



BÖLÜM 5

MİGRENE NEDEN OLAN MEKANİZMALAR VE PATO FİZYOLOJİLER

Filiz DEMİRDÖĞEN¹

GİRİŞ

Migren; yaygın görülen, meydana gelişi tam olarak açıklanamayan, multifaktöriyel, pirmer baş ağrısıdır. 2018 de Uluslararası Baş ağrısı Derneği (International Hedeache Society-IHS) klasifikasyon komitesi tarafından ICHD-3 olarak sınıflandırılmıştır. Migrenin patofizyolojisi ilgili önemli gelişmeler kaydedilse de fizyolojik, moleküler, anatomik ve genetik temeller hala tam olarak bilinmemektedir. Duyusal trigeminal sinir liflerinden oluşan trigeminovasküler sistemin aktivasyonu, serebral kan damarlarını ve dura materi innerve etmesine bağlı olarak uzun süredir baş ağrısının altında yatan neden olduğu varsayılmıştır (1). Trigeminal sinirin klinik ilişkili bağlantıları özetle şöyle açıklanabilir; Trigeminal afferentler, trigeminal gangliondan (TG) kaynaklanır ve kraniyal yapıları, damarları ve durayı innerve eder. Bu duyusal afferentler, beyin sapı ve üst servikal omurgadaki trigeminoservikal komplekste (TCC) üst servikal dorsal kök ganglionundan (CG) gelen servikal afferentlerle birleşir. İkinci sıra nöronlar, TCC' den talamusa, oradan da talamokortikal nöronların duyusal bilgiyi çoklu kortikal alanlara ilettiği talamusa projekte olur. Rostroventral medulla (RVM), locus coeruleus (LC), periaquaduktal gri alan (periaqueduktal grey: PAG) ve hipotalamik çekirdek-

¹ Uzm. Dr., Mengücek Gazi Eğitim ve Araştırma Hastanesi, fdemirdogen@gmail.com



FHM'ye neden olan ajan olarak tanımlanan ikinci gen, ATP1A2'dir. Bu özel gen, Na⁺/K⁺-ATPase iyon taşıma pompası (α 2 izoformu) katalitik alanını kodlar. Bu alan kalp, iskelet kası ve merkezi sinir sisteminde (CNS) bulunan düz kas hücrelerindeki elektrokimyasal gradientlerin sürdürülmesinden sorumludur (96). Mutasyonlar otozomal dominant kalıtlı ve epilepsi, nöbetler, tekrarlayan koma, ateş ve (76) zekâ geriliği kliniği ile kendini gösterir (97).

FHM ile ilişkili üçüncü mutasyon SCN1A'dır. Bu gen 2q24.3 kromozomunda bulunur ve FHM'den sorumludur. Bu, diğer ikisiyle karşılaştırıldığında nadir bir varyanttır. SCN1A, CNS'de bulunan uyarılabilir zarların geçirgenliğini korumaktan sorumlu olan voltaj kapılı sodyum kanalı Nav1.1 proteinini kodlar (98). SCN1A bölgesindeki mutasyonlar, epilepsi sendromlarında yaygın olarak rapor edilmektedir. Toplu olarak, otozomal dominant bir özellik olarak kalıtılan FHM bozukluğu olan hastalarda 11 mutasyon bildirilmiştir (99).

SONUÇ

Migren multi faktörel bir hastalıktır. Bu neden ile tedavisi planlanırken tüm etmenler iyi araştırılmalıdır. Ek olarak spor, uyku düzeni, beslenme önerilerinde bulunulmalıdır.

KAYNAKLAR

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine – Current Understanding and Treatment. *New England Journal of Medicine*. 2002;346(4): 257–270. doi:10.1056/nejmra010917
2. Moulton EA, Burstein R, Tully S, et al. Interictal dysfunction of a brainstem descending modulatory center in migraine patients. *PLoS ONE*. 2008;3(11): 1–5. doi:10.1371/journal.pone.0003799
3. Eftekhari S, Warfvinge K, Blixt F, et al. Differentiation of nerve fibers storing CGRP and CGRP receptors in the peripheral trigeminovascular system. *The Journal of Headache and Pain*. 2013;14(S1): 2013. doi:10.1186/1129-2377-14-s1-p89
4. May A. Morphing voxels: The hype around structural imaging of headache patients. *Brain*. 2009;132(6): 1419–1425. doi:10.1093/brain/awp116
5. Dai Z, Zhong J, Xiao P, et al. Gray matter correlates of migraine and gender effect: A meta-analysis of voxel-based morphometry studies. *Neuroscience*. IBRO; 2015;299: 88–96. doi:10.1016/j.neuroscience.2015.04.066
6. Jia Z, Yu S. Grey matter alterations in migraine: A systematic review and meta-analysis. *NeuroImage: Clinical*. The Authors; 2017;14: 130–140. doi:10.1016/j.nicl.2017.01.019
7. Hu W, Guo J, Chen N, et al. A meta-analysis of voxel-based morphometric studies on migraine. *International Journal of Clinical and Experimental Medicine*. 2015;8(3): 4311–4319. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4443181/pdf/ijcem0008-4311>.



pdf

8. Sheng LQ, Zhao PW, Ma HR, et al. A lack of consistent brain grey matter alterations in migraine. *Brain*. 2020;143(6): e45. doi:10.1093/brain/awaa123
9. Hansen JM, Goadsby PJ, Charles AC. Variability of clinical features in attacks of migraine with aura. *Cephalalgia* 2016;36(3):216–224. doi:10.1177/0333102415584601
10. Viana M, Sances G, Ghiotto N, et al. Variability of the characteristics of a migraine attack within patients. *Cephalalgia* 2016;36(9):825–830. doi:10.1177/0333102415613612
11. Quintela E, Castillo J, Muñoz P, et al. Premonitory and resolution symptoms in migraine: A prospective study in 100 unselected patients. *Cephalalgia*. 2006;26(9): 1051–1060. doi:10.1111/j.1468-2982.2006.01157.x
12. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: An electronic diary study. *Neurology*. 2003;60(6): 935–940. doi:10.1212/01.WNL.0000052998.58526.A9
13. Karsan N, Goadsby PJ. Biological insights from the premonitory symptoms of migraine. *Nature Reviews Neurology*. Springer US; 2018;14(12): 699–710. doi:10.1038/s41582-018-0098-4
14. Denuelle M, Fabre N, Payoux P, et al. Hypothalamic activation in spontaneous migraine attacks. *Headache*. 2007;47(10): 1418–1426. doi:10.1111/j.1526-4610.2007.00776.x
15. Meylakh N, Marciszewski KK, Di Pietro F, et al. Deep in the brain: Changes in subcortical function immediately preceding a migraine attack. *Human Brain Mapping*. 2018;39(6): 2651–2663. doi:10.1002/hbm.24030
16. Schulte LH, May A. The migraine generator revisited: Continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain*. 2016;139(7): 1987–1993. doi:10.1093/brain/aww097
17. Maniyar FH, Sprenger T, Monteith T, et al. The premonitory phase of migraine - What can we learn from it? *Headache*. 2015;55(5): 609–620. doi:10.1111/head.12572
18. Sand T, Zhitniy N, White LR, et al. Visual evoked potential latency, amplitude and habituation in migraine: A longitudinal study. *Clinical Neurophysiology*. 2008;119(5): 1020–1027. doi:10.1016/j.clinph.2008.01.009
19. Kaube H, Keay KA, Hoskin KL, et al. Expression of c-Fos-like immunoreactivity in the caudal medulla and upper cervical spinal cord following stimulation of the superior sagittal sinus in the cat. *Brain Research*. Elsevier; 1993;629(1): 95–102. doi:10.1016/0006-8993(93)90486-7
20. Hoskin KL, Lambert GA, Donaldson C, et al. The 5-hydroxytryptamine1B/1D/1F receptor agonists eletriptan and naratriptan inhibit trigeminovascular input to the nucleus tractus solitarius in the cat. *Brain Research*. 2004;998(1): 91–99. doi:10.1016/j.brainres.2003.11.018
21. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. *Nature Reviews Neuroscience*. Nature Publishing Group; 2011;12(10): 570–584. doi:10.1038/nrn3057
22. Goadsby PJ, Holland PR. An Update: Pathophysiology of Migraine. 2019;37(4): 651–671
23. Ashina M, Katsarava Z, Do TP, et al. Migraine: epidemiology and systems of care. *The Lancet*. 2021;397(10283): 1485–1495. doi:10.1016/S0140-6736(20)32160-7
24. Russell MB, Iversen HK, Olesen J. Improved description of the migraine aura by a diagnostic aura diary. *Cephalalgia*. 1994;14(2): 107–117
25. Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proceedings of the National Academy of Sciences*



- of the United States of America. 2001;98(8): 4687–4692. doi:10.1073/pnas.071582498
26. Leao AAP. Further observations on the spreading depression of activity in the cerebral cortex. *J Neurophysiol* 1947;10(6):409–414. doi:10.1152/jn.1947.10.6.409
 27. Leao, A.A.P. Spreading depression of activity in the cerebral cortex. *J. Neurophysiol.* 1944, 7, 359–390
 28. Sugaya, E.; Takato, M.; Noda, Y. Neuronal and glial activity during spreading depression in cerebral cortex of cat. *J. Neurophysiol.* 1975, 38, 822–841
 29. Kraig, R.P.; Nicholson, C. Extracellular ionic variations during spreading depression. *Neuroscience* 1978, 3, 1045–1059
 30. Tozzi A, De Iure A, Di Filippo M, et al. Critical role of calcitonin gene-related peptide receptors in cortical spreading depression. *Proceedings of the National Academy of Sciences of the United States of America.* 2012;109(46): 18985–18990. doi:10.1073/pnas.1215435109
 31. Olesen J, Diener H-C, Husstedt IW, et al. Calcitonin Gene-Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine. *New England Journal of Medicine.* 2004;350(11): 1104–1110. doi:10.1056/nejmoa030505
 32. Dodick DW, Goadsby PJ, Silberstein SD, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: A randomised, double-blind, placebo-controlled, exploratory phase 2 trial. *The Lancet Neurology.* Elsevier Ltd; 2014;13(11): 1100–1107. doi:10.1016/S1474-4422(14)70209-1
 33. Dodick DW, Goadsby PJ, Spierings ELH, et al. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: A phase 2, randomised, double-blind, placebo-controlled study. *The Lancet Neurology.* Elsevier Ltd; 2014;13(9): 885–892. doi:10.1016/S1474-4422(14)70128-0
 34. Dohmen C, Sakowitz OW, Fabricius M, et al. Spreading depolarizations occur in human ischemic stroke with high incidence. *Annals of Neurology.* 2008;63(6): 720–728. doi:10.1002/ana.21390
 35. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: Results of the American Migraine prevalence and prevention (AMPP) study. *Headache.* 2013;53(8): 1278–1299. doi:10.1111/head.12150
 36. Ashina H, Iljazi A, Al-Khazali HM, et al. Hypersensitivity to Calcitonin Gene-Related Peptide in Post-Traumatic Headache. *Annals of Neurology.* 2020;88(6): 1220–1228. doi:10.1002/ana.25915
 37. Yiangou A, Mitchell JL, Fisher C, et al. Erenumab for headaches in idiopathic intracranial hypertension: A prospective open-label evaluation. *Headache.* 2021;61(1): 157–169. doi:10.1111/head.14026
 38. Yiangou A, Mitchell JL, Vijay V, et al. Calcitonin gene related peptide monoclonal antibody treats headache in patients with active idiopathic intracranial hypertension. *Journal of Headache and Pain.* The Journal of Headache and Pain; 2020;21(1): 1–8. doi:10.1186/s10194-020-01182-7
 39. Ashina H, Moskowitz MA. Shared biological foundations of post-traumatic headache and migraine. *Headache.* 2021;61(3): 558–559. doi:10.1111/head.14084
 40. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38(1):1–211. doi:10.1177/0333102417738202
 41. Goadsby PJ, Holland PR, Martins-Oliveira M, et al. Pathophysiology of migraine: A disorder



- der of sensory processing. *Physiological Reviews*. 2017;97(2): 553–622. doi:10.1152/physrev.00034.2015
42. Olesen J, Burstein R, Ashina M, et al. Origin of pain in migraine: evidence for peripheral sensitisation. *The Lancet Neurology*. Elsevier Ltd; 2009;8(7): 679–690. doi:10.1016/S1474-4422(09)70090-0
 43. Rodriguez E, Sakurai K, Xu J, et al. A craniofacial-specific monosynaptic circuit enables heightened affective pain. *Nature Neuroscience*. 2017;20(12): 1734–1743. doi:10.1038/s41593-018-0103-7
 44. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. *Annu Rev Physiol* 2013;75:365–391. doi:10.1146/annurev-physiol-030212-183717
 45. Stankewitz A, Aderjan D, Eippert F, et al. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. *Journal of Neuroscience*. 2011;31(6): 1937–1943. doi:10.1523/JNEUROSCI.4496-10.2011
 46. Mo J, Maizels M, Ding M, Ahn AH. Does throbbing pain have a brain signature? *Pain* 2013;154(7):1150–1155. doi:10.1016/j.pain.2013.02.013
 47. Lipton RB, Buse DC, Saiers J, et al. Frequency and burden of headache-related nausea: Results from the american migraine prevalence and prevention (AMPP) study. *Headache*. 2013;53(1): 93–103. doi:10.1111/j.1526-4610.2012.02292.x
 48. Maniyar FH, Sprenger T, Schankin C, et al. The origin of nausea in migraine—A PET study. *Journal of Headache and Pain*. 2014;15(1): 1–6. doi:10.1186/1129-2377-15-84
 49. Giffin NJ, Lipton RB, Silberstein SD, et al. The migraine prodrome. *Neurology* ®. 2016;87(3): 309–313
 50. Peng KP, May A. Redefining migraine phases – a suggestion based on clinical, physiological, and functional imaging evidence. *Cephalalgia*. 2020;40(8): 866–870. doi:10.1177/0333102419898868
 51. Martins IP, Westerfield M, Lopes M, et al. Brain state monitoring for the future prediction of migraine attacks. *Cephalalgia* 2020;40(3):255–265. doi:10.1177/0333102419877660
 52. McKendrick AM, Chan YM, Vingrys AJ, et al. Daily vision testing can expose the prodromal phase of migraine. *Cephalalgia* 2018;38(9):1575–1584. doi:10.1177/0333102417741130
 53. Skorobogatikh K, Van Hoogstraten WS, Degan D, et al. Functional connectivity studies in migraine: What have we learned? *Journal of Headache and Pain*. The Journal of Headache and Pain; 2019;20(1). doi:10.1186/s10194-019-1047-3
 54. Xue T, Yuan K, Cheng P, et al. Alterations of regional spontaneous neuronal activity and corresponding brain circuit changes during resting state in migraine without aura. *NMR in Biomedicine*. 2013;26(9): 1051–1058. doi:10.1002/nbm.2917
 55. Amin FM, Hougaard A, Magon S, et al. Altered thalamic connectivity during spontaneous attacks of migraine without aura: a resting-state fMRI study. *Cephalalgia* 2018;38(7):1237–1244. doi:10.1177/0333102417729113
 56. Moulton EA, Becerra L, Johnson A, et al. Altered hypothalamic functional connectivity with autonomic circuits and the locus coeruleus in migraine. *PLoS ONE*. 2014;9(4). doi:10.1371/journal.pone.0095508
 57. Chen Z, Chen X, Liu M, et al. Altered functional connectivity of amygdala underlying the neuromechanism of migraine pathogenesis. *Journal of Headache and Pain*. The Journal of Headache and Pain; 2017;18(1): 1–8. doi:10.1186/s10194-017-0722-5
 58. Jin C, Yuan K, Zhao L, et al. Structural and functional abnormalities in migraine patients without aura. *NMR in Biomedicine*. 2013;26(1): 58–64. doi:10.1002/nbm.2819
 59. Strupf M, Fraunberger B, Messlinger K, Namer B. Cyclic changes in sensati-



- ons to painful stimuli in migraine patients. *Cephalalgia* 2019;39(5):585–596. doi:10.1177/0333102418793641
60. Wattiez AS, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): Role in migraine pathophysiology and therapeutic targeting. *Expert Opin Ther Targets*. 2020;24(2): 91–100. doi:10.1080/14728222.2020.1724285
61. Close LN, Eftekhari S, Wang M, et al. Cortical spreading depression as a site of origin for migraine: Role of CGRP. 2019;39(3): 428–434. doi:10.1177/0333102418774299
62. Recober A, Kuburas A, Zhang Z, et al. Role of calcitonin gene-related peptide in light-averse behavior: Implications for migraine. *Journal of Neuroscience*. 2009;29(27): 8798–8804. doi:10.1523/JNEUROSCI.1727-09.2009
63. Kaiser EA, Rea BJ, Kuburas A, et al. Anti-CGRP antibodies block CGRP-induced diarrhea in mice. *Neuropeptides*. Elsevier Ltd; 2017;64: 95–99. doi:10.1016/j.npep.2016.11.004
64. Edvinsson L, Tajti J, Szalárdy L, et al. PACAP and its role in primary headaches. *Journal of Headache and Pain*. The Journal of Headache and Pain; 2018;19(1): 10194-018-0852–0854. doi:10.1186/s10194-018-0852-4
65. Villalón CM, VanDenBrink AM. The role of 5-hydroxytryptamine in the pathophysiology of migraine and its relevance to the design of novel treatments. *Mini Rev Med Chem* 2017;17(11):928–938. doi:10.2174/13895575166661607281210 50
66. Bartsch T, Levy MJ, Knight YE, et al. Differential modulation of nociceptive dural input to [hypocretin] orexin A and B receptor activation in the posterior hypothalamic area. *Pain*. 2004;109(3): 367–378. doi:10.1016/j.pain.2004.02.005
67. Biswas SK. Does the Interdependence between Oxidative Stress and Inflammation Explain the Antioxidant Paradox? *Oxidative Medicine and Cellular Longevity*. Hindawi Publishing Corporation; 2016;2016: 1–9. doi:10.1155/2016/5698931
68. Yildirim S, Akar S, Kuyucu M, et al. Paraoxonase 1 gene polymorphisms, paraoxonase/ arylesterase activities and oxidized low-density lipoprotein levels in patients with migraine. *Cell Biochemistry and Function*. 2011;29(7): 549–554. doi:10.1002/cbf.1785
69. Borkum JM. The Migraine Attack as a Homeostatic, Neuroprotective Response to Brain Oxidative Stress: Preliminary Evidence for a Theory. *Headache*. 2018;58(1): 118–135. doi:10.1111/head.13214
70. Ghosh J, Joshi G, Pradhan S, et al. Investigation of TNFA 308G > A and TNFB 252G > A polymorphisms in genetic susceptibility to migraine. *Journal of Neurology*. 2010;257(6): 898–904. doi:10.1007/s00415-009-5430-x
71. Yilmaz Avci A, Akkucuk MH, Torun E, et al. Migraine and subclinical atherosclerosis: endothelial dysfunction biomarkers and carotid intima-media thickness: a case-control study. *Neurological Sciences*. Neurological Sciences; 2019;40(4): 703–711. doi:10.1007/s10072-019-3710-5
72. Empl M, Sostak P, Breckner M, et al. T-cell subsets and expression of integrins in peripheral blood of patients with migraine. *Cephalalgia*. 1999 Oct; 19(8):713-7; discussion 697
73. Zeller JA, Frahm K, Baron R, et al. Platelet-leukocyte interaction and platelet activation in migraine: A link to ischemic stroke? *Journal of Neurology, Neurosurgery and Psychiatry*. 2004;75(7): 984–987. doi:10.1136/jnnp.2003.019638
74. Tietjen GE, Khubchandani J. Platelet dysfunction and stroke in the female migraineur. *Current Pain and Headache Reports*. 2009;13(5): 386–391. doi:10.1007/s11916-009-0063-4
75. Gabrielli M, Santarelli L, Addolorato G, et al. High prevalence of antiendothelial cell antibodies in migraine [1]. *Headache*. 2002;42(5): 385–386. doi:10.1046/j.1526-



- 4610.2002.02114.x
76. Peroutka SJ. Neurogenic inflammation and migraine: Implications for therapeutics. *Molecular Interventions*. 2005;5(5): 304–311. doi:10.1124/mi.5.5.10
 77. Mason BN, Russo AF. Vascular contributions to migraine: Time to revisit? *Frontiers in Cellular Neuroscience*. 2018;12(August): 1–10. doi:10.3389/fncel.2018.00233
 78. Yücel M, Kotan D, Guroł Çiftçi G, Çiftçi IH CH. Serum levels of endocan, claudin-5 and cytokines in migraine. *Eur Rev Med Pharmacol*. 2016;20: 930–936
 79. Oterino A, Toriello M, Valle N, et al. The relationship between homocysteine and genes of folate-related enzymes in migraine patients. *Headache*. 2010;50(1): 99–168. doi:10.1111/j.1526-4610.2009.01484.x
 80. Michalak S, Kalinowska-Lyszczarz A, Wegrzyn D, et al. The Levels of Circulating Pro-angiogenic Factors in Migraineurs. *NeuroMolecular Medicine*. Springer US; 2017;19(4): 510–517. doi:10.1007/s12017-017-8465-7
 81. Rodríguez-Osorio X, Sobrino T, Brea D, et al. Endothelial progenitor cells: a new key for endothelial dysfunction in migraine. *Neurology*. 2012 Jul 31; 79(5):474-9
 82. Tietjen GE. Migraine as a systemic vasculopathy. *Cephalalgia*. 2009 Sep;29(9):987-96. doi: 10.1111/j.1468-2982.2009.01937.x. PMID: 19689607
 83. Iljazi A, Ayata C, Ashina M, et al. The Role of Endothelin in the Pathophysiology of Migraine—a Systematic Review. *Current Pain and Headache Reports*. 2018;22(4): 1–9. doi:10.1007/s11916-018-0682-8
 84. Tietjen GE, Al-Qasbi MM, Athanas K, et al. Increased von Willebrand factor in migraine. *Neurology*. 2001;57:334–336
 85. Cesar JM, García-Avello A, Vecino AM, et al. Increased levels of plasma von Willebrand factor in migraine crisis. *Acta Neurol Scand*. 1995;91:412–413
 86. Tietjen GE, Herial NA, Utley C, et al. Association of von Willebrand factor activity with ACE I/D and MTHFR C677T polymorphisms in migraine. *Cephalalgia*. 2009;29:960–968
 87. Tietjen GE, Khubchandani J, Herial N, Palm-Meinders IH, Koppen H TG et al. Migraine and vascular disease biomarkers: a population-based case-control study. *Physiology & behavior*. 2018;38(3): 511–518. doi:10.1177/0333102417698936.Migraine
 88. Mulder EJ, Van Baal C, Gaist D, et al. Genetic and Environmental Influences on Migraine: A Twin Study Across Six Countries. *Twin Research*. 2003;6(5): 422–431. doi:10.1375/136905203770326420
 89. Sutherland HG, Albury CL, Griffiths LR. Advances in genetics of migraine. *Journal of Headache and Pain*. The Journal of Headache and Pain; 2019;20(1): 1–20. doi:10.1186/s10194-019-1017-9
 90. Thomsen LL, Eriksen MK, Romer SF, et al. An epidemiological survey of hemiplegic migraine. *Cephalalgia*. 2002;22(5): 361–375. doi:10.1046/j.1468-2982.2002.00371.x
 91. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca²⁺ channel gene CACNL1A4. *Cell*. 1996;87(3): 543–552. doi:10.1016/S0092-8674(00)81373-2
 92. Grieco GS, Gagliardi S, Ricca I, et al. New CACNA1A deletions are associated to migraine phenotypes. *Journal of Headache and Pain*. The Journal of Headache and Pain; 2018;19(1): 1–6. doi:10.1186/s10194-018-0891-x
 93. Pereira M da C, Morais S, Sequeiros J, et al. Large-scale functional RNAi Screen in *C. elegans* identifies TGF- β and notch signaling pathways as modifiers of CACNA1A. *ASN Neuro*. 2016;8(2): 1–10. doi:10.1177/1759091416637025
 94. Di Lorenzo C, Grieco GS, Santorelli FM. Migraine headache: A review of the molecular



- genetics of a common disorder. *Journal of Headache and Pain*. 2012;13(7): 571–580. doi:10.1007/s10194-012-0478-x
95. Blumenfeld AE, Victorio MC, Berenson FR. Complicated Migraines. *Seminars in Pediatric Neurology*. Elsevier; 2016;23(1): 18–22. doi:10.1016/j.spen.2016.01.007
96. Friedrich T, Tavrız NN, Junghans C. ATP1A2 mutations in migraine: Seeing through the facets of an ion pump onto the neurobiology of disease. *Frontiers in Physiology*. 2016;7(JUN): 1–21. doi:10.3389/fphys.2016.00239
97. N. Pelzer, D. Blom, A. Stam, L. et al. Recurrent coma and fever in familial hemiplegic migraine type 2. A prospective 15-year follow-up of a large family with a novel ATP1A2 mutation. *Cephalalgia*, 37 (2017), pp. 737-755
98. Dichgans M, Freilinger T, Eckstein G, et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. *Lancet*. 2005;366(9483): 371–377. doi:10.1016/S0140-6736(05)66786-4
99. H.G. Sutherland, C.L. Albury, L.R. Griffiths. Advances in genetics of migraine. *J. Headache Pain*, 20 (2019), p. 72