References

- ¹N Risch and K Merikangas. The future of genetic studies of complex human diseases. *Science*, 273(5281):1516–1517, September 1996. PMID: 8801636
- ² P M Visscher, M A Brown, and M I McCarthy. Five years of GWAS discovery. *The American Journal of Human Genetics*, 2012. PMC3257326
- ³ The International Schizophrenia Consortium, Manuscript preparation, Data analysis, GWAS analysis subgroup, Polygene analyses subgroup, Management committee, Cardiff University, Karolinska Institutet/University of North Carolina at Chapel Hill, Trinity College Dublin, University College London, University of Aberdeen, University of Edinburgh, Queensland Institute of Medical Research, University of Southern California, Massachusetts General Hospital, and Stanley Center for Psychiatric Research and Broad Institute of MIT and Harvard. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, 460(7256):748–752, June 2009. PMC3912837
- ⁴ S Hong Lee, Teresa R DeCandia, Stephan Ripke, Jian Yang, Patrick F Sullivan, Michael E Goddard, Matthew C Keller, Peter M Visscher, and Naomi R Wray. Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. *Nature Genetics*, 44(3):247–250, February 2012. PMC3327879
- ⁵ Po-Ru Loh, Gaurav Bhatia, Alexander Gusev, Hilary K Finucane, Brendan K Bulik-Sullivan, Samuela J Pollack, Teresa R de Candia, Sang Hong Lee, Naomi R Wray, Kenneth S Kendler, Michael C O'Donovan, Benjamin M Neale, Nick Patterson, and Alkes L Price. Contrasting genetic architectures of schizophrenia and other complex diseases using fast variance-components analysis. *Nature Publishing Group*, 47(12):1385–1392, November 2015. PMC4666835
- ⁶ Stephan Ripke, Benjamin M Neale, Aiden Corvin, James T R Walters, Kai-How Farh, Peter A Holmans, Phil Lee, Brendan Bulik-Sullivan, David A Collier, Hailiang Huang, Tune H Pers, Ingrid Agartz, Esben Agerbo, Margot Albus, Madeline Alexander, Faroog Amin, Silviu A Bacanu, Martin Begemann, Richard A Belliveau Jr, Judit Bene, Sarah E Bergen, Elizabeth Bevilacqua, Tim B Bigdeli, Donald W Black, Richard Bruggeman, Nancy G Buccola, Randy L Buckner, William Byerley, Wiepke Cahn, Guiqing Cai, Dominique Campion, Rita M Cantor, Vaughan J Carr. Noa Carrera, Stanley V Catts, Kimberly D Chambert, Raymond C K Chan, Ronald Y L Chen, Eric Y H Chen, Wei Cheng, Eric F C Cheung, Siow Ann Chong, C Robert Cloninger, David Cohen, Nadine Cohen, Paul Cormican, Nick Craddock, James J Crowley, David Curtis, Michael Davidson, Kenneth L Davis, Franziska Degenhardt, Jurgen Del Favero, Ditte Demontis, Dimitris Dikeos, Timothy Dinan, Srdjan Djurovic, Gary Donohoe, Elodie Drapeau, Jubao Duan, Frank Dudbridge, Naser Durmishi, Peter Eichhammer, Johan Eriksson, Valentina Escott-Price, Laurent Essioux, Ayman H Fanous, Martilias S Farrell, Josef Frank, Lude Franke, Robert Freedman, Nelson B Freimer, Marion Friedl, Joseph I Friedman, Menachem Fromer, Giulio Genovese, Lyudmila Georgieva, Ina Giegling, Paola Giusti-Rodríguez, Stephanie Godard, Jacqueline I Goldstein, Vera Golimbet, Srihari Gopal, Jacob Gratten, Lieuwe de Haan, Christian Hammer, Marian L Hamshere, Mark Hansen, Thomas Hansen, Vahram Haroutunian, Annette M Hartmann, Frans A Henskens, Stefan Herms, Joel N Hirschhorn, Per Hoffmann, Andrea Hofman, Mads V Hollegaard, David M Hougaard, Masashi Ikeda, Inge Joa, Antonio Julià, René S Kahn, Luba Kalaydjieva, Sena Karachanak-Yankova, Juha Karjalainen, David Kavanagh, Matthew C Keller, James L Kennedy, Andrey Khrunin, Yunjung Kim, Janis Klovins, James A Knowles, Bettina Konte, Vaidutis Kucinskas, Zita Ausrele Kucinskiene, Hana Kuzelova-Ptackova, Anna K Kähler, Claudine Laurent, Jimmy Lee Chee Keong, S Hong Lee, Sophie E Legge, Bernard Lerer, Miaoxin Li, Tao Li, Kung-Yee Liang, Jeffrey Lieberman, Svetlana Limborska, Carmel M Loughland, Jan Lubinski, Jouko Lönngvist, Milan Macek Jr, Patrik K E Magnusson, Brion S Maher, Wolfgang Maier, Jacques Mallet, Sara Marsal, Manuel Mattheisen, Morten Mattingsdal, Robert W McCarley, Colm McDonald, Andrew M McIntosh, Sandra Meier, Carin J Meijer, Bela Melegh, Ingrid Melle, Raquelle I Mesholam-Gately, Andres Metspalu, Patricia T Michie, Lili Milani, Vihra Milanova, Younes Mokrab, Derek W Morris, Ole Mors, Kieran C Murphy, Robin M Murray, Inez Myin-Germeys, Bertram Müller-Myhsok, Mari Nelis, Igor Nenadic, Deborah A Nertney, Gerald Nestadt, Kristin K Nicodemus, Liene Nikitina-Zake, Laura Nisenbaum, Annelie Nordin, Eadbhard O'Callaghan, Colm O'Dushlaine, F Anthony O'Neill, Sang-Yun Oh, Ann Olincy, Line Olsen, Jim Van Os, Psychosis Endophenotypes International Consortium, Christos Pantelis, George N Papadimitriou, Sergi Papiol, Elena Parkhomenko, Michele T Pato, Tiina

Paunio, Milica Pejovic-Milovancevic, Diana O Perkins, Olli Pietiläinen, Jonathan Pimm, Andrew J Pocklington, John Powell, Alkes Price, Ann E Pulver, Shaun M Purcell, Digby Quested, Henrik B Rasmussen, Abraham Reichenberg, Mark A Reimers, Alexander L Richards, Joshua L Roffman, Panos Roussos, Douglas M Ruderfer, Veikko Salomaa, Alan R Sanders, Ulrich Schall, Christian R Schubert, Thomas G Schulze, Sibvlle G Schwab, Edward M Scolnick, Rodney J Scott, Larry J Seidman, Jianxin Shi, Engilbert Sigurdsson, Teimuraz Silagadze, Jeremy M Silverman, Kang Sim, Petr Slominsky, Jordan W Smoller, Hon-Cheong So, ChrisC A Spencer, Eli A Stahl, Hreinn Stefansson, Stacy Steinberg, Elisabeth Stogmann, Richard E Straub, Eric Strengman, Jana Strohmaier, T Scott Stroup, Mythily Subramaniam, Jaana Suvisaari, Dragan M Svrakic, Jin P Szatkiewicz, Erik Söderman, Srinivas Thirumalai, Draga Toncheva, Sarah Tosato, Juha Veijola, John Waddington, Dermot Walsh, Dai Wang, Qiang Wang, Bradley T Webb, Mark Weiser, Dieter B Wildenauer, Nigel M Williams, Stephanie Williams, Stephanie H Witt, Aaron R Wolen, Emily H M Wong, Brandon K Wormley, Hualin Simon Xi, Clement C Zai, Xuebin Zheng, Fritz Zimprich, Naomi R Wray, Kari Stefansson, Peter M Visscher, Wellcome Trust Case-Control Consortium, Rolf Adolfsson, Ole A Andreassen, Douglas H R Blackwood, Elvira Bramon, Joseph D Buxbaum, Anders D Børglum, Sven Cichon, Ariel Darvasi, Enrico Domenici, Hannelore Ehrenreich, Tõnu Esko, Pablo V Gejman, Michael Gill, Hugh Gurling, Christina M Hultman, Nakao Iwata, Assen V Jablensky, Erik G Jönsson, Kenneth S Kendler, George Kirov, Jo Knight, Todd Lencz, Douglas F Levinson, Qingqin S Li, Jianjun Liu, Anil K Malhotra, Steven A McCarroll, Andrew McQuillin, Jennifer L Moran, Preben B Mortensen, Bryan J Mowry, Markus M Nöthen, Roel A Ophoff, Michael J Owen, Aarno Palotie, Carlos N Pato, Tracev L Petryshen, Danielle Posthuma, Marcella Rietschel, Brien P Riley, Dan Ruiescu, Pak C Sham, Pamela Sklar, David St Clair, Daniel R Weinberger, Jens R Wendland, Thomas Werge, Mark J Daly, Patrick F Sullivan, and Michael C O'Donovan. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, 511(7510):421-427, July 2014. PMC4112379

- ⁷ A L Richards, G Leonenko, J T Walters, D H Kavanagh, E G Rees, A Evans, K D Chambert, J L Moran, J Goldstein, B M Neale, S A McCarroll, A J Pocklington, P A Holmans, M J Owen, and M C O'Donovan. Exome arrays capture polygenic rare variant contributions to schizophrenia. *Human Molecular Genetics*, 25(5):1001–1007, February 2016. PMC4754044
- ⁸ Giulio Genovese, Menachem Fromer, Eli A Stahl, Douglas M Ruderfer, Kimberly Chambert, Mikael Landén, Jennifer L Moran, Shaun M Purcell, Pamela Sklar, Patrick F Sullivan, Christina M Hultman, and Steven A McCarroll. Increased burden of ultra-rare protein-altering variants among 4,877 individuals with schizophrenia. *Nature Neuroscience*, 19(11):1433–1441, October 2016.PMC5104192
- ⁹ Shaun M Purcell, Jennifer L Moran, Menachem Fromer, Douglas Ruderfer, Nadia Solovieff, Panos Roussos, Colm O'Dushlaine, Kimberly Chambert, Sarah E Bergen, Anna Kähler, Laramie Duncan, Eli Stahl, Giulio Genovese, Esperanza Fernández, Mark O Collins, Noboru H Komiyama, Jyoti S Choudhary, Patrik K E Magnusson, Eric Banks, Khalid Shakir, Kiran Garimella, Tim Fennell, Mark DePristo, Seth G N Grant, Stephen J Haggarty, Stacey Gabriel, Edward M Scolnick, Eric S Lander, Christina M Hultman, Patrick F Sullivan, Steven A McCarroll, and Pamela Sklar. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*, 506(7487):185–190, February 2014. PMC4136494
- ¹⁰ Jian Yang, Beben Benyamin, Brian P McEvoy, Scott Gordon, Anjali K Henders, Dale R Nyholt, Pamela A Madden, Andrew C Heath, Nicholas G Martin, Grant W Montgomery, Michael E Goddard, and Peter M Visscher. Common SNPs explain a large proportion of the heritability for human height. *Nature Genetics*, 42(7):565–569, June 2010.PMC3232052
- Huwenbo Shi, Gleb Kichaev, and Bogdan Pasaniuc. Contrasting the Genetic Architecture of 30 Complex Traits from Summary Association Data. *The American Journal of Human Genetics*, 99(1):139–153, July 2016. PMC5005444
- ¹² Carlos Eduardo Guerra Amorim, Ziuye Gao, Zachary Baker, Jose Francisco Diesel, Yuval B Simons, Imran S Haque, Joseph Pickrell, and Molly Przeworski. The population genetics of human disease: the case of recessive, lethal mutations. *bioRxiv*, pages 1–43, December 2016. [preprint]
- ¹³ Toby Johnson and Nick Barton. Theoretical models of selection and mutation on quantitative traits. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360(1459):1411–1425, July 2005.PMC1569515

- ¹⁴ Teri A Manolio, Francis S Collins, Nancy J Cox, David B Goldstein, Lucia A Hindorff, David J Hunter, Mark I McCarthy, Erin M Ramos, Lon R Cardon, Aravinda Chakravarti, Judy H Cho, Alan E Guttmacher, Augustine Kong, Leonid Kruglyak, Elaine Mardis, Charles N Rotimi, Montgomery Slatkin, David Valle, Alice S Whittemore, Michael Boehnke, Andrew G Clark, Evan E Eichler, Greg Gibson, Jonathan L Haines, Trudy F C Mackay, Steven A McCarroll, and Peter M Visscher. Finding the missing heritability of complex diseases. *Nature*, 461(7265):747–753, August 2009. PMC2831613
- ¹⁵ Y B Simons, M C Turchin, J K Pritchard, and G Sella. The deleterious mutation load is insensitive to recent population history. *Nature Genetics*, 2014.PMC3953611
- ¹⁶ B Bulik-Sullivan, H K Finucane, V Anttila, and A Gusev. An atlas of genetic correlations across human diseases and traits. *Nature*, 2015.PMC4797329
- ¹⁷ Joseph K Pickrell, Tomaz Berisa, Jimmy Z Liu, Laure Ségurel, Joyce Y Tung, and David A Hinds. Detection and interpretation of shared genetic influences on 42 human traits. *Nature Publishing Group*, 48(7):709–717, May 2016.PMC5207801
- ¹⁸ Peter M Visscher and Jian Yang. A plethora of pleiotropy across complex traits. *Nature Publishing Group*, 48(7):707–708, July 2016.PMID: 27350602
- ¹⁹ Hunter B Fraser. Gene expression drives local adaptation in humans. *Genome Research*, 23(7):1089–1096, July 2013. PMC3698502
- ²⁰ J J Berg and G Coop. A population genetic signal of polygenic adaptation. *PLOS Genetics*, 2014.PMC4125079
- ²¹ E Corona, R Chen, M Sikora, A A Morgan, and C J Patel. Analysis of the genetic basis of disease in the context of worldwide human relationships and migration. *PLoS Genetics*, 2013. PMC3662561
- ²² R Chen, E Corona, M Sikora, J T Dudley, and A A Morgan. Type 2 diabetes risk alleles demonstrate extreme directional differentiation among human populations, compared to other diseases. *PLoS Genetics*, 2012. PMC3325177
- ²³ Q Ayub, L Moutsianas, and Y Chen. Revisiting the thrifty gene hypothesis via 65 loci associated with susceptibility to type 2 diabetes. *The American Journal of Human Genetics*, 2014. PMC3928649
- ²⁴ Renato Polimanti and Joel Gelernter. Widespread signatures of positive selection in common risk alleles associated to autism spectrum disorder. *PLOS Genetics*, 13(2):e1006618–14, February 2017. PMC5328401
- ²⁵ James V Neel. Diabetes Mellitus: A "Thrifty" Genotype Rendered Detrimental by "Progress"? *American journal of human genetics*, 14(4):353–362, December 1962.PMC2557712
- ²⁶ J V Neel. The "thrifty genotype" in 1998. *Nutrition reviews*, 1999. PMID: 10391020
- ²⁷ M Franco, U Bilal, P Ordunez, M Benet, A Morejon, B Caballero, J F Kennelly, and R S Cooper. Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends. *BMJ*, 346(apr09 2):f1515–f1515, April 2013.PMID: 23571838
- ²⁸ G Gibson and G Wagner. Canalization in evolutionary genetics: a stabilizing theory? *BioEssays*, 2000. PMID: 10723034
- ²⁹ G Gibson. Decanalization and the origin of complex disease. *Nature Reviews Genetics*, 10(2):134–140, 2009. PMID: 19119265
- ³⁰ J K Pritchard. Are rare variants responsible for susceptibility to complex diseases? *The American Journal of Human Genetics*, 2001. PMC1226027
- ³¹ J K Pritchard and N J Cox. The allelic architecture of human disease genes: common disease–common variant... or not? *Human Molecular Genetics*, 2002. PMID: 12351577
- ³² A Eyre-Walker. Genetic architecture of a complex trait and its implications for fitness and genome-wide association studies. In *Proceedings of the National Academy of Sciences*, 2010. PMC2868283

- ³³ Vineeta Agarwala, Jason Flannick, Shamil Sunyaev, and David Altshuler. Evaluating empirical bounds on complex disease genetic architecture. *Nature Publishing Group*, 45(12):1418–1427, October 2013.PMC2868283
- ³⁴ Christian Fuchsberger, Jason Flannick, Tanya M Teslovich, Anubha Mahajan, Vineeta Agarwala, Kyle J Gaulton, Clement Ma, Pierre Fontanillas, Loukas Moutsianas, Davis J McCarthy, Manuel A Rivas, John R B Perry, Xueling Sim, Thomas W Blackwell, Neil R Robertson, N William Rayner, Pablo Cingolani, Adam E Locke, Juan Fernandez Tajes, Heather M Highland, Josee Dupuis, Peter S Chines, Cecilia M Lindgren, Christopher Hartl, Anne U Jackson, Han Chen, Jeroen R Huyghe, Martijn van de Bunt, Richard D Pearson, Ashish Kumar, Martina Müller-Nurasyid, Niels Grarup, Heather M Stringham, Eric R Gamazon, Jaehoon Lee, Yuhui Chen, Robert A Scott, Jennifer E Below, Peng Chen, Jinyan, Huang, Min Jin Go, Michael L Stitzel, Dorota Pasko, Stephen C J Parker, Tibor V Varga, Todd Green, Nicola L Beer, Aaron G Day-Williams, Teresa Ferreira, Tasha Fingerlin, Momoko Horikoshi, Cheng Hu, Iksoo Huh, Mohammad Kamran Ikram, Bong-Jo Kim, Yongkang Kim. Young Jin Kim, Min-Seok Kwon, Juyoung Lee, Selyeong Lee, Keng-Han Lin, Taylor J Maxwell, Yoshihiko Nagai, Xu Wang, Ryan P Welch, Joon Yoon, Weihua Zhang, Nir Barzilai, Benjamin F Voight, Bok-Ghee Han, Christopher P Jenkinson, Teemu Kuulasmaa, Johanna Kuusisto, Alisa Manning, Maggie C Y Ng, Nicholette D Palmer, Beverley Balkau, Alena Stanc áková, Hanna E Abboud, Heiner Boeing, Vilmantas Giedraitis, Dorairaj Prabhakaran, Omri Gottesman, James Scott, Jason Carey, Phoenix Kwan, George Grant, Joshua D Smith, Benjamin M Neale, Shaun Purcell, Adam S Butterworth, Joanna M M Howson, Heung Man Lee, Yingchang Lu, Soo-Heon Kwak, Wei Zhao, John Danesh, Vincent K L Lam, Kyong Soo Park, Danish Saleheen, Wing Yee So, Claudia H T Tam, Uzma Afzal, David Aguilar, Rector Arya, Tin Aung, Edmund Chan, Carmen Navarro, Ching-Yu Cheng, Domenico Palli, Adolfo Correa, Joanne E Curran, Denis Rybin, Vidya S Farook, Sharon P Fowler, Barry I Freedman, Michael Griswold, Daniel Esten Hale, Pamela J Hicks, Chiea-Chuen Khor, Satish Kumar, Benjamin Lehne, Dorothée Thuillier, Wei Yen Lim, Jianjun Liu, Yvonne T van der Schouw, Marie Loh, Solomon K Musani, Sobha Puppala, William R Scott, Loïc Yengo, Sian-Tsung Tan, Herman A Taylor, Farook Thameem, Gregory Wilson, Tien Yin Wong, Pål Rasmus Njølstad, Jonathan C Levy, Massimo Mangino, Lori L Bonnycastle, Thomas Schwarzmayr, João Fadista, Gabriela L Surdulescu, Christian Herder, Christopher J Groves, Thomas Wieland, Jette Bork-Jensen, Ivan Brandslund, Cramer Christensen, Heikki A Koistinen, Alex S F Doney, Leena Kinnunen, Tõnu Esko, Andrew J Farmer, Liisa Hakaste, Dylan Hodgkiss, Jasmina Kravic, Valeriya Lyssenko, Mette Hollensted, Marit E Jørgensen, Torben Jørgensen, Claes Ladenvall, Johanne Marie Justesen, Annemari Käräiämäki, Jennifer Kriebel, Wolfgang Rathmann, Lars Lannfelt, Torsten Lauritzen, Narisu Narisu, Allan Linneberg, Olle Melander, Lili Milani, Matt Neville, Marju Orho-Melander, Lu Qi, Qibin Qi, Michael Roden, Olov Rolandsson, Amy Swift, Anders H Rosengren, Kathleen Stirrups, Andrew R Wood, Evelin Mihailov, Christine Blancher, Mauricio O Carneiro, Jared Maguire, Ryan Poplin, Khalid Shakir, Timothy Fennell, Mark DePristo, Martin Hrabé de Angelis, Panos Deloukas, Anette P Gjesing, Goo Jun, Peter Nilsson, Jacquelyn Murphy, Robert Onofrio, Barbara Thorand, Torben Hansen, Christa Meisinger, Frank B Hu, Bo Isomaa, Fredrik Karpe, Liming Liang, Annette Peters, Cornelia Huth, Stephen P O'Rahilly, Colin N A Palmer, Oluf Pedersen, Rainer Rauramaa, Jaakko Tuomilehto, Veikko Salomaa, Richard M Watanabe, Ann-Christine Syvänen, Richard N Bergman, Dwaipayan Bharadwai, Erwin P Bottinger, Yoon Shin Cho, Giriraj R Chandak, Juliana C N Chan, Kee Seng Chia, Mark J Daly, Shah B Ebrahim, Claudia Langenberg, Paul Elliott, Kathleen A Jablonski, Donna M Lehman, Weiping Jia, Ronald C W Ma, Toni I Pollin, Manjinder Sandhu, Nikhil Tandon. Philippe Froquel, Inês Barroso, Yik Ying Teo, Eleftheria Zeggini, Ruth J F Loos, Kerrin S Small, Janina S Ried, Ralph A DeFronzo, Harald Grallert, Benjamin Glaser, Andres Metspalu, Nicholas J Wareham, Mark Walker, Eric Banks, Christian Gieger, Erik Ingelsson, Hae Kyung Im, Thomas Illig, Paul W Franks, Gemma Buck, Joseph Trakalo, David Buck, Inga Prokopenko, Reedik Mägi, Lars Lind, Yossi Farjoun, Katharine R Owen, Anna L Gloyn, Konstantin Strauch, Tiinamaija Tuomi, Jaspal Singh Kooner, Jong-Young Lee, Taesung Park, Peter Donnelly, Andrew D Morris, Andrew T Hattersley, Donald W Bowden, Francis S Collins, Gil Atzmon, John C Chambers, Timothy D Spector, Markku Laakso, Tim M Strom, Graeme I Bell, John Blangero, Ravindranath Duggirala, E Shyong Tai, Gilean McVean, Craig L Hanis, James G Wilson, Mark Seielstad, Timothy M Frayling, James B Meigs, Nancy J Cox, Rob Sladek, Eric S Lander, Stacey Gabriel, Noël P Burtt, Karen L Mohlke, Thomas Meitinger, Leif Groop, Goncalo Abecasis, Jose C Florez, Laura J Scott, Andrew P Morris, Hyun Min Kang, Michael Boehnke, David Altshuler, and Mark I McCarthy. The genetic architecture of type 2 diabetes. Nature, 536(7614):41-47, August 2016. PMC5034897

³⁵ N Mancuso, N Rohland, K A Rand, A Tandon, and A Allen. The contribution of rare variation to prostate cancer

heritability. Nature, 2015. PMID: 26569126

- ³⁶ A Caballero, A Tenesa, and P D Keightley. The nature of genetic variation for complex traits revealed by GWAS and regional heritability mapping analyses. *Genetics*, 2015. PMID: 26569126
- ³⁷ S Wright. An analysis of variability in number of digits in an inbred strain of guinea pigs. *Genetics*, 1934. PMC1208511
- ³⁸ J L Lush, W F Lamoreux, and L N Hazel. The heritability of resistance to death in the fowl. *Poultry Science*, 1948.
- ³⁹ Douglas Falconer and Trudy Mackay. *Introduction to Quantitative Genetics*. Pearson Education Limited, 80 Strand, London, UK, 1996.
- ⁴⁰ D S Falconer. The inheritance of liability to certain diseases, estimated from the incidence among relatives. *Annals of human genetics*, 1965.
- ⁴¹ N Risch. Linkage strategies for genetically complex traits. I. Multilocus models. *American journal of human genetics*, 46(2):222–228, February 1990. PMC1684987
- ⁴² M Slatkin. Exchangeable Models of Complex Inherited Diseases. *Genetics*, 179(4):2253–2261, August 2008. PMC2516095
- ⁴³ Naomi R Wray and Michael E Goddard. Multi-locus models of genetic risk of disease. *Genome Medicine*, 2(2):10, February 2010.PMC2847701
- ⁴⁴ Brian Charlesworth and Deborah Charlesworth. *Elements of Evolutionary Genetics*. Roberts and Company, 4950 South Yosemite Street, F2 #197, Greenwood Village, Colorado 80111 USA, 2010.
- ⁴⁵ Warren Ewens. *Introduction to Quantitative Genetics*. Springer, 11 W 42nd St, New York, NY 10036 USA, 2004.
- ⁴⁶ M Turelli. Heritable genetic variation via mutation-selection balance: Lerch's zeta meets the abdominal bristle. *Theoretical population biology*, 25(2):138–193, April 1984.PMID: 6729751
- ⁴⁷ N H Barton and M Turelli. Evolutionary quantitative genetics: how little do we know? *Annual review of genetics*, 23(1):337–370, 1989. PMID: 2694935
- ⁴⁸ J G Kingsolver, H E Hoekstra, J M Hoekstra, D Berrigan, S N Vignieri, C E Hill, A Hoang, P Gibert, and P Beerli. The strength of phenotypic selection in natural populations. *The American naturalist*, 157(3):245–261, March 2001.PMID: 18707288
- ⁴⁹ Alan Robertson. The effect of selection against extreme deviants based on deviation or on homozygosis. *Journal of Genetics*, 54(2):236–248, 1956.
- ⁵⁰ Xiang Zhou and Matthew Stephens. Efficient multivariate linear mixed model algorithms for genome-wide association studies. *Nature methods*, 11(4):407–409, April 2014. PMC4211878
- ⁵¹ I I Gottesman and T D Gould. The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry*, 2003.PMID: 12668349
- ⁵² J Flint and M R Munafò. The endophenotype concept in psychiatric genetics. *Psychological medicine*, 2007. PMC2829981
- ⁵³ K S Kendler and M C Neale. Endophenotype: a conceptual analysis. *Molecular Psychiatry*, 15(8):789–797, February 2010.PMC2909487
- ⁵⁴ Kevin J Mitchell. What is complex about complex disorders? *Genome biology*, 13(1):237, January 2012. PMC3334577
- ⁵⁵ Jacob A Tennessen, Abigail W Bigham, Timothy D O'Connor, Wenqing Fu, Eimear E Kenny, Simon Gravel, Sean McGee, Ron Do, Xiaoming Liu, Goo Jun, Hyun Min Kang, Daniel Jordan, Suzanne M Leal, Stacey Gabriel, Mark J Rieder, Goncalo Abecasis, David Altshuler, Deborah A Nickerson, Eric Boerwinkle, Shamil Sunyaev, Carlos D Bustamante, Michael J Bamshad, Joshua M Akey, Broad GO, Seattle GO, and NHLBI Exome Sequencing Project. Evolution and functional impact of rare coding variation from deep sequencing of human exomes. *Science*, 337(6090):64–69, July 2012. PMC3708544

- ⁵⁶ Alon Keinan and Andrew G Clark. Recent Explosive Human Population Growth Has Resulted in an Excess of Rare Genetic Variants. *Science*, 336(6082):740–743, May 2012. PMC3586590
- ⁵⁷ F Gao and A Keinan. High burden of private mutations due to explosive human population growth and purifying selection. *BMC genomics*, 2014. PMC4083409
- ⁵⁸ E Gazave, D Chang, A G Clark, and A Keinan. Population growth inflates the per-individual number of deleterious mutations and reduces their mean effect. *Genetics*, 2013.PMC3813877
- ⁵⁹ K E Lohmueller. The impact of population demography and selection on the genetic architecture of complex traits. *PLOS Genetics*, 2014.PMC4038606
- ⁶⁰ S Schiffels and R Durbin. Inferring human population size and separation history from multiple genome sequences. *Nature Genetics*. 2014. PMC4116295
- ⁶¹ Adam Eyre-Walker and Peter D Keightley. The distribution of fitness effects of new mutations. *Nature Reviews Genetics*, 8(8):610–618, August 2007. PMID: 17637733
- ⁶² J K Pickrell. Joint analysis of functional genomic data and genome-wide association studies of 18 human traits. *The American Journal of Human Genetics*, 2014. PMC3980523
- ⁶³ Fernando Racimo and Joshua G Schraiber. Approximation to the Distribution of Fitness Effects across Functional Categories in Human Segregating Polymorphisms. *PLOS Genetics*, 10(11):e1004697–14, November 2014.PMC4222666
- ⁶⁴ F Larribe and P Fearnhead. On composite likelihoods in statistical genetics. *Statistica Sinica*, 2011. PMC4222666
- ⁶⁵ Alec J Coffman, Ping Hsun Hsieh, Simon Gravel, and Ryan N Gutenkunst. Computationally Efficient Composite Likelihood Statistics for Demographic Inference. *Molecular biology and evolution*, 33(2):591–593, February 2016.PMID: 26545922
- ⁶⁶ P C Sham and S M Purcell. Statistical power and significance testing in large-scale genetic studies. *Nature Reviews Genetics*, 2014. PMID: 24739678
- ⁶⁷ D Speed, N Cai, M Johnson, S Nejentsev, and D Balding. Re-evaluation of SNP heritability in complex human traits. *bioRxiv*, 2016. [preprint]
- ⁶⁸ X Zhu and M Stephens. Bayesian large-scale multiple regression with summary statistics from genome-wide association studies. *bioRxiv*, 2016. [preprint]
- ⁶⁹ L Evans, R Tahmasbi, S Vrieze, G Abecasis, and S Das. Comparison of methods that use whole genome data to estimate the heritability and genetic architecture of complex traits. *bioRxiv*, 2017. [preprint]