

# Publications arising from this work

Coffey AJ, Kokocinski F, **Calafato MS**, Scott CE, Palta P, Drury E, Joyce CJ, Leproust EM, Harrow J, Hunt S, Lehesjoki AE, Turner DJ, Hubbard TJ, Palotie A. *The GENCODE exome: sequencing the complete human exome*. Eur J Hum Genet. 2011 Jul;19(7):827-31.

Anttila V, Stefansson H, Kallela M, Todt U, Terwindt GM, **Calafato MS**, Nyholt DR, Dimas AS, Freilinger T, Mller-Myhsok B, Artto V, Inouye M, Alakurtti K, Kaunisto MA, Hamalainen E, de Vries B, Stam AH, Weller CM, Heinze A, Heinze-Kuhn K, Goebel I, Borck G, Gbel H, Steinberg S, Wolf C, Bjrnsson A, Gudmundsson G, Kirchmann M, Hauge A, Werge T, Schoenen J, Eriksson JG, Hagen K, Stovner L, Wichmann HE, Meitinger T, Alexander M, Moebus S, Schreiber S, Aulchenko YS, Breteler MM, Uitterlinden AG, Hofman A, van Duijn CM, Tikka-Kleemola P, Vepslinen S, Lucae S, Tozzi F, Muglia P, Barrett J, Kaprio J, Frkkil M, Peltonen L, Stefansson K, Zwart JA, Ferrari MD, Olesen J, Daly M, Wessman M, van den Maagdenberg AM, Dichgans M, Kubisch C, Dermitzakis ET, Frants RR, Palotie A; International Headache Genetics Consortium. *Genome-wide as-*

*sociation study of migraine implicates a common susceptibility variant on 8q22.1.*

Nat Genet. 2010 Oct;42(10):869-73.

# Bibliography

- [1] P. D. Turnpenny, *Emery's Elements of Medical Genetics, chapter 2*. Churchill Livingstone, 2007.
- [2] L. Kruglyak and D. A. Nickerson, "Variation is the spice of life," *Nat Genet*, vol. 27, no. 3, pp. 234–6, 2001.
- [3] International HapMap Consortium, "Finishing the euchromatic sequence of the human genome," *Nature*, vol. 431, no. 7011, pp. 931–45, 2004. International Human Genome Sequencing Consortium.
- [4] International HapMap Consortium, "A map of human genome variation from population-scale sequencing," *Lancet*, vol. 377, no. 9766, pp. 641–649, 2011. International Parkinson Disease Genomics Consortium.
- [5] K. A. Frazer, S. S. Murray, N. J. Schork, and E. J. Topol, "Human genetic variation and its contribution to complex traits," *Nat Rev Genet*, vol. 10, no. 4, pp. 241–51, 2009.
- [6] International HapMap Consortium, "A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms.," *Nature*,

- vol. 409, no. 6822, pp. 928–933, 2001. International SNP Map Working Group.
- [7] International HapMap Consortium, “The international hapmap project,” *Nature*, vol. 426, no. 6968, pp. 789–96, 2003. International HapMap Consortium.
- [8] International HapMap Consortium, “A haplotype map of the human genome,” *Nature*, vol. 437, no. 7063, pp. 1299–320, 2005. International HapMap Consortium.
- [9] International HapMap Consortium, “A second generation human haplotype map of over 3.1 million snps,” *Nature*, vol. 449, no. 7164, pp. 851–861, 2007. International HapMap Consortium.
- [10] 1000 Genomes Project Consortium, “A map of human genome variation from population-scale sequencing,” *Nature*, vol. 467, no. 7319, pp. 1061–73, 2010. 1000 Genomes Project Consortium.
- [11] K. A. Frazer, D. G. Ballinger, D. R. Cox, D. A. Hinds, L. L. Stuve, R. A. Gibbs, J. W. Belmont, A. Boudreau, P. Hardenbol, S. M. Leal, S. Pasternak, D. A. Wheeler, T. D. Willis, F. Yu, H. Yang, C. Zeng, Y. Gao, H. Hu, W. Hu, C. Li, W. Lin, S. Liu, H. Pan, X. Tang, J. Wang, W. Wang, J. Yu, B. Zhang, Q. Zhang, H. Zhao, H. Zhao, J. Zhou, S. B. Gabriel, R. Barry, B. Blumenstiel, A. Camargo, M. Defelice, M. Faggart, M. Goyette, S. Gupta, J. Moore, H. Nguyen, R. C. Onofrio, M. Parkin, J. Roy, E. Stahl, E. Winchester, L. Ziaugra, D. Altshuler, Y. Shen, Z. Yao, W. Huang, X. Chu, Y. He, L. Jin, Y. Liu, Y. Shen, W. Sun, H. Wang, Y. Wang, Y. Wang, X. Xiong, L. Xu,

- M. M. Waye, S. K. Tsui, H. Xue, J. T. Wong, L. M. Galver, J. B. Fan, K. Gunderson, S. S. Murray, A. R. Oliphant, M. S. Chee, A. Montpetit, F. Chagnon, V. Ferretti, M. Leboeuf, J. F. Olivier, M. S. Phillips, S. Roumy, C. Sallee, A. Verner, T. J. Hudson, P. Y. Kwok, D. Cai, D. C. Koboldt, R. D. Miller, L. Pawlikowska, P. Taillon-Miller, M. Xiao, L. C. Tsui, W. Mak, Y. Q. Song, P. K. Tam, Y. Nakamura, T. Kawaguchi, T. Kitamoto, T. Morizono, A. Nagashima, Y. Ohnishi, *et al.*, “A second generation human haplotype map of over 3.1 million snps,” *Nature*, vol. 449, no. 7164, pp. 851–61, 2007.
- [12] L. Feuk, A. R. Carson, and S. W. Scherer, “Structural variation in the human genome,” *Nat Rev Genet*, vol. 7, no. 2, pp. 85–97, 2006.
- [13] R. Mills, K. Walter, and . G. Project., “Mapping copy number variation by population-scale genome sequencing,” *Nature*, vol. 470, no. 7332, pp. 59–65, 2011.
- [14] P. D. Turnpenny, *Emery’s Elements of Medical Genetics, chapter 23*. Churchill Livingstone, 2007.
- [15] P. Deloukas, G. D. Schuler, G. Gyapay, E. M. Beasley, C. Soderlund, P. Rodriguez-Tome, L. Hui, T. C. Matise, K. B. McKusick, J. S. Beckmann, S. Bentolila, M. Bihoreau, B. B. Birren, J. Browne, A. Butler, A. B. Castle, N. Chiannikulchai, C. Clee, P. J. Day, A. Dehejia, T. Dibling, N. Drouot, S. Duprat, C. Fizames, S. Fox, S. Gelling, L. Green, P. Harrison, R. Hocking, E. Holloway, S. Hunt, S. Keil, P. Lijnzaad, C. Louis-Dit-Sully, J. Ma, A. Mendis, J. Miller, J. Morissette, D. Muselet, H. C. Nusbaum, A. Peck, S. Rozen, D. Simon, D. K. Slonim, R. Staples, L. D. Stein, E. A. Stew-

art, M. A. Suchard, T. Thangarajah, N. Vega-Czarny, C. Webber, X. Wu, J. Hudson, C. Auffray, N. Nomura, J. M. Sikela, M. H. Polymeropoulos, M. R. James, E. S. Lander, T. J. Hudson, R. M. Myers, D. R. Cox, J. Weissenbach, M. S. Boguski, and D. R. Bentley, “A physical map of 30,000 human genes,” *Science*, vol. 282, no. 5389, pp. 744–6, 1998.

- [16] M. Olivier, A. Aggarwal, J. Allen, A. A. Almendras, E. S. Bajorek, E. M. Beasley, S. D. Brady, J. M. Bushard, V. I. Bustos, A. Chu, T. R. Chung, A. De Witte, M. E. Denys, R. Dominguez, N. Y. Fang, B. D. Foster, R. W. Freudenberg, D. Hadley, L. R. Hamilton, T. J. Jeffrey, L. Kelly, L. Lazzeroni, M. R. Levy, S. C. Lewis, X. Liu, F. J. Lopez, B. Louie, J. P. Marquis, R. A. Martinez, M. K. Matsuura, N. S. Misherghi, J. A. Norton, A. Olshen, S. M. Perkins, A. J. Perou, C. Piercy, M. Piercy, F. Qin, T. Reif, K. Sheppard, V. Shokoohi, G. A. Smick, W. L. Sun, E. A. Stewart, J. Fernando, Tejada, N. M. Tran, T. Trejo, N. T. Vo, S. C. Yan, D. L. Zierten, S. Zhao, R. Sachidanandam, B. J. Trask, R. M. Myers, and D. R. Cox, “A high-resolution radiation hybrid map of the human genome draft sequence,” *Science*, vol. 291, no. 5507, pp. 1298–302, 2001.

- [17] E. S. Lander, L. M. Linton, B. Birren, C. Nusbaum, M. C. Zody, J. Baldwin, K. Devon, K. Dewar, M. Doyle, W. FitzHugh, R. Funke, D. Gage, K. Harris, A. Heaford, J. Howland, L. Kann, J. Lehoczkzy, R. LeVine, P. McEwan, K. McKernan, J. Meldrim, J. P. Mesirov, C. Miranda, W. Morris, J. Naylor, C. Raymond, M. Rosetti, R. Santos, A. Sheridan, C. Sougnez, N. Stange-Thomann, N. Stojanovic, A. Subramanian, D. Wyman, J. Rogers, J. Sulston, R. Ainscough, S. Beck, D. Bentley, J. Burton, C. Clee, N. Carter, A. Coulson,

R. Deadman, P. Deloukas, A. Dunham, I. Dunham, R. Durbin, L. French, D. Grafham, S. Gregory, T. Hubbard, S. Humphray, A. Hunt, M. Jones, C. Lloyd, A. McMurray, L. Matthews, S. Mercer, S. Milne, J. C. Mullikin, A. Mungall, R. Plumb, M. Ross, R. Shownkeen, S. Sims, R. H. Waterston, R. K. Wilson, L. W. Hillier, J. D. McPherson, M. A. Marra, E. R. Mardis, L. A. Fulton, A. T. Chinwalla, K. H. Pepin, W. R. Gish, S. L. Chissoe, M. C. Wendl, K. D. Delehaunty, T. L. Miner, A. Delehaunty, J. B. Kramer, L. L. Cook, R. S. Fulton, D. L. Johnson, P. J. Minx, S. W. Clifton, T. Hawkins, E. Branscomb, P. Predki, P. Richardson, S. Wenning, T. Slezak, N. Doggett, J. F. Cheng, A. Olsen, S. Lucas, C. Elkin, E. Uberbacher, M. Frazier, *et al.*, “Initial sequencing and analysis of the human genome,” *Nature*, vol. 409, no. 6822, pp. 860–921, 2001.

[18] R. M. Myers, J. Stamatoyannopoulos, M. Snyder, I. Dunham, R. C. Hardison, B. E. Bernstein, T. R. Gingeras, W. J. Kent, E. Birney, B. Wold, and G. E. Crawford, “A user’s guide to the encyclopedia of dna elements (encode),” *PLoS Biol*, vol. 9, no. 4, p. e1001046, 2011.

[19] International HapMap Consortium, “Integrating common and rare genetic variation in diverse human populations,” *Nature*, vol. 467, no. 1038, pp. 52–58, 2010. International HapMap Consortium.

[20] P. R. Burton, M. D. Tobin, and J. L. Hopper, “Key concepts in genetic epidemiology,” *Lancet*, vol. 366, no. 9489, pp. 941–51, 2005.

[21] P. D. Turnpenny, *Emery’s Elements of Medical Genetics, chapter 9*. Churchill Livingstone, 2007.

- [22] D. Clayton, “Prediction and interaction in complex disease genetics: experience in type 1 diabetes.,” *PLoS Genet.*, vol. 5, no. 7, p. e1000540, 2009.
- [23] M. Butler, “Genetics of hypertension. current status.,” *J. Med.*, vol. 58, no. 3, pp. 175–8, 2010.
- [24] S. Ramachandrappa and S. Farooqi, “Genetic approaches to understanding human obesity.,” *J. Clin. Invest.*, vol. 121, no. 6, pp. 2080–2086, 2011.
- [25] E. J. Mulder, C. Van Baal, D. Gaist, M. Kallela, J. Kaprio, D. A. Svensson, D. R. Nyholt, N. G. Martin, A. J. MacGregor, L. F. Cherkas, D. I. Boomsma, and A. Palotie, “Genetic and environmental influences on migraine: a twin study across six countries,” *Twin Res.*, vol. 6, no. 5, pp. 422–31, 2003.
- [26] T. Willemsen, G. van Beijsterveldt, C. van Baal, D. Postma, and D. Boomsma, “Heritability of self-reported asthma and allergy: a study in adult dutch twins, siblings and parents.,” *Twin Res Hum Genet.*, vol. 11, no. 2, pp. 132–142, 2008.
- [27] M. Fischer, B. Mayer, A. Baessler, G. Riegger, J. Erdmann, C. Hengstenberg, and H. Schunkert, “Familial aggregation of left main coronary artery disease and future risk of coronary events in asymptomatic siblings of affected patients.,” *Eur Heart J.*, vol. 28, no. 20, pp. 2432–7, 2007.
- [28] D. Bhugra, “The global prevalence of schizophrenia,” *PLoS Med.*, vol. 2, no. 5, p. e151, 2005.
- [29] S. Menzel, “Genetic and molecular analyses of complex metabolic disorders: genetic linkage,” *Ann N Y Acad Sci.*, vol. 967, pp. 249–57, 2002.

- [30] C. M. Stein and R. C. Elston, "Finding genes underlying human disease," *Clin Genet*, vol. 75, no. 2, pp. 101–6, 2009.
- [31] J. H. Barrett, N. A. Sheehan, A. Cox, J. Worthington, C. Cannings, and M. D. Teare, "Family based studies and genetic epidemiology: theory and practice," *Hum Hered*, vol. 64, no. 2, pp. 146–8, 2007.
- [32] J. M. Hall, M. K. Lee, B. Newman, J. E. Morrow, L. A. Anderson, B. Huey, and M. C. King, "Linkage of early-onset familial breast cancer to chromosome 17q21," *Science*, vol. 250, no. 4988, pp. 1684–9, 1990.
- [33] J. M. Hall, L. Friedman, C. Guenther, M. K. Lee, J. L. Weber, D. M. Black, and M. C. King, "Closing in on a breast cancer gene on chromosome 17q," *Am J Hum Genet*, vol. 50, no. 6, pp. 1235–42, 1992.
- [34] R. NJ, "Searching for genetic determinants in the new millennium," *Nature*, vol. 405, no. 6788, pp. 847–56, 2000.
- [35] H. J. Cordell and D. G. Clayton, "Genetic association studies," *Lancet*, vol. 366, no. 9491, pp. 1121–31, 2005.
- [36] J. N. Hirschhorn and Z. K. Gajdos, "Genome-wide association studies: results from the first few years and potential implications for clinical medicine," *Annu Rev Med*, vol. 62, pp. 11–24, 2011.
- [37] J. N. Hirschhorn and M. J. Daly, "Genome-wide association studies for common diseases and complex traits," *Nat Rev Genet*, vol. 6, no. 2, pp. 95–108, 2005.

- [38] R. Klein, C. Zeiss, E. Chew, and a. et, “Complement factor h polymorphism in age-related macular degeneration.,” *Lancet*, vol. 308, no. 5720, pp. 385–389, 2005.
- [39] T. Frayling, N. Timpson, M. Weedon, E. Zeggini, and a. et, “A common variant in the *fto* gene is associated with body mass index and predisposes to childhood and adult obesity,” *Science*, vol. 316, no. 5826, pp. 889–894, 2007.
- [40] Wellcome Trust Case Control Consortium, “Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls,” *Nature*, vol. 447, no. 7145, pp. 661–78, 2007.
- [41] J. A. Todd, N. Walker, J. Cooper, D. Smyth, K. Downes, V. Plagnol, and W. T. C. C. Consortium., “Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes.,” *Nat Gen*, vol. 39, no. 7, pp. 857–864, 2007.
- [42] D. Smyth, J. Cooper, R. Bailey, S. Field, O. Burren, L. Smink, C. Guja, C. Ionescu-Tirgoviste, B. Widmer, D. Dunger, D. Savage, N. Walker, D. Clayton, and J. Todd, “A genome-wide association study of nonsynonymous snps identifies a type 1 diabetes locus in the interferon-induced helicase (*ifih1*) region.,” *Nat Gen.*, vol. 38, no. 6, pp. 617–619, 2006.
- [43] R. Sladek, G. Rocheleau, J. Rung, C. Dina, L. Shen, D. Serre, P. Boutin, D. Vincent, A. Belisle, S. Hadjadj, B. Balkau, B. Heude, G. Charpentier, T. Hudson, A. Montpetit, A. Pshezhetsky, M. Prentki, B. Posner, D. Balding, D. Meyre, C. Polychronakos, and P. Froguel, “A genome-wide associa-

tion study identifies novel risk loci for type 2 diabetes.,” *Nature*, vol. 445, no. 7130, pp. 881–885, 2007.

- [44] K. Bilguvar, K. Yasuno, M. Niemela, Y. M. Ruigrok, M. von Und Zu Fraunberg, C. M. van Duijn, L. H. van den Berg, S. Mane, C. E. Mason, M. Choi, E. Gaal, Y. Bayri, L. Kolb, Z. Arlier, S. Ravuri, A. Ronkainen, A. Tajima, A. Laakso, A. Hata, H. Kasuya, T. Koivisto, J. Rinne, J. Ohman, M. M. Breteler, C. Wijmenga, M. W. State, G. J. Rinkel, J. Hernesniemi, J. E. Jaaskelainen, A. Palotie, I. Inoue, R. P. Lifton, and M. Gunel, “Susceptibility loci for intracranial aneurysm in european and japanese populations,” *Nat Genet*, vol. 40, no. 12, pp. 1472–7, 2008.
- [45] D. A. Hafler, A. Compston, S. Sawcer, E. S. Lander, M. J. Daly, P. L. De Jager, P. I. de Bakker, S. B. Gabriel, D. B. Mirel, A. J. Ivinson, M. A. Pericak-Vance, S. G. Gregory, J. D. Rioux, J. L. McCauley, J. L. Haines, L. F. Barcellos, B. Cree, J. R. Oksenberg, and S. L. Hauser, “Risk alleles for multiple sclerosis identified by a genomewide study,” *N Engl J Med*, vol. 357, no. 9, pp. 851–62, 2007.
- [46] J. B. Harley, M. E. Alarcon-Riquelme, L. A. Criswell, C. O. Jacob, R. P. Kimberly, K. L. Moser, B. P. Tsao, T. J. Vyse, C. D. Langefeld, S. K. Nath, J. M. Guthridge, B. L. Cobb, D. B. Mirel, M. C. Marion, A. H. Williams, J. Divers, W. Wang, S. G. Frank, B. Namjou, S. B. Gabriel, A. T. Lee, P. K. Gregersen, T. W. Behrens, K. E. Taylor, M. Fernando, R. Zidovetzki, P. M. Gaffney, J. C. Edberg, J. D. Rioux, J. O. Ojwang, J. A. James, J. T. Merrill, G. S. Gilkeson, M. F. Seldin, H. Yin, E. C. Baechler, Q. Z. Li, E. K. Wakeland, G. R. Bruner, K. M. Kaufman, and J. A. Kelly, “Genome-

wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in *itgam*, *pxk*, *kiaa1542* and other loci,” *Nat Genet*, vol. 40, no. 2, pp. 204–10, 2008.

- [47] M. I. McCarthy, G. R. Abecasis, L. R. Cardon, D. B. Goldstein, J. Little, J. P. Ioannidis, and J. N. Hirschhorn, “Genome-wide association studies for complex traits: consensus, uncertainty and challenges,” *Nat Rev Genet*, vol. 9, no. 5, pp. 356–69, 2008.
- [48] J. D. Rioux, R. J. Xavier, K. D. Taylor, M. S. Silverberg, P. Goyette, A. Huett, T. Green, P. Kuballa, M. M. Barmada, L. W. Datta, Y. Y. Shugart, A. M. Griffiths, S. R. Targan, A. F. Ippoliti, E. J. Bernard, L. Mei, D. L. Nicolae, M. Regueiro, L. P. Schumm, A. H. Steinhardt, J. I. Rotter, R. H. Duerr, J. H. Cho, M. J. Daly, and S. R. Brant, “Genome-wide association study identifies new susceptibility loci for crohn disease and implicates autophagy in disease pathogenesis,” *Nat Genet*, vol. 39, no. 5, pp. 596–604, 2007.
- [49] R. Saxena, B. F. Voight, V. Lyssenko, N. P. Burtt, P. I. de Bakker, H. Chen, J. J. Roix, S. Kathiresan, J. N. Hirschhorn, M. J. Daly, T. E. Hughes, L. Groop, D. Altshuler, P. Almgren, J. C. Florez, J. Meyer, K. Ardlie, K. Bengtsson Bostrom, B. Isomaa, G. Lettre, U. Lindblad, H. N. Lyon, O. Melander, C. Newton-Cheh, P. Nilsson, M. Orho-Melander, L. Rastam, E. K. Speliotes, M. R. Taskinen, T. Tuomi, C. Guiducci, A. Berglund, J. Carlson, L. Gianniny, R. Hackett, L. Hall, J. Holmkvist, E. Laurila, M. Sjogren, M. Sterner, A. Surti, M. Svensson, R. Tewhey, B. Blumensiel, M. Parkin, M. Defelice, R. Barry, W. Brodeur, J. Camarata, N. Chia,

- M. Fava, J. Gibbons, B. Handsaker, C. Healy, K. Nguyen, C. Gates, C. Sougnez, D. Gage, M. Nizzari, S. B. Gabriel, G. W. Chirn, Q. Ma, H. Parikh, D. Richardson, D. Ricke, and S. Purcell, “Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels,” *Science*, vol. 316, no. 5829, pp. 1331–6, 2007.
- [50] R. J. Smith, “Adherence to antiretroviral hiv drugs: how many doses can you miss before resistance emerges?,” *Proc Biol Sci*, vol. 273, no. 1586, pp. 617–24, 2006.
- [51] E. T. Cirulli and D. B. Goldstein, “Uncovering the roles of rare variants in common disease through whole-genome sequencing,” *Nat Rev Genet*, vol. 11, no. 6, pp. 415–25, 2010.
- [52] Y. S. Aulchenko, S. Ripatti, I. Lindqvist, D. Boomsma, I. M. Heid, P. P. Pramstaller, B. W. Penninx, A. C. Janssens, J. F. Wilson, T. Spector, N. G. Martin, N. L. Pedersen, K. O. Kyvik, J. Kaprio, A. Hofman, N. B. Freimer, M. R. Jarvelin, U. Gyllensten, H. Campbell, I. Rudan, A. Johansson, F. Marroni, C. Hayward, V. Vitart, I. Jonasson, C. Pattaro, A. Wright, N. Hastie, I. Pichler, A. A. Hicks, M. Falchi, G. Willemsen, J. J. Hottenga, E. J. de Geus, G. W. Montgomery, J. Whitfield, P. Magnusson, J. Saharinen, M. Perola, K. Silander, A. Isaacs, E. J. Sijbrands, A. G. Uitterlinden, J. C. Witteman, B. A. Oostra, P. Elliott, A. Ruukonen, C. Sabatti, C. Gieger, T. Meitinger, F. Kronenberg, A. Doring, H. E. Wichmann, J. H. Smit, M. I. McCarthy, C. M. van Duijn, and L. Peltonen, “Loci influencing lipid levels and coronary heart disease risk in 16 european population cohorts,” *Nat Genet*, vol. 41, no. 1, pp. 47–55, 2009.

- [53] E. Zeggini, L. J. Scott, R. Saxena, B. F. Voight, J. L. Marchini, T. Hu, P. I. de Bakker, G. R. Abecasis, P. Almgren, G. Andersen, K. Ardlie, K. B. Bostrom, R. N. Bergman, L. L. Bonnycastle, K. Borch-Johnsen, N. P. Burtt, H. Chen, P. S. Chines, M. J. Daly, P. Deodhar, C. J. Ding, A. S. Doney, W. L. Duren, K. S. Elliott, M. R. Erdos, T. M. Frayling, R. M. Freathy, L. Gianniny, H. Grallert, N. Grarup, C. J. Groves, C. Guiducci, T. Hansen, C. Herder, G. A. Hitman, T. E. Hughes, B. Isomaa, A. U. Jackson, T. Jorgensen, A. Kong, K. Kubalanza, F. G. Kuruvilla, J. Kuusisto, C. Langenberg, H. Lango, T. Lauritzen, Y. Li, C. M. Lindgren, V. Lyssenko, A. F. Marvelle, C. Meisinger, K. Midthjell, K. L. Mohlke, M. A. Morken, A. D. Morris, N. Narisu, P. Nilsson, K. R. Owen, C. N. Palmer, F. Payne, J. R. Perry, E. Pettersen, C. Platou, I. Prokopenko, L. Qi, L. Qin, N. W. Rayner, M. Rees, J. J. Roix, A. Sandbaek, B. Shields, M. Sjogren, V. Steinthorsdottir, H. M. Stringham, A. J. Swift, G. Thorleifsson, U. Thorsteinsdottir, N. J. Timpson, T. Tuomi, J. Tuomilehto, M. Walker, R. M. Watanabe, M. N. Weedon, C. J. Willer, T. Illig, K. Hveem, F. B. Hu, M. Laakso, K. Stefansson, O. Pedersen, N. J. Wareham, I. Barroso, A. T. Hattersley, F. S. Collins, L. Groop, M. I. McCarthy, M. Boehnke, and D. Altshuler, “Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes,” *Nat Genet*, vol. 40, no. 5, pp. 638–45, 2008.
- [54] T. A. Manolio, F. S. Collins, N. J. Cox, D. B. Goldstein, L. A. Hindorff, D. J. Hunter, M. I. McCarthy, E. M. Ramos, L. R. Cardon, A. Chakravarti, J. H. Cho, A. E. Guttmacher, A. Kong, L. Kruglyak, E. Mardis, C. N. Rotimi,

- M. Slatkin, D. Valle, A. S. Whittemore, M. Boehnke, A. G. Clark, E. E. Eichler, G. Gibson, J. L. Haines, T. F. Mackay, S. A. McCarroll, and P. M. Visscher, "Finding the missing heritability of complex diseases," *Nature*, vol. 461, no. 7265, pp. 747–53, 2009.
- [55] A. G. Day-Williams and E. Zeggini, "The effect of next-generation sequencing technology on complex trait research," *Eur J Clin Invest*, vol. 41, no. 5, pp. 561–7, 2011.
- [56] M. L. Metzker, "Sequencing technologies - the next generation," *Nat Rev Genet*, vol. 11, no. 1, pp. 31–46, 2010.
- [57] E. E. Schadt, S. Turner, and A. Kasarskis, "A window into third-generation sequencing," *Hum Mol Genet*, vol. 19, no. R2, pp. R227–40, 2010.
- [58] IHS, "The international classification of headache disorders: 2nd edition," *Cephalalgia*, vol. 24 Suppl 1, pp. 9–160, 2004.
- [59] A. Ropper and M. Victor, *Adams and Victor's Principles Of Neurology*. Churchill Livingstone, 2007.
- [60] L. Kelman, "The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs," *Headache*, vol. 44, no. 9, pp. 865–72, 2004.
- [61] B. K. Rasmussen and J. Olesen, "Migraine with aura and migraine without aura: an epidemiological study," *Cephalalgia*, vol. 12, no. 4, pp. 221–8; discussion 186, 1992.
- [62] L. Kelman, "The aura: a tertiary care study of 952 migraine patients," *Cephalalgia*, vol. 24, no. 9, pp. 728–34, 2004.

- [63] B. de Vries, R. R. Frants, M. D. Ferrari, and A. M. van den Maagdenberg, “Molecular genetics of migraine,” *Hum Genet*, vol. 126, no. 1, pp. 115–32, 2009.
- [64] D. R. Nyholt, N. G. Gillespie, A. C. Heath, K. R. Merikangas, D. L. Duffy, and N. G. Martin, “Latent class and genetic analysis does not support migraine with aura and migraine without aura as separate entities,” *Genet Epidemiol*, vol. 26, no. 3, pp. 231–44, 2004.
- [65] R. A. Purdy, “Migraine with and without aura share the same pathogenic mechanisms,” *Neurol Sci*, vol. 29 Suppl 1, pp. S44–6, 2008.
- [66] L. Stovner, K. Hagen, R. Jensen, Z. Katsarava, R. Lipton, A. Scher, T. Steiner, and J. A. Zwart, “The global burden of headache: a documentation of headache prevalence and disability worldwide,” *Cephalalgia*, vol. 27, no. 3, pp. 193–210, 2007.
- [67] R. B. Lipton, M. E. Bigal, M. Diamond, F. Freitag, M. L. Reed, and W. F. Stewart, “Migraine prevalence, disease burden, and the need for preventive therapy,” *Neurology*, vol. 68, no. 5, pp. 343–9, 2007.
- [68] L. J. Stovner and C. Andree, “Impact of headache in europe: a review for the eurolight project,” *J Headache Pain*, vol. 9, no. 3, pp. 139–46, 2008.
- [69] L. J. Launer, G. M. Terwindt, and M. D. Ferrari, “The prevalence and characteristics of migraine in a population-based cohort: the gem study,” *Neurology*, vol. 53, no. 3, pp. 537–42, 1999.

- [70] R. B. Lipton, M. E. Bigal, K. Kolodner, W. F. Stewart, J. N. Liberman, and T. J. Steiner, “The family impact of migraine: population-based studies in the usa and uk,” *Cephalalgia*, vol. 23, no. 6, pp. 429–40, 2003.
- [71] R. B. Lipton, J. N. Liberman, K. B. Kolodner, M. E. Bigal, A. Dowson, and W. F. Stewart, “Migraine headache disability and health-related quality-of-life: a population-based case-control study from england,” *Cephalalgia*, vol. 23, no. 6, pp. 441–50, 2003.
- [72] P. Tfelt-Hansen, “Triptans vs other drugs for acute migraine. are there differences in efficacy? a comment,” *Headache*, vol. 48, no. 4, pp. 601–5, 2008.
- [73] N. M. Ramadan, L. L. Schultz, and S. J. Gilkey, “Migraine prophylactic drugs: proof of efficacy, utilization and cost,” *Cephalalgia*, vol. 17, no. 2, pp. 73–80, 1997.
- [74] M. M. Bianchin, R. G. Londero, J. E. Lima, and M. E. Bigal, “Migraine and epilepsy: a focus on overlapping clinical, pathophysiological, molecular, and therapeutic aspects,” *Curr Pain Headache Rep*, vol. 14, no. 4, pp. 276–83, 2010.
- [75] M. E. Bigal, R. B. Lipton, J. Cohen, and S. D. Silberstein, “Epilepsy and migraine,” *Epilepsy Behav*, vol. 4 Suppl 2, pp. S13–24, 2003.
- [76] Z. Katsarava and C. Weimar, “Migraine and stroke,” *J Neurol Sci*, vol. 299, no. 1-2, pp. 42–4, 2010.

- [77] M. E. Bigal, T. Kurth, N. Santanello, D. Buse, W. Golden, M. Robbins, and R. B. Lipton, “Migraine and cardiovascular disease: a population-based study,” *Neurology*, vol. 74, no. 8, pp. 628–35, 2010.
- [78] F. Antonaci, G. Nappi, F. Galli, G. C. Manzoni, P. Calabresi, and A. Costa, “Migraine and psychiatric comorbidity: a review of clinical findings,” *J Headache Pain*, vol. 12, no. 2, pp. 115–25, 2011.
- [79] M. Lauritzen, “Cortical spreading depression in migraine,” *Cephalalgia*, vol. 21, no. 7, pp. 757–60, 2001.
- [80] B. Larrosa, J. Pastor, L. Lopez-Aguado, and O. Herreras, “A role for glutamate and glia in the fast network oscillations preceding spreading depression,” *Neuroscience*, vol. 141, no. 2, pp. 1057–68, 2006.
- [81] R. Marrannes, R. Willems, E. De Prins, and A. Wauquier, “Evidence for a role of the n-methyl-d-aspartate (nmda) receptor in cortical spreading depression in the rat,” *Brain Res*, vol. 457, no. 2, pp. 226–40, 1988.
- [82] N. Hadjikhani, M. Sanchez Del Rio, O. Wu, D. Schwartz, D. Bakker, B. Fischl, K. K. Kwong, F. M. Cutrer, B. R. Rosen, R. B. Tootell, A. G. Sorensen, and M. A. Moskowitz, “Mechanisms of migraine aura revealed by functional mri in human visual cortex,” *Proc Natl Acad Sci U S A*, vol. 98, no. 8, pp. 4687–92, 2001.
- [83] M. Denuelle, N. Fabre, P. Payoux, F. Chollet, and G. Geraud, “Posterior cerebral hypoperfusion in migraine without aura,” *Cephalalgia*, vol. 28, no. 8, pp. 856–62, 2008.

- [84] T. J. Schwedt and D. W. Dodick, “Advanced neuroimaging of migraine,” *Lancet Neurol*, vol. 8, no. 6, pp. 560–8, 2009.
- [85] T. Sprenger and P. J. Goadsby, “Migraine pathogenesis and state of pharmacological treatment options,” *BMC Med*, vol. 7, p. 71, 2009.
- [86] H. Bolay, U. Reuter, A. K. Dunn, Z. Huang, D. A. Boas, and M. A. Moskowitz, “Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model,” *Nat Med*, vol. 8, no. 2, pp. 136–42, 2002.
- [87] D. Pietrobon and J. Striessnig, “Neurobiology of migraine.,” *Nat Rev Neurosci.*, vol. 5, no. 4, pp. 386–398, 2003.
- [88] D. Cologno, A. De Pascale, and G. C. Manzoni, “Familial occurrence of migraine with aura in a population-based study,” *Headache*, vol. 43, no. 3, pp. 231–4, 2003.
- [89] E. A. Schur, C. Noonan, D. Buchwald, J. Goldberg, and N. Afari, “A twin study of depression and migraine: evidence for a shared genetic vulnerability,” *Headache*, vol. 49, no. 10, pp. 1493–502, 2009.
- [90] C. Lemos, M. J. Castro, J. Barros, J. Sequeiros, J. Pereira-Monteiro, D. Mendonca, and A. Sousa, “Familial clustering of migraine: further evidence from a portuguese study,” *Headache*, vol. 49, no. 3, pp. 404–11, 2009.
- [91] V. Ulrich, M. Gervil, K. O. Kyvik, J. Olesen, and M. B. Russell, “Evidence of a genetic factor in migraine with aura: a population-based danish twin study,” *Ann Neurol*, vol. 45, no. 2, pp. 242–6, 1999.

- [92] M. Gervil, V. Ulrich, K. O. Kyvik, J. Olesen, and M. B. Russell, “Migraine without aura: a population-based twin study,” *Ann Neurol*, vol. 46, no. 4, pp. 606–11, 1999.
- [93] M. L. Honkasalo, J. Kaprio, T. Winter, K. Heikkila, M. Sillanpaa, and M. Koskenvuo, “Migraine and concomitant symptoms among 8167 adult twin pairs,” *Headache*, vol. 35, no. 2, pp. 70–8, 1995.
- [94] M. De Fusco, R. Marconi, L. Silvestri, L. Atorino, L. Rampoldi, L. Morgante, A. Ballabio, P. Aridon, and G. Casari, “Haploinsufficiency of *atp1a2* encoding the  $na^+/k^+$  pump  $\alpha_2$  subunit associated with familial hemiplegic migraine type 2,” *Nat Genet*, vol. 33, no. 2, pp. 192–6, 2003.
- [95] B. de Vries, T. Freilinger, K. R. Vanmolkot, J. B. Koenderink, A. H. Stam, G. M. Terwindt, E. Babini, E. H. van den Boogerd, J. J. van den Heuvel, R. R. Frants, J. Haan, M. Pusch, A. M. van den Maagdenberg, M. D. Ferrari, and M. Dichgans, “Systematic analysis of three *fhm* genes in 39 sporadic patients with hemiplegic migraine,” *Neurology*, vol. 69, no. 23, pp. 2170–6, 2007.
- [96] M. Dichgans, T. Freilinger, G. Eckstein, E. Babini, B. Lorenz-Depiereux, S. Biskup, M. D. Ferrari, J. Herzog, A. M. van den Maagdenberg, M. Pusch, and T. M. Strom, “Mutation in the neuronal voltage-gated sodium channel *scn1a* in familial hemiplegic migraine,” *Lancet*, vol. 366, no. 9483, pp. 371–7, 2005.
- [97] A. Ducros, A. Joutel, K. Vahedi, M. Cecillon, A. Ferreira, E. Bernard, A. Verrier, B. Echenne, A. Lopez de Munain, M. G. Bousser, and E. Tournier-

- Lasserre, "Mapping of a second locus for familial hemiplegic migraine to 1q21-q23 and evidence of further heterogeneity," *Ann Neurol*, vol. 42, no. 6, pp. 885–90, 1997.
- [98] A. Joutel, M. G. Bousser, V. Biousse, P. Labauge, H. Chabriat, A. Nibbio, J. Maciazek, B. Meyer, M. A. Bach, J. Weissenbach, and et al., "A gene for familial hemiplegic migraine maps to chromosome 19," *Nat Genet*, vol. 5, no. 1, pp. 40–5, 1993.
- [99] A. Gallanti, A. Tonelli, V. Cardin, G. Bussone, N. Bresolin, and M. T. Bassi, "A novel de novo nonsense mutation in *atp1a2* associated with sporadic hemiplegic migraine and epileptic seizures," *J Neurol Sci*, vol. 273, no. 1-2, pp. 123–6, 2008.
- [100] R. Marconi, M. De Fusco, P. Aridon, K. Plewnia, M. Rossi, S. Carapelli, A. Ballabio, L. Morgante, R. Musolino, A. Epifanio, G. Micieli, G. De Michele, and G. Casari, "Familial hemiplegic migraine type 2 is linked to 0.9mb region on chromosome 1q23," *Ann Neurol*, vol. 53, no. 3, pp. 376–81, 2003.
- [101] R. A. Ophoff, G. M. Terwindt, M. N. Vergouwe, R. van Eijk, P. J. Oefner, S. M. Hoffman, J. E. Lamerdin, H. W. Mohrenweiser, D. E. Bulman, M. Ferrari, J. Haan, D. Lindhout, G. J. van Ommen, M. H. Hofker, M. D. Ferrari, and R. R. Frants, "Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the  $ca^{2+}$  channel gene *cacn1a4*," *Cell*, vol. 87, no. 3, pp. 543–52, 1996.

- [102] G. Terwindt, E. Kors, J. Haan, F. Vermeulen, A. Van den Maagdenberg, R. Frants, and M. Ferrari, "Mutation analysis of the cacna1a calcium channel subunit gene in 27 patients with sporadic hemiplegic migraine," *Arch Neurol*, vol. 59, no. 6, pp. 1016–8, 2002.
- [103] L. L. Thomsen, E. Oestergaard, A. Bjornsson, H. Stefansson, A. C. Fasquel, J. Gulcher, K. Stefansson, and J. Olesen, "Screen for cacna1a and atp1a2 mutations in sporadic hemiplegic migraine patients," *Cephalalgia*, vol. 28, no. 9, pp. 914–21, 2008.
- [104] A. Tonelli, A. Gallanti, A. Bersano, V. Cardin, E. Ballabio, G. Airoidi, F. Redaelli, L. Candelise, N. Bresolin, and M. T. Bassi, "Amino acid changes in the amino terminus of the na,k-adenosine triphosphatase alpha-2 subunit associated to familial and sporadic hemiplegic migraine," *Clin Genet*, vol. 72, no. 6, pp. 517–23, 2007.
- [105] M. Wessman, G. M. Terwindt, M. A. Kaunisto, A. Palotie, and R. A. Ophoff, "Migraine: a complex genetic disorder," *Lancet Neurol*, vol. 6, no. 6, pp. 521–32, 2007.
- [106] S. Debiais, C. Hommet, I. Bonnaud, M. A. Barthez, S. Rimbaux, F. Riant, and A. Autret, "The fhm1 mutation s218l: a severe clinical phenotype? a case report and review of the literature," *Cephalalgia*, vol. 29, no. 12, pp. 1337–9, 2009.
- [107] O. Zhuchenko, J. Bailey, P. Bonnen, T. Ashizawa, D. W. Stockton, C. Amos, W. B. Dobyns, S. H. Subramony, H. Y. Zoghbi, and C. C. Lee, "Autosomal

- dominant cerebellar ataxia (sca6) associated with small polyglutamine expansions in the alpha 1a-voltage-dependent calcium channel,” *Nat Genet*, vol. 15, no. 1, pp. 62–9, 1997.
- [108] F. J. Urbano, M. D. Rosato-Siri, and O. D. Uchitel, “Calcium channels involved in neurotransmitter release at adult, neonatal and p/q-type deficient neuromuscular junctions (review),” *Mol Membr Biol*, vol. 19, no. 4, pp. 293–300, 2002.
- [109] R. L. Kraus, M. J. Sinnegger, H. Glossmann, S. Hering, and J. Striessnig, “Familial hemiplegic migraine mutations change alpha1a ca<sup>2+</sup> channel kinetics,” *J Biol Chem*, vol. 273, no. 10, pp. 5586–90, 1998.
- [110] R. L. Kraus, M. J. Sinnegger, A. Koschak, H. Glossmann, S. Stenirri, P. Carrera, and J. Striessnig, “Three new familial hemiplegic migraine mutants affect p/q-type ca(2+) channel kinetics,” *J Biol Chem*, vol. 275, no. 13, pp. 9239–43, 2000.
- [111] A. Tottene, T. Fellin, S. Pagnutti, S. Luvisetto, J. Striessnig, C. Fletcher, and D. Pietrobon, “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*, vol. 99, no. 20, pp. 13284–9, 2002.
- [112] A. van den Maagdenberg, D. Pietrobon, T. Pizzorusso, S. Kaja, L. Broos, T. Cesetti, R. van de Ven, A. Tottene, J. van der Kaa, J. Plomp, R. Frants, and M. Ferrari, “A cacna1a knockin migraine mouse model with increased

- susceptibility to cortical spreading depression,” *Neuron*, vol. 41, no. 5, pp. 701–10, 2004.
- [113] L. Claes, J. Del-Favero, B. Ceulemans, L. Lagae, C. Van Broeckhoven, and P. De Jonghe, “De novo mutations in the sodium-channel gene *scn1a* cause severe myoclonic epilepsy of infancy,” *Am J Hum Genet*, vol. 68, no. 6, pp. 1327–32, 2001.
- [114] A. Escayg, B. T. MacDonald, M. H. Meisler, S. Baulac, G. Huberfeld, I. An-Gourfinkel, A. Brice, E. LeGuern, B. Moulard, D. Chaigne, C. Buresi, and A. Malafosse, “Mutations of *scn1a*, encoding a neuronal sodium channel, in two families with *gefs+2*,” *Nat Genet*, vol. 24, no. 4, pp. 343–5, 2000.
- [115] C. E. Stafstrom, “Severe epilepsy syndromes of early childhood: the link between genetics and pathophysiology with a focus on *scn1a* mutations,” *J Child Neurol*, vol. 24, no. 8 Suppl, pp. 15S–23S, 2009.
- [116] R. H. Wallace, I. E. Scheffer, S. Barnett, M. Richards, L. Dibbens, R. R. Desai, T. Lerman-Sagie, D. Lev, A. Mazarib, N. Brand, B. Ben-Zeev, I. Goikhman, R. Singh, G. Kremmidiotis, A. Gardner, G. R. Sutherland, J. George, A. L., J. C. Mulley, and S. F. Berkovic, “Neuronal sodium-channel  $\alpha 1$ -subunit mutations in generalized epilepsy with febrile seizures plus,” *Am J Hum Genet*, vol. 68, no. 4, pp. 859–65, 2001.
- [117] M. J. Castro, B. Nunes, B. de Vries, C. Lemos, K. R. Vanmolkot, J. J. van den Heuvel, T. Temudo, J. Barros, J. Sequeiros, R. R. Frants, J. B. Koenderink, J. M. Pereira-Monteiro, and A. M. van den Maagdenberg, “Two novel functional mutations in the  $na^+,k^+$ -atpase  $\alpha 2$ -subunit *atp1a2* gene

- in patients with familial hemiplegic migraine and associated neurological phenotypes,” *Clin Genet*, vol. 73, no. 1, pp. 37–43, 2008.
- [118] K. M. Kahlig, T. H. Rhodes, M. Pusch, T. Freilinger, J. M. Pereira-Monteiro, M. D. Ferrari, A. M. van den Maagdenberg, M. Dichgans, and J. George, A. L., “Divergent sodium channel defects in familial hemiplegic migraine,” *Proc Natl Acad Sci U S A*, vol. 105, no. 28, pp. 9799–804, 2008.
- [119] T. H. Rhodes, C. Lossin, C. G. Vanoye, D. W. Wang, and J. George, A. L., “Noninactivating voltage-gated sodium channels in severe myoclonic epilepsy of infancy,” *Proc Natl Acad Sci U S A*, vol. 101, no. 30, pp. 11147–52, 2004.
- [120] M. Dobretsov and J. R. Stimers, “Neuronal function and alpha3 isoform of the na/k-atpase,” *Front Biosci*, vol. 10, pp. 2373–96, 2005.
- [121] J. Cressman, J. R., G. Ullah, J. Ziburkus, S. J. Schiff, and E. Barreto, “The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: I. single neuron dynamics,” *J Comput Neurosci*, vol. 26, no. 2, pp. 159–70, 2009.
- [122] M. A. Kaunisto, H. Harno, K. R. Vanmolkot, J. J. Gargus, G. Sun, E. Hamalainen, E. Liukkonen, M. Kallela, A. M. van den Maagdenberg, R. R. Frants, M. Farkkila, A. Palotie, and M. Wessman, “A novel missense atp1a2 mutation in a finnish family with familial hemiplegic migraine type 2,” *Neurogenetics*, vol. 5, no. 2, pp. 141–6, 2004.
- [123] A. Lebas, L. Guyant-Marechal, D. Hannequin, F. Riant, E. Tournier-Lasserre, and D. Parain, “Severe attacks of familial hemiplegic migraine,

- childhood epilepsy and atp1a2 mutation,” *Cephalalgia*, vol. 28, no. 7, pp. 774–7, 2008.
- [124] L. L. Thomsen, M. Kirchmann, A. Bjornsson, H. Stefansson, R. M. Jensen, A. C. Fasquel, H. Petursson, M. Stefansson, M. L. Frigge, A. Kong, J. Gulcher, K. Stefansson, and J. Olesen, “The genetic spectrum of a population-based sample of familial hemiplegic migraine,” *Brain*, vol. 130, no. Pt 2, pp. 346–56, 2007.
- [125] N. N. Tavraz, T. Friedrich, K. L. Durr, J. B. Koenderink, E. Bamberg, T. Freilinger, and M. Dichgans, “Diverse functional consequences of mutations in the na<sup>+</sup>/k<sup>+</sup>-atpase alpha2-subunit causing familial hemiplegic migraine type 2,” *J Biol Chem*, vol. 283, no. 45, pp. 31097–106, 2008.
- [126] M. B. Russell and A. Ducros, “Sporadic and familial hemiplegic migraine: pathophysiological mechanisms, clinical characteristics, diagnosis, and management,” *Lancet Neurol*, vol. 10, no. 5, pp. 457–70, 2011.
- [127] G. M. Terwindt, R. A. Ophoff, J. Haan, R. R. Frants, and M. D. Ferrari, “Familial hemiplegic migraine: a clinical comparison of families linked and unlinked to chromosome 19.dmg rg,” *Cephalalgia*, vol. 16, no. 3, pp. 153–5, 1996.
- [128] G. M. Terwindt, R. A. Ophoff, J. Haan, M. N. Vergouwe, R. van Eijk, R. R. Frants, and M. D. Ferrari, “Variable clinical expression of mutations in the p/q-type calcium channel gene in familial hemiplegic migraine. dutch migraine genetics research group,” *Neurology*, vol. 50, no. 4, pp. 1105–10, 1998.

- [129] A. Ducros, C. Denier, A. Joutel, M. Cecillon, C. Lescoat, K. Vahedi, F. Darcel, E. Vicaud, M. G. Bousser, and E. Tournier-Lasserre, “The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel,” *N Engl J Med*, vol. 345, no. 1, pp. 17–24, 2001.
- [130] A. Ducros, C. Denier, A. Joutel, K. Vahedi, A. Michel, F. Darcel, M. Madigand, D. Guerouaou, F. Tison, J. Julien, E. Hirsch, F. Chedru, C. Bisgard, G. Lucotte, P. Despres, C. Billard, M. A. Barthez, G. Ponsot, M. G. Bousser, and E. Tournier-Lasserre, “Recurrence of the t666m calcium channel cacna1a gene mutation in familial hemiplegic migraine with progressive cerebellar ataxia,” *Am J Hum Genet*, vol. 64, no. 1, pp. 89–98, 1999.
- [131] K. L. Friend, D. Crimmins, T. G. Phan, C. M. Sue, A. Colley, V. S. Fung, J. G. Morris, G. R. Sutherland, and R. I. Richards, “Detection of a novel missense mutation and second recurrent mutation in the cacna1a gene in individuals with ea-2 and fhm,” *Hum Genet*, vol. 105, no. 3, pp. 261–5, 1999.
- [132] E. E. Kors, G. M. Terwindt, F. L. Vermeulen, R. B. Fitzsimons, P. E. Jardine, P. Heywood, S. Love, A. M. van den Maagdenberg, J. Haan, R. R. Frants, and M. D. Ferrari, “Delayed cerebral edema and fatal coma after minor head trauma: role of the cacna1a calcium channel subunit gene and relationship with familial hemiplegic migraine,” *Ann Neurol*, vol. 49, no. 6, pp. 753–60, 2001.
- [133] I. Alonso, J. Barros, A. Tuna, J. Coelho, J. Sequeiros, I. Silveira, and P. Coutinho, “Phenotypes of spinocerebellar ataxia type 6 and familial hemi-

- plegic migraine caused by a unique cacna1a missense mutation in patients from a large family,” *Arch Neurol*, vol. 60, no. 4, pp. 610–4, 2003.
- [134] E. E. Kors, J. Haan, N. J. Giffin, L. Pazdera, C. Schnittger, G. G. Lennox, G. M. Terwindt, F. L. Vermeulen, A. M. Van den Maagdenberg, R. R. Frants, and M. D. Ferrari, “Expanding the phenotypic spectrum of the cacna1a gene t666m mutation: a description of 5 families with familial hemiplegic migraine,” *Arch Neurol*, vol. 60, no. 5, pp. 684–8, 2003.
- [135] T. Takahashi, S. Igarashi, T. Kimura, I. Hozumi, I. Kawachi, O. Onodera, H. Takano, M. Saito, and S. Tsuji, “Japanese cases of familial hemiplegic migraine with cerebellar ataxia carrying a t666m mutation in the cacna1a gene,” *J Neurol Neurosurg Psychiatry*, vol. 72, no. 5, pp. 676–7, 2002.
- [136] T. Wada, N. Kobayashi, Y. Takahashi, T. Aoki, T. Watanabe, and S. Saitoh, “Wide clinical variability in a family with a cacna1a t666m mutation: hemiplegic migraine, coma, and progressive ataxia,” *Pediatr Neurol*, vol. 26, no. 1, pp. 47–50, 2002.
- [137] K. R. Vanmolkot, H. Stroink, J. B. Koenderink, E. E. Kors, J. J. van den Heuvel, E. H. van den Boogerd, A. H. Stam, J. Haan, B. B. De Vries, G. M. Terwindt, R. R. Frants, M. D. Ferrari, and A. M. van den Maagdenberg, “Severe episodic neurological deficits and permanent mental retardation in a child with a novel fhm2 atp1a2 mutation,” *Ann Neurol*, vol. 59, no. 2, pp. 310–4, 2006.

- [138] S. Marti, R. W. Baloh, J. C. Jen, D. Straumann, and H. H. Jung, “Progressive cerebellar ataxia with variable episodic symptoms—phenotypic diversity of r1668w cacna1a mutation,” *Eur Neurol*, vol. 60, no. 1, pp. 16–20, 2008.
- [139] J. C. Jen, G. W. Kim, K. A. Dudding, and R. W. Baloh, “No mutations in cacna1a and atp1a2 in probands with common types of migraine,” *Arch Neurol*, vol. 61, no. 6, pp. 926–8, 2004.
- [140] M. Dichgans, J. Herzog, T. Freilinger, M. Wilke, and D. P. Auer, “1h-mrs alterations in the cerebellum of patients with familial hemiplegic migraine type 1,” *Neurology*, vol. 64, no. 4, pp. 608–13, 2005.
- [141] I. Yabe, M. Kitagawa, Y. Suzuki, K. Fujiwara, T. Wada, T. Tsubuku, N. Takeichi, K. Sakushima, H. Soma, S. Tsuji, M. Niino, S. Saitoh, and H. Sasaki, “Downbeat positioning nystagmus is a common clinical feature despite variable phenotypes in an fhm1 family,” *J Neurol*, vol. 255, no. 10, pp. 1541–4, 2008.
- [142] T. Freilinger, M. Bohe, B. Wegener, B. Muller-Myhsok, M. Dichgans, and H. Knoblauch, “Expansion of the phenotypic spectrum of the cacna1a t666m mutation: a family with familial hemiplegic migraine type 1, cerebellar atrophy and mental retardation,” *Cephalalgia*, vol. 28, no. 4, pp. 403–7, 2008.
- [143] I. Alonso, J. Barros, A. Tuna, A. Seixas, P. Coutinho, J. Sequeiros, and I. Silveira, “A novel r1347q mutation in the predicted voltage sensor segment of the p/q-type calcium-channel alpha-subunit in a family with progressive cerebellar ataxia and hemiplegic migraine,” *Clin Genet*, vol. 65, no. 1, pp. 70–2, 2004.

- [144] A. H. Stam, K. R. Vanmolkot, H. P. Kremer, J. Gartner, J. Brown, E. Leshinsky-Silver, R. Gilad, E. E. Kors, W. S. Frankhuizen, H. B. Ginjaar, J. Haan, R. R. Frants, M. D. Ferrari, A. M. van den Maagdenberg, and G. M. Terwindt, “Cacna1a r1347q: a frequent recurrent mutation in hemiplegic migraine,” *Clin Genet*, vol. 74, no. 5, pp. 481–5, 2008.
- [145] E. E. Kors, A. Melberg, K. R. Vanmolkot, E. Kumlien, J. Haan, R. Raininko, R. Flink, H. B. Ginjaar, R. R. Frants, M. D. Ferrari, and A. M. van den Maagdenberg, “Childhood epilepsy, familial hemiplegic migraine, cerebellar ataxia, and a new cacna1a mutation,” *Neurology*, vol. 63, no. 6, pp. 1136–7, 2004.
- [146] T. Freilinger, N. Ackl, A. Ebert, C. Schmidt, B. Rautenstrauss, M. Dichgans, and A. Danek, “A novel mutation in cacna1a associated with hemiplegic migraine, cerebellar dysfunction and late-onset cognitive decline,” *J Neurol Sci*, vol. 300, no. 1-2, pp. 160–3, 2011.
- [147] K. R. Vanmolkot, E. E. Kors, J. J. Hottenga, G. M. Terwindt, J. Haan, W. A. Hoefnagels, D. F. Black, L. A. Sandkuijl, R. R. Frants, M. D. Ferrari, and A. M. van den Maagdenberg, “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*, vol. 54, no. 3, pp. 360–6, 2003.
- [148] K. J. Swoboda, E. Kanavakis, A. Xaidara, J. E. Johnson, M. F. Leppert, M. B. Schlesinger-Massart, L. J. Ptacek, K. Silver, and S. Youroukos, “Alternating hemiplegia of childhood or familial hemiplegic migraine? a novel atp1a2 mutation,” *Ann Neurol*, vol. 55, no. 6, pp. 884–7, 2004.

- [149] J. P. Dreier, K. Jurkat-Rott, G. C. Petzold, O. Tomkins, R. Klingebiel, U. A. Kopp, F. Lehmann-Horn, A. Friedman, and M. Dichgans, "Opening of the blood-brain barrier preceding cortical edema in a severe attack of fhm type ii," *Neurology*, vol. 64, no. 12, pp. 2145–7, 2005.
- [150] J. C. Jen, A. Klein, E. Boltshauser, M. S. Cartwright, E. S. Roach, H. Mamsa, and R. W. Baloh, "Prolonged hemiplegic episodes in children due to mutations in atp1a2," *J Neurol Neurosurg Psychiatry*, vol. 78, no. 5, pp. 523–6, 2007.
- [151] L. Deprez, S. Weckhuysen, K. Peeters, T. Deconinck, K. G. Claeys, L. R. Claes, A. Suls, T. Van Dyck, A. Palmi, G. Matthijs, W. Van Paesschen, and P. De Jonghe, "Epilepsy as part of the phenotype associated with atp1a2 mutations," *Epilepsia*, vol. 49, no. 3, pp. 500–8, 2008.
- [152] D. M. Fernandez, C. K. Hand, B. J. Sweeney, and N. A. Parfrey, "A novel atp1a2 gene mutation in an irish familial hemiplegic migraine kindred," *Headache*, vol. 48, no. 1, pp. 101–8, 2008.
- [153] B. de Vries, A. H. Stam, M. Kirkpatrick, K. R. Vanmolkot, J. B. Koenderink, J. J. van den Heuvel, B. Stunnenberg, D. Goudie, J. Shetty, V. Jain, J. van Vark, G. M. Terwindt, R. R. Frants, J. Haan, A. M. van den Maagdenberg, and M. D. Ferrari, "Familial hemiplegic migraine is associated with febrile seizures in an fhm2 family with a novel de novo atp1a2 mutation," *Epilepsia*, vol. 50, no. 11, pp. 2503–4, 2009.
- [154] F. Riant, A. Ducros, C. Ploton, C. Barbance, C. Depienne, and E. Tournier-Lasserre, "De novo mutations in atp1a2 and cacna1a are frequent in early-

- onset sporadic hemiplegic migraine,” *Neurology*, vol. 75, no. 11, pp. 967–72, 2010.
- [155] K. R. Vanmolkot, E. Babini, B. de Vries, A. H. Stam, T. Freilinger, G. M. Terwindt, L. Norris, J. Haan, R. R. Frants, N. M. Ramadan, M. D. Ferrari, M. Pusch, A. M. van den Maagdenberg, and M. Dichgans, “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*, vol. 28, no. 5, p. 522, 2007.
- [156] M. J. Castro, A. H. Stam, C. Lemos, B. de Vries, K. R. Vanmolkot, J. Barros, G. M. Terwindt, R. R. Frants, J. Sequeiros, M. D. Ferrari, J. M. Pereira-Monteiro, and A. M. van den Maagdenberg, “First mutation in the voltage-gated nav1.1 subunit gene scn1a with co-occurring familial hemiplegic migraine and epilepsy,” *Cephalalgia*, vol. 29, no. 3, pp. 308–13, 2009.
- [157] K. Vahedi, C. Depienne, D. Le Fort, F. Riant, P. Chaine, O. Trouillard, A. Gaudric, M. A. Morris, E. Leguern, E. Tournier-Lasserre, and M. G. Boussier, “Elicited repetitive daily blindness: a new phenotype associated with hemiplegic migraine and scn1a mutations,” *Neurology*, vol. 72, no. 13, pp. 1178–83, 2009.
- [158] R. W. Labrum, S. Rajakulendran, T. D. Graves, L. H. Eunson, R. Bevan, M. G. Sweeney, S. R. Hammans, N. Tubridy, T. Britton, L. J. Carr, J. R. Ostergaard, C. R. Kennedy, A. Al-Memar, D. M. Kullmann, S. Schorge, K. Temple, M. B. Davis, and M. G. Hanna, “Large scale calcium channel gene

- rearrangements in episodic ataxia and hemiplegic migraine: implications for diagnostic testing,” *J Med Genet*, vol. 46, no. 11, pp. 786–91, 2009.
- [159] L. Veneziano, S. Guida, E. Mantuano, P. Bernard, P. Tarantino, L. Boccone, F. M. Hisama, P. Carrera, C. Jodice, and M. Frontali, “Newly characterised 5’ and 3’ regions of cacna1a gene harbour mutations associated with familial hemiplegic migraine and episodic ataxia,” *J Neurol Sci*, vol. 276, no. 1-2, pp. 31–7, 2009.
- [160] P. Bradshaw and M. Parsons, “Hemiplegic migraine, a clinical study,” *Q J Med*, vol. 34, pp. 65–85, 1965.
- [161] K. Jurkat-Rott, T. Freilinger, J. P. Dreier, J. Herzog, H. Gobel, G. C. Petzold, P. Montagna, T. Gasser, F. Lehmann-Horn, and M. Dichgans, “Variability of familial hemiplegic migraine with novel a1a2 na+/k+-atpase variants,” *Neurology*, vol. 62, no. 10, pp. 1857–61, 2004.
- [162] V. Anttila, M. Kallela, G. Oswell, M. Kaunisto, D. Nyholt, E. Hamalainen, H. Havanka, M. Wessman, A. Palotie, and a. et, “Trait components provide tools to dissect the genetic susceptibility of migraine,” *Am J Hum Genet*, vol. 79, no. 1, pp. 85–99, 2006.
- [163] V. Anttila, D. R. Nyholt, M. Kallela, V. Artto, S. Vepsalainen, E. Jakkula, A. Wennerstrom, P. Tikka-Kleemola, M. A. Kaunisto, E. Hamalainen, E. Widen, J. Terwilliger, K. Merikangas, G. W. Montgomery, N. G. Martin, M. Daly, J. Kaprio, L. Peltonen, M. Farkkila, M. Wessman, and A. Palotie, “Consistently replicating locus linked to migraine on 10q22-q23,” *Am J Hum Genet*, vol. 82, no. 5, pp. 1051–63, 2008.

- [164] A. Bjornsson, G. Gudmundsson, E. Gudfinnsson, M. Hrafnisdottir, J. Benedikz, S. Skuladottir, K. Kristjansson, M. L. Frigge, A. Kong, K. Stefansson, and J. R. Gulcher, "Localization of a gene for migraine without aura to chromosome 4q21," *Am J Hum Genet*, vol. 73, no. 5, pp. 986–93, 2003.
- [165] A. Carlsson, L. Forsgren, P. O. Nylander, U. Hellman, K. Forsman-Semb, G. Holmgren, D. Holmberg, and M. Holmberg, "Identification of a susceptibility locus for migraine with and without aura on 6p12.2-p21.1," *Neurology*, vol. 59, no. 11, pp. 1804–7, 2002.
- [166] R. A. Lea, A. G. Shepherd, R. P. Curtain, D. R. Nyholt, S. Quinlan, P. J. Brimage, and L. R. Griffiths, "A typical migraine susceptibility region localizes to chromosome 1q31," *Neurogenetics*, vol. 4, no. 1, pp. 17–22, 2002.
- [167] R. A. Lea, D. R. Nyholt, R. P. Curtain, M. Ovcaric, R. Sciascia, C. Bellis, J. Macmillan, S. Quinlan, R. A. Gibson, L. C. McCarthy, J. H. Riley, Y. J. Smithies, S. Kinrade, and L. R. Griffiths, "A genome-wide scan provides evidence for loci influencing a severe heritable form of common migraine," *Neurogenetics*, vol. 6, no. 2, pp. 67–72, 2005.
- [168] D. R. Nyholt, J. L. Dawkins, P. J. Brimage, P. J. Goadsby, G. A. Nicholson, and L. R. Griffiths, "Evidence for an x-linked genetic component in familial typical migraine," *Hum Mol Genet*, vol. 7, no. 3, pp. 459–63, 1998.
- [169] D. R. Nyholt, R. A. Lea, P. J. Goadsby, P. J. Brimage, and L. R. Griffiths, "Familial typical migraine: linkage to chromosome 19p13 and evidence for genetic heterogeneity," *Neurology*, vol. 50, no. 5, pp. 1428–32, 1998.

- [170] D. R. Nyholt, K. I. Morley, M. A. Ferreira, S. E. Medland, D. I. Boomsma, A. C. Heath, K. R. Merikangas, G. W. Montgomery, and N. G. Martin, “Genomewide significant linkage to migrainous headache on chromosome 5q21,” *Am J Hum Genet*, vol. 77, no. 3, pp. 500–12, 2005.
- [171] M. B. Russell, L. Iselius, and J. Olesen, “Inheritance of migraine investigated by complex segregation analysis,” *Hum Genet*, vol. 96, no. 6, pp. 726–30, 1995.
- [172] M. Wessman, M. Kallela, M. A. Kaunisto, P. Marttila, E. Sobel, J. Hartiala, G. Oswell, S. M. Leal, J. C. Papp, E. Hamalainen, P. Broas, G. Joslyn, I. Hovatta, T. Hiekkalinna, J. Kaprio, J. Ott, R. M. Cantor, J. A. Zwart, M. Ilmavirta, H. Havanka, M. Farkkila, L. Peltonen, and A. Palotie, “A susceptibility locus for migraine with aura, on chromosome 4q24,” *Am J Hum Genet*, vol. 70, no. 3, pp. 652–62, 2002.
- [173] N. J. Colson, R. A. Lea, S. Quinlan, J. MacMillan, and L. R. Griffiths, “The estrogen receptor 1 g594a polymorphism is associated with migraine susceptibility in two independent case/control groups,” *Neurogenetics*, vol. 5, no. 2, pp. 129–33, 2004.
- [174] N. J. Colson, R. A. Lea, S. Quinlan, and L. R. Griffiths, “No role for estrogen receptor 1 gene intron 1 pvu ii and exon 4 c325g polymorphisms in migraine susceptibility,” *BMC Med Genet*, vol. 7, p. 12, 2006.
- [175] R. Curtain, R. A. Lea, S. Quinlan, C. Bellis, L. Tajouri, R. Hughes, J. Macmillan, and L. R. Griffiths, “Investigation of the low-density lipopro-

- tein receptor gene and cholesterol as a risk factor for migraine,” *J Neurol Sci*, vol. 227, no. 1, pp. 95–100, 2004.
- [176] M. A. Kaunisto, M. Kallela, E. Hamalainen, R. Kilpikari, H. Havanka, H. Harno, M. Nissila, E. Sako, M. Ilmavirta, J. Liukkonen, H. Teirmaa, O. Tornwall, M. Jussila, J. Terwilliger, M. Farkkila, J. Kaprio, A. Palotie, and M. Wessman, “Testing of variants of the *mthfr* and *esr1* genes in 1798 finnish individuals fails to confirm the association with migraine with aura,” *Cephalalgia*, vol. 26, no. 12, pp. 1462–72, 2006.
- [177] R. A. Lea, M. Ovcaric, J. Sundholm, J. MacMillan, and L. R. Griffiths, “The methylenetetrahydrofolate reductase gene variant c677t influences susceptibility to migraine with aura,” *BMC Med*, vol. 2, p. 3, 2004.
- [178] L. C. McCarthy, D. A. Hosford, J. H. Riley, M. I. Bird, N. J. White, D. R. Hewett, S. J. Peroutka, L. R. Griffiths, P. R. Boyd, R. A. Lea, S. M. Bhatti, L. K. Hosking, C. M. Hood, K. W. Jones, A. R. Handley, R. Rallan, K. F. Lewis, A. J. Yeo, P. M. Williams, R. C. Priest, P. Khan, C. Donnelly, S. M. Lumsden, J. O’Sullivan, C. G. See, D. H. Smart, S. Shaw-Hawkins, J. Patel, T. C. Langrish, W. Feniuk, R. G. Knowles, M. Thomas, V. Libri, D. S. Montgomery, P. K. Manasco, C. F. Xu, C. Dykes, P. P. Humphrey, A. D. Roses, and I. J. Purvis, “Single-nucleotide polymorphism alleles in the insulin receptor gene are associated with typical migraine,” *Genomics*, vol. 78, no. 3, pp. 135–49, 2001.
- [179] M. Mochi, S. Cevoli, P. Cortelli, G. Pierangeli, C. Scapoli, S. Soriani, and P. Montagna, “Investigation of an *ldlr* gene polymorphism (19p13.2) in sus-

- ceptibility to migraine without aura,” *J Neurol Sci*, vol. 213, no. 1-2, pp. 7–10, 2003.
- [180] C. Netzer, J. Freudenberg, A. Heinze, K. Heinze-Kuhn, I. Goebel, L. C. McCarthy, A. D. Roses, H. Gobel, U. Todt, and C. Kubisch, “Replication study of the insulin receptor gene in migraine with aura,” *Genomics*, vol. 91, no. 6, pp. 503–7, 2008.
- [181] A. Oterino, N. Valle, Y. Bravo, P. Munoz, P. Sanchez-Velasco, C. Ruiz-Alegria, J. Castillo, F. Leyva-Cobian, A. Vadillo, and J. Pascual, “Mthfr t677 homozygosis influences the presence of aura in migraineurs,” *Cephalalgia*, vol. 24, no. 6, pp. 491–4, 2004.
- [182] A. Oterino, J. Pascual, C. Ruiz de Alegria, N. Valle, J. Castillo, Y. Bravo, F. Gonzalez, P. Sanchez-Velasco, A. Cayon, F. Leyva-Cobian, A. Alonso-Arranz, and P. Munoz, “Association of migraine and esr1 g325c polymorphism,” *Neuroreport*, vol. 17, no. 1, pp. 61–4, 2006.
- [183] E. Rubino, M. Ferrero, I. Rainero, E. Binello, G. Vaula, and L. Pinessi, “Association of the c677t polymorphism in the mthfr gene with migraine: a meta-analysis,” *Cephalalgia*, vol. 29, no. 8, pp. 818–25, 2009.
- [184] A. I. Scher, G. M. Terwindt, W. M. Verschuren, M. C. Kruit, H. J. Blom, H. Kowa, R. R. Frants, A. M. van den Maagdenberg, M. van Buchem, M. D. Ferrari, and L. J. Launer, “Migraine and mthfr c677t genotype in a population-based sample,” *Ann Neurol*, vol. 59, no. 2, pp. 372–5, 2006.

- [185] Z. Cader, S. Noble-Topham, D. Dymment, S. Cherny, J. Brown, G. Rice, and G. Ebers, "Significant linkage to migraine with aura on chromosome 11q24," *Hum Mol Genet*, vol. 12, no. 19, pp. 2511–7, 2003.
- [186] D. Soragna, A. Vettori, G. Carraro, E. Marchioni, G. Vazza, S. Bellini, R. Tupler, F. Savoldi, and M. L. Mostacciolo, "A locus for migraine without aura maps on chromosome 14q21.2-q22.3," *Am J Hum Genet*, vol. 72, no. 1, pp. 161–7, 2003.
- [187] N. Risch and K. Merikangas, "The future of genetic studies of complex human diseases," *Science*, vol. 273, no. 5281, pp. 1516–7, 1996.
- [188] Colson, Lea, Quinlan., and Griffiths, "No role for estrogen receptor 1 gene intron 1 pvu ii and exon 4 c325g polymorphisms in migraine susceptibility," *BMC Med Genet.*, vol. 1471, no. 12, pp. 7–12, 2006.
- [189] N. Colson, R. Lea, S. Quinlan, J. MacMillan, and L. Griffiths, "Investigation of hormone receptor genes in migraine," *Neurogenetics*, vol. 6, no. 1, pp. 17–23, 2005.
- [190] A. Scher, G. Terwindt, W. Verschuren, M. Kruit, H. Blom, H. Kowa, R. Frants, A. van den Maagdenberg, M. van Buchem, M. Ferrari, and L. Launer, "Migraine and mthfr c677t genotype in a population-based sample.," *Ann Neurolog*, vol. 59, no. 2, pp. 372–375, 2006.
- [191] F. Fernandez, S. Quinlan, J. MacMillan, R. Lea, and L. Griffiths, "Association between migraine and a functional polymorphism at the dopamine beta-hydroxylase locus.," *Neurogenetics*, vol. 10, no. 3, pp. 199–208, 2009.

- [192] U. Todt, C. Netzer, M. Toliat, and C. Kubisch, “New genetic evidence for involvement of the dopamine system in migraine with aura.,” *Hum Genet*, vol. 125, no. 3, pp. 265–279, 2009.
- [193] Corominas, Ribases, and Macaya, “Two-stage case-control association study of dopamine-related genes and migraine,” *BMC Med Genet*, p. 10, 2009.
- [194] J. N. Hirschhorn, “Genomewide association studies—illuminating biologic pathways,” *N Engl J Med*, vol. 360, no. 17, 2009.
- [195] E. R. Mardis, “The impact of next-generation sequencing technology on genetics,” *Trends Genet*, vol. 24, no. 3, pp. 133–41, 2008.
- [196] T. J. Albert, M. N. Molla, D. M. Muzny, L. Nazareth, D. Wheeler, X. Song, T. A. Richmond, C. M. Middle, M. J. Rodesch, C. J. Packard, G. M. Weinstein, and R. A. Gibbs, “Direct selection of human genomic loci by microarray hybridization,” *Nat Methods*, vol. 4, no. 11, pp. 903–5, 2007.
- [197] A. Gnirke, A. Melnikov, J. Maguire, P. Rogov, E. M. LeProust, W. Brockman, T. Fennell, G. Giannoukos, S. Fisher, C. Russ, S. Gabriel, D. B. Jaffe, E. S. Lander, and C. Nusbaum, “Solution hybrid selection with ultra-long oligonucleotides for massively parallel targeted sequencing,” *Nat Biotechnol*, vol. 27, no. 2, pp. 182–9, 2009.
- [198] E. Hodges, Z. Xuan, V. Baliya, M. Kramer, M. N. Molla, S. W. Smith, C. M. Middle, M. J. Rodesch, T. J. Albert, G. J. Hannon, and W. R. McCombie, “Genome-wide in situ exon capture for selective resequencing,” *Nat Genet*, vol. 39, no. 12, pp. 1522–7, 2007.

- [199] D. T. Okou, K. M. Steinberg, C. Middle, D. J. Cutler, T. J. Albert, and M. E. Zwick, “Microarray-based genomic selection for high-throughput resequencing,” *Nat Methods*, vol. 4, no. 11, pp. 907–9, 2007.
- [200] J. Harrow, F. Denoeud, A. Frankish, A. Reymond, C. K. Chen, J. Chrast, J. Lagarde, J. G. Gilbert, R. Storey, D. Swarbreck, C. Rossier, C. Ucla, T. Hubbard, S. E. Antonarakis, and R. Guigo, “Gencode: producing a reference annotation for encode,” *Genome Biol*, vol. 7 Suppl 1, pp. S4 1–9, 2006.
- [201] M. Kallela, M. Wessman, and M. Farkkila, “Validation of a migraine-specific questionnaire for use in family studies,” *Eur J Neurol*, vol. 8, no. 1, pp. 61–6, 2001.
- [202] H. Wichmann, C. Gieger, T. Illig, and M. S. Group, “Kora-gen—resource for population genetics, controls and a broad spectrum of disease phenotypes,” *Gesundheitswesen*, vol. 67, no. Suppl 1, pp. S26–30, 2005.
- [203] A. Schmermund, S. Mhlenkamp, A. Stang, D. Grnemeyer, R. Seibel, H. Hirche, K. Mann, W. Siffert, K. Lauterbach, J. Siegrist, K. Jckel, and R. Erbel, “Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the heinz nixdorf recall study. risk factors, evaluation of coronary calcium and lifestyle,” *Am Heart J*, vol. 144, no. 2, pp. 212–8, 2002.
- [204] A. Hofman, M. Breteler, C. van Duijn, G. Krestin, H. Pols, B. Stricker, H. Tiemeier, A. Uitterlinden, J. Vingerling, and J. Witteman, “The rotter-

- dam study: objectives and design update,” *Eur J Epidemiol*, vol. 22, no. 11, pp. 819–29, 2007.
- [205] D. Barker, C. Osmond, T. Forsn, E. Kajantie, and J. Eriksson, “Trajectories of growth among children who have coronary events as adults,” *N Engl J Med*, vol. 353, no. 17, pp. 1802–9, 2005.
- [206] M. Krawczak, S. Nikolaus, H. von Eberstein, P. Croucher, N. El Mokhtari, and S. Schreiber, “Popgen: population-based recruitment of patients and controls for the analysis of complex genotype-phenotype relationships,” *Community Genet*, vol. 9, no. 1, pp. 55–61, 2006.
- [207] P. Muglia, F. Tozzi, N. Galwey, C. Francks, R. Upmanyu, X. Kong, A. Antoniadis, E. Domenici, J. Perry, S. Rothen, C. Vandeleur, V. Mooser, G. Waeber, P. Vollenweider, M. Preisig, S. Lucae, B. Mller-Myhsok, F. Holsboer, L. Middleton, and A. Roses, “Genome-wide association study of recurrent major depressive disorder in two european case-control cohorts,” *Mol Psychiatry*, 2008.
- [208] Y. Teo, M. Inouye, K. Small, R. Gwilliam, P. Deloukas, D. Kwiatkowski, and T. Clark, “A genotype calling algorithm for the illumina beadarray platform,” *Bioinformatics.*, vol. 23, no. 20, pp. 2741–6, 2007.
- [209] S. Purcell, B. Neale, K. Todd-Brown, L. Thomas, M. Ferreira, D. Bender, J. Maller, P. Sklar, P. deBakker, M. Daly, and P. Sham, “Plink: a tool set for whole-genome association and population-based linkage analyses,” *Am J Hum Genet*, vol. 81, no. 3, pp. 559–75, 2007.

- [210] D. Nyholt, “A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other.,” *Am J Hum Genet.*, vol. 74, no. 4, pp. 765–769, 2004.
- [211] B. N. Howie, P. Donnelly, and J. Marchini, “A flexible and accurate genotype imputation method for the next generation of genome-wide association studies,” *PLoS Genet.*, vol. 5, no. 6, p. e1000529, 2009.
- [212] A. Dimas, S. Deutsch, B. Stranger, S. Montgomery, C. Borel, H. Attar-Cohen, C. Ingle, C. Beazley, M. Gutierrez Arcelus, M. Sekowska, M. Gagnebin, J. Nisbett, P. Deloukas, E. Dermitzakis, and S. Antonarakis, “Common regulatory variation impacts gene expression in a cell type-dependent manner,” *Science*, vol. 325, no. 5945, pp. 1246–50, 2009.
- [213] J. Marchini, B. Howie, S. Myers, G. McVean, and P. Donnelly, “A new multipoint method for genome-wide association studies by imputation of genotypes,” *Nat Genet.*, vol. 39, no. 7, pp. 906–13, 2007.
- [214] R. Magi and A. P. Morris, “Gwama: software for genome-wide association meta-analysis,” *BMC Bioinformatics*, vol. 11, p. 288, 2010.
- [215] P. Flicek, B. L. Aken, B. Ballester, K. Beal, E. Bragin, S. Brent, Y. Chen, P. Clapham, G. Coates, S. Fairley, S. Fitzgerald, J. Fernandez-Banet, L. Gordon, S. Graf, S. Haider, M. Hammond, K. Howe, A. Jenkinson, N. Johnson, A. Kahari, D. Keefe, S. Keenan, R. Kinsella, F. Kokocinski, G. Koscielny, E. Kulesha, D. Lawson, I. Longden, T. Massingham, W. McLaren, K. Megy, B. Overduin, B. Pritchard, D. Rios, M. Ruffier, M. Schuster, G. Slater, D. Smedley, G. Spudich, Y. A. Tang, S. Trevanion, A. Vilella, J. Vogel,

- S. White, S. P. Wilder, A. Zadissa, E. Birney, F. Cunningham, I. Dunham, R. Durbin, X. M. Fernandez-Suarez, J. Herrero, T. J. Hubbard, A. Parker, G. Proctor, J. Smith, and S. M. Searle, “Ensembl’s 10th year,” *Nucleic Acids Res*, vol. 38, no. Database issue, pp. D557–62, 2010.
- [216] L. G. Wilming, J. G. Gilbert, K. Howe, S. Trevanion, T. Hubbard, and J. L. Harrow, “The vertebrate genome annotation (vega) database,” *Nucleic Acids Res*, vol. 36, no. Database issue, pp. D753–60, 2008.
- [217] H. Li, J. Ruan, and R. Durbin, “Mapping short dna sequencing reads and calling variants using mapping quality scores,” *Genome Res*, vol. 18, no. 11, pp. 1851–8, 2008.
- [218] H. Li, B. Handsaker, A. Wysoker, T. Fennell, J. Ruan, N. Homer, G. Marth, G. Abecasis, and R. Durbin, “The sequence alignment/map format and sam-tools,” *Bioinformatics*, vol. 25, no. 16, pp. 2078–9, 2009.
- [219] A. R. Quinlan and I. M. Hall, “Bedtools: a flexible suite of utilities for comparing genomic features,” *Bioinformatics*, vol. 26, no. 6, pp. 841–2, 2010.
- [220] J. C. Barrett, B. Fry, J. Maller, and M. J. Daly, “Haploview: analysis and visualization of ld and haplotype maps,” *Bioinformatics*, vol. 21, no. 2, pp. 263–5, 2005.
- [221] S. B. Gabriel, S. F. Schaffner, H. Nguyen, J. M. Moore, J. Roy, B. Blumenstiel, J. Higgins, M. DeFelice, A. Lochner, M. Faggart, S. N. Liu-Cordero, C. Rotimi, A. Adeyemo, R. Cooper, R. Ward, E. S. Lander, M. J. Daly, and D. Altshuler, “The structure of haplotype blocks in the human genome,” *Science*, vol. 296, no. 5576, pp. 2225–9, 2002.

- [222] M. Morley, C. M. Molony, T. M. Weber, J. L. Devlin, K. G. Ewens, R. S. Spielman, and V. G. Cheung, “Genetic analysis of genome-wide variation in human gene expression,” *Nature*, vol. 430, no. 7001, pp. 743–7, 2004.
- [223] E. E. Schadt, S. A. Monks, T. A. Drake, A. J. Lusis, N. Che, V. Colinayo, T. G. Ruff, S. B. Milligan, J. R. Lamb, G. Cavet, P. S. Linsley, M. Mao, R. B. Stoughton, and S. H. Friend, “Genetics of gene expression surveyed in maize, mouse and man,” *Nature*, vol. 422, no. 6929, pp. 297–302, 2003.
- [224] Y. Nishimura, C. Martin, A. Vazquez-Lopez, S. Spence, A. Alvarez-Retuerto, M. Sigman, C. Steindler, S. Pellegrini, N. Schanen, S. Warren, and D. Geschwind, “Genome-wide expression profiling of lymphoblastoid cell lines distinguishes different forms of autism and reveals shared pathways.,” *Hum Mol Genet.*, vol. 16, no. 14, pp. 1682–1698, 2007.
- [225] R. Gingras, C. Richard, M. El-Alfy, C. R. Morales, M. Potier, and A. V. Pshezhetsky, “Purification, cdna cloning, and expression of a new human blood plasma glutamate carboxypeptidase homologous to n-acetyl-aspartyl-alpha-glutamate carboxypeptidase/prostate-specific membrane antigen,” *J Biol Chem*, vol. 274, no. 17, pp. 11742–50, 1999.
- [226] Z. Alam, N. Coombes, R. H. Waring, A. C. Williams, and G. B. Steventon, “Plasma levels of neuroexcitatory amino acids in patients with migraine or tension headache,” *J Neurol Sci*, vol. 156, no. 1, pp. 102–6, 1998.
- [227] M. D. Ferrari, J. Odink, K. D. Bos, M. J. Malessy, and G. W. Bruyn, “Neuroexcitatory plasma amino acids are elevated in migraine,” *Neurology*, vol. 40, no. 10, pp. 1582–6, 1990.

- [228] A. Ferrari, L. Spaccapelo, D. Pinetti, R. Tacchi, and A. Bertolini, “Effective prophylactic treatments of migraine lower plasma glutamate levels,” *Cephalalgia*, vol. 29, no. 4, pp. 423–9, 2009.
- [229] M. Vaccaro, C. Riva, L. Tremolizzo, M. Longoni, A. Aliprandi, E. Agostoni, A. Rigamonti, M. Leone, G. Bussone, and C. Ferrarese, “Platelet glutamate uptake and release in migraine with and without aura,” *Cephalalgia*, vol. 27, no. 1, pp. 35–40, 2007.
- [230] H. H. Schaumburg, R. Byck, R. Gerstl, and J. H. Mashman, “Monosodium l-glutamate: its pharmacology and role in the chinese restaurant syndrome,” *Science*, vol. 163, no. 869, pp. 826–8, 1969.
- [231] D. C. Kang, Z. Z. Su, D. Sarkar, L. Emdad, D. J. Volsky, and P. B. Fisher, “Cloning and characterization of hiv-1-inducible astrocyte elevated gene-1, aeg-1,” *Gene*, vol. 353, no. 1, pp. 8–15, 2005.
- [232] Z. Z. Su, D. C. Kang, Y. Chen, O. Pekarskaya, W. Chao, D. J. Volsky, and P. B. Fisher, “Identification and cloning of human astrocyte genes displaying elevated expression after infection with hiv-1 or exposure to hiv-1 envelope glycoprotein by rapid subtraction hybridization, rash,” *Oncogene*, vol. 21, no. 22, pp. 3592–602, 2002.
- [233] Z. Z. Su, Y. Chen, D. C. Kang, W. Chao, M. Simm, D. J. Volsky, and P. B. Fisher, “Customized rapid subtraction hybridization (rash) gene microarrays identify overlapping expression changes in human fetal astrocytes resulting from human immunodeficiency virus-1 infection or tumor necrosis factor-alpha treatment,” *Gene*, vol. 306, pp. 67–78, 2003.

- [234] F. A. Chaudhry, K. P. Lehre, M. van Lookeren Campagne, O. P. Ottersen, N. C. Danbolt, and J. Storm-Mathisen, "Glutamate transporters in glial plasma membranes: highly differentiated localizations revealed by quantitative ultrastructural immunocytochemistry," *Neuron*, vol. 15, no. 3, pp. 711–20, 1995.
- [235] G. Pines, N. C. Danbolt, M. Bjoras, Y. Zhang, A. Bendahan, L. Eide, H. Koepsell, J. Storm-Mathisen, E. Seeberg, and B. I. Kanner, "Cloning and expression of a rat brain l-glutamate transporter," *Nature*, vol. 360, no. 6403, pp. 464–7, 1992.
- [236] J. D. Rothstein, L. Martin, A. I. Levey, M. Dykes-Hoberg, L. Jin, D. Wu, N. Nash, and R. W. Kuncl, "Localization of neuronal and glial glutamate transporters," *Neuron*, vol. 13, no. 3, pp. 713–25, 1994.
- [237] M. A. Moskowitz, K. Nozaki, and R. P. Kraig, "Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms," *J Neurosci*, vol. 13, no. 3, pp. 1167–77, 1993.
- [238] R. P. Woods, M. Iacoboni, and J. C. Mazziotta, "Brief report: bilateral spreading cerebral hypoperfusion during spontaneous migraine headache," *N Engl J Med*, vol. 331, no. 25, pp. 1689–92, 1994.
- [239] B. de Vries, H. Mamsa, A. H. Stam, J. Wan, S. L. Bakker, K. R. Vanmolkot, J. Haan, G. M. Terwindt, E. M. Boon, B. D. Howard, R. R. Frants, R. W. Baloh, M. D. Ferrari, J. C. Jen, and A. M. van den Maagdenberg, "Episodic

- ataxia associated with *eaat1* mutation c186s affecting glutamate reuptake,” *Arch Neurol*, vol. 66, no. 1, pp. 97–101, 2009.
- [240] M. Peeters, M. J. Gunthorpe, P. J. Strijbos, P. Goldsmith, N. Upton, and M. F. James, “Effects of pan- and subtype-selective n-methyl-d-aspartate receptor antagonists on cortical spreading depression in the rat: therapeutic potential for migraine,” *J Pharmacol Exp Ther*, vol. 321, no. 2, pp. 564–72, 2007.
- [241] M. Bigal, A. Rapoport, F. Sheftell, D. Tepper, and S. Tepper, “Memantine in the preventive treatment of refractory migraine,” *Headache*, vol. 48, no. 9, pp. 1337–42, 2008.
- [242] A. Charles, C. Flippen, M. Romero Reyes, and K. C. Brennan, “Memantine for prevention of migraine: a retrospective study of 60 cases,” *J Headache Pain*, vol. 8, no. 4, pp. 248–50, 2007.
- [243] V. Anttila, H. Stefansson, M. Kallela, U. Todt, G. M. Terwindt, M. S. Calafato, D. R. Nyholt, A. S. Dimas, T. Freilinger, B. Muller-Myhsok, V. Arto, M. Inouye, K. Alakurtti, M. A. Kaunisto, E. Hamalainen, B. de Vries, A. H. Stam, C. M. Weller, A. Heinze, K. Heinze-Kuhn, I. Goebel, G. Borck, H. Gobel, S. Steinberg, C. Wolf, A. Bjornsson, G. Gudmundsson, M. Kirchmann, A. Hauge, T. Werge, J. Schoenen, J. G. Eriksson, K. Hagen, L. Stovner, H. E. Wichmann, T. Meitinger, M. Alexander, S. Moebus, S. Schreiber, Y. S. Aulchenko, M. M. Breteler, A. G. Uitterlinden, A. Hofman, C. M. van Duijn, P. Tikka-Kleemola, S. Vepsalainen, S. Lucae, F. Tozzi, P. Muglia, J. Barrett, J. Kaprio, M. Farkkila, L. Peltonen, K. Ste-

- fansson, J. A. Zwart, M. D. Ferrari, J. Olesen, M. Daly, M. Wessman, A. M. van den Maagdenberg, M. Dichgans, C. Kubisch, E. T. Dermitzakis, R. R. Frants, and A. Palotie, “Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1,” *Nat Genet*, vol. 42, no. 10, pp. 869–73, 2010.
- [244] D. I. Chasman, M. Schurks, V. Anttila, B. de Vries, U. Schminke, L. J. Launer, G. M. Terwindt, A. M. van den Maagdenberg, K. Fendrich, H. Volzke, F. Ernst, L. R. Griffiths, J. E. Buring, M. Kallela, T. Freilinger, C. Kubisch, P. M. Ridker, A. Palotie, M. D. Ferrari, W. Hoffmann, R. Y. Zee, and T. Kurth, “Genome-wide association study reveals three susceptibility loci for common migraine in the general population,” *Nat Genet*, vol. 43, no. 7, pp. 695–8, 2011.
- [245] J. Marchini and B. Howie, “Genotype imputation for genome-wide association studies,” *Nat Rev Genet*, vol. 11, no. 7, pp. 499–511, 2010.
- [246] W. Knowlton, R. Daniels, R. Palkar, D. McCoy, and M. DD., “Pharmacological blockade of trpm8 ion channels alters cold and cold pain responses in mice,” *Plos*, vol. 6, no. 9, p. e25894, 2011.
- [247] P. Wrigley, H. Jeong, and C. Vaughan, “Primary afferents with trpm8 and trpa1 profiles target distinct subpopulations of rat superficial dorsal horn neurones,” *Br J Pharmacol.*, vol. 157, no. 3, pp. 371–80, 2009.
- [248] Y. Liu and N. Qin, “Trpm8 in health and disease: cold sensing and beyond,” *Adv Exp Med Biol.*, vol. 704, pp. 185–208, 2011.

- [249] Biondi, “Is migraine a neuropathic pain syndrome?,” *Curr Pain Headache Rep.*, vol. 10, no. 3, pp. 167–78, 2006.
- [250] L. Broad, A. Mogg, R. Beattie, A. Ogden, M. Blanco, and D. Bleakman, “Trp channels as emerging targets for pain therapeutics,” *Expert Opin Ther Targets.*, vol. 13, no. 1, pp. 69–81, 2009.
- [251] M. Franchini and M. Montagnana, “Low-density lipoprotein receptor-related protein 1: new functions for an old molecule,” *Clin Chem Lab Med.*, vol. 49, no. 6, pp. 967–70, 2011.
- [252] S. Ranganathan, C. Cao, J. Catania, M. Migliorini, L. Zhang, and D. Strickland, “Molecular basis for the interaction of low density lipoprotein receptor-related protein 1 (lrp1) with integrin alphabeta2: identification of binding sites within alphabeta2 for lrp1,” *J Biol Chem.*, vol. 286, no. 35, p. 30535, 2011.
- [253] A. Lillis, L. Van Duyn, J. Murphy-Ullrich, and D. Strickland, “Ldl receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies,” *Physiol Rev.*, vol. 88, no. 3, pp. 887–918, 2008.
- [254] P. Boucher, M. Gotthardt, W. Li, R. Anderson, and J. Herz, “Lrp: role in vascular wall integrity and protection from atherosclerosis,” *Science*, vol. 300, no. 5617, pp. 329–32, 2003.
- [255] Q. Liu, J. Trotter, J. Zhang, M. Peters, H. Cheng, J. Bao, X. Han, E. Weeber, and G. Bu, “Neuronal lrp1 knockout in adult mice leads to impaired brain lipid metabolism and progressive, age-dependent synapse loss and neurodegeneration,” *J Neurosci*, vol. 30, no. 50, pp. 17068–78, 2010.

- [256] M. Vikelis and D. Mitsikostas, “The role of glutamate and its receptors in migraine.,” *CNS Neurol Disord Drug Targets*, vol. 6, no. 4, pp. 251–7, 2007.
- [257] A. Kanai, K. Suzuki, K. Tanimoto, J. Mizushima-Sugano, Y. Suzuki, and S. Sugano, “Characterization of stat6 target genes in human b cells and lung epithelial cells.,” *DNA Res*, vol. 18, no. 5, pp. 379–92, 2011.
- [258] M. Bennett, R. Pollitt, S. Goodman, D. Hale, and J. Vamecq, “Atypical riboflavin-responsive glutaric aciduria, and deficient peroxisomal glutaryl-coa oxidase activity: a new peroxisomal disorder,” *J Inherit Metab Dis*, vol. 14, no. 2, pp. 165–73, 1991.
- [259] E. Sherman, K. Strauss, S. Tortorelli, M. Bennett, I. Knerr, D. Morton, and E. Puffenberger, “Genetic mapping of glutaric aciduria, type 3, to chromosome 7 and identification of mutations in *c7orf10*,” *Am J Hum Genet*, vol. 83, no. 5, pp. 604–609, 2008.
- [260] Y. Even, S. Durieux, M. Escande, J. Lozano, G. Peaucellier, D. Weil, and A. Genevir, “Cdc215, a cdk-like kinase with rs domain, interacts with the asf/sf2-associated protein p32 and affects splicing in vivo.,” *J Cell Biochem.*, vol. 99, no. 3, pp. 890–904, 2006.
- [261] S. B. Ng, A. W. Bigham, K. J. Buckingham, M. C. Hannibal, M. J. McMillin, H. I. Gildersleeve, A. E. Beck, H. K. Tabor, G. M. Cooper, H. C. Mefford, C. Lee, E. H. Turner, J. D. Smith, M. J. Rieder, K. Yoshiura, N. Matsumoto, T. Ohta, N. Niikawa, D. A. Nickerson, M. J. Bamshad, and J. Shendure, “Exome sequencing identifies *mll2* mutations as a cause of kabuki syndrome,” *Nat Genet*, vol. 42, no. 9, pp. 790–3, 2010.

- [262] M. Choi, U. I. Scholl, W. Ji, T. Liu, I. R. Tikhonova, P. Zumbo, A. Nayir, A. Bakkaloglu, S. Ozen, S. Sanjad, C. Nelson-Williams, A. Farhi, S. Mane, and R. P. Lifton, “Genetic diagnosis by whole exome capture and massively parallel dna sequencing,” *Proc Natl Acad Sci U S A*, vol. 106, no. 45, pp. 19096–101, 2009.
- [263] S. B. Ng, E. H. Turner, P. D. Robertson, S. D. Flygare, A. W. Bigham, C. Lee, T. Shaffer, M. Wong, A. Bhattacharjee, E. E. Eichler, M. Bamshad, D. A. Nickerson, and J. Shendure, “Targeted capture and massively parallel sequencing of 12 human exomes,” *Nature*, vol. 461, no. 7261, pp. 272–6, 2009.
- [264] K. D. Pruitt, J. Harrow, R. A. Harte, C. Wallin, M. Diekhans, D. R. Maglott, S. Searle, C. M. Farrell, J. E. Loveland, B. J. Ruef, E. Hart, M. M. Suner, M. J. Landrum, B. Aken, S. Ayling, R. Baertsch, J. Fernandez-Banet, J. L. Cherry, V. Curwen, M. Dicuccio, M. Kellis, J. Lee, M. F. Lin, M. Schuster, A. Shkeda, C. Amid, G. Brown, O. Dukhanina, A. Frankish, J. Hart, B. L. Maidak, J. Mudge, M. R. Murphy, T. Murphy, J. Rajan, B. Rajput, L. D. Riddick, C. Snow, C. Steward, D. Webb, J. A. Weber, L. Wilming, W. Wu, E. Birney, D. Haussler, T. Hubbard, J. Ostell, R. Durbin, and D. Lipman, “The consensus coding sequence (ccds) project: Identifying a common protein-coding gene set for the human and mouse genomes,” *Genome Res*, vol. 19, no. 7, pp. 1316–23, 2009.
- [265] A. J. Coffey, F. Kokocinski, M. S. Calafato, C. E. Scott, P. Palta, E. Drury, C. J. Joyce, E. M. Leproust, J. Harrow, S. Hunt, A. E. Lehesjoki, D. J. Turner, T. J. Hubbard, and A. Palotie, “The gencode exome: sequencing

- the complete human exome,” *Eur J Hum Genet*, vol. 19, no. 7, pp. 827–31, 2011.
- [266] C. A. Hubner and T. J. Jentsch, “Ion channel diseases,” *Hum Mol Genet*, vol. 11, no. 20, pp. 2435–45, 2002.
- [267] P. Futreal, L. Coin, M. Marshall, T. Down, T. Hubbard, R. Wooster, N. Rahman, and M. Stratton, “A census of human cancer genes,” *Nat Rev Canc*, vol. 4, no. 3, pp. 177–83, 2004.
- [268] E. Kalay, G. Yigit, Y. Aslan, K. Brown, E. Pohl, L. Bicknell, H. Kayserili, Y. Li, a. et, and B. Wollnik, “Cep152 is a genome maintenance protein disrupted in seckel syndrome.,” *Nat Gen*, vol. 43, no. 1, pp. 23–26, 2011.
- [269] C. A. Albers, A. Cvejic, R. Favier, E. E. Bouwmans, M. C. Alessi, P. Bertone, G. Jordan, R. N. Kettleborough, G. Kiddle, M. Kostadima, R. J. Read, B. Sipos, S. Sivapalaratnam, P. A. Smethurst, J. Stephens, K. Voss, A. Nurden, A. Rendon, P. Nurden, and W. H. Ouwehand, “Exome sequencing identifies nbeal2 as the causative gene for gray platelet syndrome,” *Nat Genet*, 2011.
- [270] M. Krawczak, J. Reiss, and D. N. Cooper, “The mutational spectrum of single base-pair substitutions in mrna splice junctions of human genes: causes and consequences,” *Hum Genet*, vol. 90, no. 1-2, pp. 41–54, 1992.
- [271] G. S. Wang and T. A. Cooper, “Splicing in disease: disruption of the splicing code and the decoding machinery,” *Nat Rev Genet*, vol. 8, no. 10, pp. 749–61, 2007.

- [272] S. G. Amara and A. C. Fontana, “Excitatory amino acid transporters: keeping up with glutamate,” *Neurochem Int*, vol. 41, no. 5, pp. 313–8, 2002.
- [273] J. Johnson, J. Mandrioli, M. Benatar, Y. Abramzon, V. Van Deerlin, J. Trojanowski, J. Gibbs, M. Brunetti, S. Gronka, J. Wu, D. J., L. McCluskey, M. Martinez-Lage, D. Falcone, D. Hernandez, S. Arepalli, S. Chong, J. Schymick, J. Rothstein, F. Landi, Y. Wang, A. Calvo, G. Mora, M. Sabatelli, M. Monsurr, S. Battistini, F. Salvi, R. Spataro, P. Sola, G. Borghero, I. Consortium, G. Galassi, S. Scholz, J. Taylor, G. Restagno, A. Chi, and B. Traynor, “Exome sequencing reveals vcp mutations as a cause of familial als,” *Neuron*, vol. 68, no. 5, p. 857, 2010.