 and progressive ataxia. *J Biol Chem* 277 (2002) 6960-6.
- Watts, A.G., Sanchez-Watts, G., Emanuel, J.R. and Levenson, R.: Cell-specific expression of mRNAs encoding Na<sup>+</sup>,K(+)-ATPase alpha- and beta-subunit isoforms within the rat central nervous system. *Proc Natl Acad Sci U S A* 88 (1991) 7425-9.
- Waxman, S.G.: Acquired channelopathies in nerve injury and MS. *Neurology* 56 (2001) 1621-7.
- Weber, J.L.: The Iceland map. *Nat Genet* 31 (2002) 225-6.
- Weeks, D., Ott, J. and Lathrop, G.: SLINK: a general simulation program for linkage analysis. *Am J Hum Genet* (1990) A204 (abstr).
- Weiss, K.M. and Terwilliger, J.D.: How many diseases does it take to map a gene with SNPs? *Nat Genet* 26 (2000) 151-7.
- Welch, K.M., D'Andrea, G., Tepley, N., Barkley, G. and Ramadan, N.M.: The concept of migraine as a state of central neuronal hyperexcitability. *Neurol Clin* 8 (1990) 817-28.
- Wessman, M., Kallela, M., Kaunisto, M.A., Marttila, P., Sobel, E., Hartiala, J., Osowell, G., Leal, S.M., Papp, J.C., Hamalainen, E., Broas, P., Joslyn, G., Hovatta, I., Hiekkalinna, T., Kaprio, J., Ott, J., Cantor, R.M., Zwart, J.A., Ilmavirta, M., Havanka, H., Farkkila, M., Peltonen, L. and Palotie, A.: A susceptibility locus for migraine with aura, on chromosome 4q24. *Am J Hum Genet* 70 (2002) 652-62.
- Wessman, M., Terwindt, G.M., Kaunisto, M.A., Palotie, A. and Ophoff, R.A.: Migraine: a complex genetic disorder. *Lancet Neurol* 6 (2007) 521-32.
- Wieser, T., Mueller, C., Evers, S., Zierz, S. and Deufel, T.: Absence of known familial hemiplegic migraine (FHM) mutations in the CACNA1A gene in patients with common migraine: implications for genetic testing. *Clin Chem Lab Med* 41 (2003) 272-5.
- Wiser, O., Bennett, M.K. and Atlas, D.: Functional interaction of syntaxin and SNAP-25 with voltage-sensitive L- and N-type Ca<sub>2+</sub> channels. *Embo J* 15 (1996) 4100-10.
- Wolff, H.: Headache And Other Head Pain. New York Oxford University Press, 1963.
- Woods, R.P., Iacoboni, M. and Mazziotta, J.C.: Brief report: bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. *N Engl J Med* 331 (1994) 1689-92.
- Wright, A.F., Carothers, A.D. and Pirastu, M.: Population choice in mapping genes for complex diseases. *Nat Genet* 23 (1999) 397-404.

**Y**okoyama, C.T., Sheng, Z.H. and Catterall, W.A.: Phosphorylation of the synaptic protein interaction site on N-type calcium channels inhibits interactions with SNARE proteins. *J Neurosci* 17 (1997) 6929-38.

**Z**amponi, G.W., Bourinet, E., Nelson, D., Nargeot, J. and Snutch, T.P.: Crosstalk between G proteins and protein kinase C mediated by the calcium channel alpha1 subunit. *Nature* 385 (1997) 442-6.

## BIBLIOGRAFIA

Z

- Zasorin, N.L., Baloh, R.W. and Myers, L.B.: Acetazolamide-responsive episodic ataxia syndrome. *Neurology* 33 (1983) 1212-4.
- Zhong, J., Dessauer, C.W., Keef, K.D. and Hume, J.R.: Regulation of L-type Ca<sup>2+</sup> channels in rabbit portal vein by G protein alphas and betagamma subunits. *J Physiol* 517 ( Pt 1) (1999) 109-20.
- Zhuchenko, O., Bailey, J., Bonnen, P., Ashizawa, T., Stockton, D.W., Amos, C., Dobyns, W.B., Subramony, S.H., Zoghbi, H.Y. and Lee, C.C.: Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel. *Nat Genet* 15 (1997) 62-9.