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## Bibliography

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1. Boomsma, D, Busjahn, A, and Peltonen, L. Classical twin studies and beyond. *Nat.Rev.Genet.* 2002:3(11), 872–882.
2. Dunn, W, Broadhurst, D, Atherton, H, Goodacre, R, and Griffin, J. Systems level studies of mammalian metabolomes: the roles of mass spectrometry and nuclear magnetic resonance spectroscopy. *Chem.Soc.Rev.* 2011:40, 387–426.
3. Naso, PO. *Metamorphoses*. AD 8.
4. van der Greef, J and Smilde, A. Symbiosis of chemometrics and metabolomics: past, present, and future. *J.Chemometrics* 2005:19, 376–386.
5. Orešič, M. Metabolomics, a novel tool for studies of nutrition, metabolism and lipid dysfunction. *Nutr.Metab.Cardiovasc.Dis.* 2009:19(11), 816–824.
6. Crick, F. On protein synthesis. *Symp.Soc.Exp.Biol.* 1958:12, 138–163.
7. Crick, F. Central dogma of molecular biology. *Nature* 1970:227(5258), 561–563.
8. Schreiber, S. Small molecules: the missing link in the central dogma. *Nat.Chem.Biol.* 2005:1(2), 64–66.
9. Goodacre, R. Metabolomics of a superorganism. *J.Nutr.* 2007:137(1 Suppl), 259S–266S.
10. Gottesman, I and Gould, T. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am.J.Psychiatry* 2003:160(4), 636–645.
11. Comuzzie, A, Funahashi, T, Sonnenberg, G, Martin, L, Jacob, H, Black, A, Maas, D, Takahashi, M, Kihara, S, Tanaka, S, Matsuzawa, Y, Blangero, J, Cohen, D, and Kissebah, A. The genetic basis of plasma variation in adiponectin, a global endophenotype for obesity and the metabolic syndrome. *J.Clin.Endocrinol.Metab* 2001:86(9), 4321–4325.
12. Gieger, C, Geistlinger, L, Altmaier, E, de Hrade, AM, Kronenberg, F, Meitinger, T, Mewes, H, Wichmann, H, Weinberger, K, Adamski, J, Illig,

- T, and Suhre, K. Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum. *PLoS.Genet.* 2008: 4(11), e1000282.
13. Henry, C. New 'ome' in town. *Chemical & Engineering Archives* 2002: 80(48), 66–70.
  14. Lederberg, J and McCray, A. 'Ome sweet 'omics – a genealogical treasury of words. *The Scientist* 2001:15(7), 8.
  15. van der Werf, M, Jellema, R, and Hankemeier, T. Microbial metabolomics: replacing trial-and-error by the unbiased selection and ranking of targets. *J.Ind.Microbiol.Biotechnol.* 2005:32(6), 234–252.
  16. Fiehn, O, Kopka, J, Dormann, P, Altmann, T, Trethewey, R, and Willmitzer, L. Metabolite profiling for plant functional genomics. *Nat.Biotechnol.* 2000:18(11), 1157–1161.
  17. Nicholls, A, Mortishire-Smith, R, and Nicholson, J. NMR spectroscopic-based metabonomic studies of urinary metabolite variation in acclimatizing germ-free rats. *Chem.Res.Toxicol.* 2003:16(11), 1395–1404.
  18. Kell, D. Metabolomic biomarkers: search, discovery and validation. *Expert.Rev.Mol.Diagn.* 2007:7(4), 329–333.
  19. Koek, M. *Gas chromatography mass spectrometry: key technology in metabolomics*. Ph.D. thesis, Leiden University, Leiden, The Netherlands, 2009.
  20. Brown, M, Dunn, W, Ellis, D, Goodacre, R, Handl, J, Knowles, J, O'Hagan, S, Spasic, I, and Kell, D. A metabolome pipeline: from concept to data to knowledge. *Metabolomics* 2005:1(1), 39–51.
  21. Scalbert, A, Brennan, L, Fiehn, O, Hankemeier, T, Kristal, B, van Ommen, B, Pujos-Guillot, E, Verheij, E, Wishart, D, and Wopereis, S. Mass-spectrometry-based metabolomics: limitations and recommendations for future progress with particular focus on nutrition research. *Metabolomics* 2009:5(4), 435–458.
  22. Craig, A, Cloarec, O, Holmes, E, Nicholson, J, and Lindon, J. Scaling and normalization effects in NMR spectroscopic metabonomic data sets. *Anal.Chem.* 2006:78(7), 2262–2267.
  23. Jolliffe, I. *Principal component analysis*. Springer-Verlag New York, Inc., New York, NY, USA, 2nd edition, 2002.
  24. Westerhuis, J, Hoefsloot, H, Smit, S, Vis, D, Smilde, A, van Velzen, E, van Duijnhoven, J, and van Dorsten, F. Assessment of PLSDA cross validation. *Metabolomics* 2008:4, 81–89.
  25. Galton, F. *Hereditary genius: an inquiry into its laws and consequences*. MacMillan & Co., London / New York, 2nd edition, 1892.
  26. Galton, F. *English men of science: their nature and nurture*. MacMillan & Co., London, 1874.
  27. Neale, M and Cardon, L. *Methodology for genetic studies of twins and families*, volume 67. Kluwer Academic Publishers, Dordrecht, 1992.
  28. Falconer, D. *Introduction to quantitative genetics*. Oliver & Boyd, Edinburgh / London, 2nd edition, 1961.

29. Medland, S and Hatemi, P. Political science, biometrical theory, and twin studies: a methodological introduction. *Political Analysis* 2009:17, 191–214.
30. Rijdsdijk, F and Sham, P. Analytic approaches to twin data using structural equation models. *Brief.Bioinform.* 2002:3(2), 119–133.
31. Sung, J, Cho, S, Song, Y, Lee, K, Choi, E, Ha, M, Kim, J, Kim, H, Kim, Y, Shin, E, Kim, Y, Yoo, K, Park, C, and Kimm, K. Do we need more twin studies? The Healthy Twin Study, Korea. *Int.J.Epidemiol.* 2006: 35(2), 488–490.
32. Bollen, K. *Structural equations with latent variables*. John Wiley & Sons, New York, 1989.
33. Hox, J and Bechger, T. An introduction to structural equation modeling. *Family Science Review* 1998:11, 354–373.
34. Wright, S. Correlation and causation. *Journal of Agricultural Research* 1921:20, 557–585.
35. Jinks, J and Fulker, D. Comparison of the biometrical genetical, MAVA, and classical approaches to the analysis of human behavior. *Psychol.Bull.* 1970:73(5), 311–349.
36. Lay, D. *Linear algebra and its applications*. Addison-Wesley, Boston, 3rd edition, 2003.
37. Visscher, P, Hill, W, and Wray, N. Heritability in the genomics era – concepts and misconceptions. *Nat.Rev.Genet.* 2008:9(4), 255–266.
38. Posthuma, D, Beem, A, de Geus, E, van Baal, G, von Hjelmberg, J, Iachine, I, and Boomsma, D. Theory and practice in quantitative genetics. *Twin Research* 2003:6(5), 361–376.
39. Evans, D, Gillespie, N, and Martin, N. Biometrical genetics. *Biol.Psychol.* 2002:61(1-2), 33–51.
40. Dolan, C. *Biometric decomposition of phenotypic means in human samples*. Ph.D. thesis, University of Amsterdam, Amsterdam, The Netherlands, 1992.
41. Kaufman, L and Rousseeuw, P. *Finding groups in data – an introduction to cluster analysis*. John Wiley & Sons, Inc., Hoboken, New Jersey, 2005.
42. Kriegel, H, Kröger, P, and Zimek, A. Clustering high-dimensional data: a survey on subspace clustering, pattern-based clustering, and correlation clustering. *ACM Transactions on knowledge discovery from data* 2009: 3(1, article 1 (58 pages)).
43. Friedman, J and Meulman, J. Clustering objects on subsets of attributes. *Journal of the Royal Statistical Society Series B* 2004:66, 815–849.
44. Davidov, E, Holland, J, Marple, E, and Naylor, S. Advancing drug discovery through systems biology. *Drug.Discov.Today* 2003:8(4), 175–183.
45. Clish, C, Davidov, E, Orešič, M, Plasterer, T, Lavine, G, Londo, T, Meys, M, Snell, P, Stochaj, W, Adourian, A, Zhang, X, Morel, N, Neumann, E, Verheij, E, Vogels, J, Havekes, L, Afeyan, N, Regnier, F, van der Greef, J, and Naylor, S. Integrative biological analysis of the APOE\*3-leiden transgenic mouse. *OMICS* 2004:8(1), 3–13.

46. Fisher, R. The correlation between relatives on the supposition of Mendelian inheritance. *Transactions of the Royal Society of Edinburgh* 1918:52, 399–433.
47. Plomin, R, Haworth, C, and Davis, O. Common disorders are quantitative traits. *Nat.Rev.Genet.* 2009:10(12), 872–878.
48. Frazer, K, Murray, S, Schork, N, and Topol, E. Human genetic variation and its contribution to complex traits. *Nat.Rev.Genet.* 2009:10(4), 241–251.
49. McCarthy, M, Abecasis, G, Cardon, L, Goldstein, D, Little, J, Ioannidis, J, and Hirschhorn, J. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat.Rev.Genet.* 2008:9(5), 356–369.
50. Pearson, T and Manolio, T. How to interpret a genome-wide association study. *JAMA* 2008:299(11), 1335–1344.
51. Illig, T, Gieger, C, Zhai, G, Romisch-Margl, W, Wang-Sattler, R, Prehn, C, Altmaier, E, Kastenmuller, G, Kato, B, Mewes, H, Meitinger, T, de Angelis, M, Kronenberg, F, Soranzo, N, Wichmann, H, Spector, T, Adamski, J, and Suhre, K. A genome-wide perspective of genetic variation in human metabolism. *Nat.Genet.* 2010:42(2), 137–141.
52. Hicks, A, Pramstaller, P, Johansson, Å, Vitart, V, Rudan, I, Ugocsai, P, Aulchenko, Y, Franklin, C, Liebisch, G, Erdmann, J, Jonasson, I, Zorkoltseva, I, Pattaro, C, Hayward, C, Isaacs, A, Hengstenberg, C, Campbell, S, Gnewuch, C, Janssens, A, Kirichenko, A, König, I, Marroni, F, Polasek, O, Demirkan, A, Kolcic, I, Schwienbacher, C, Igl, W, Biloglav, Z, Witteman, J, Pichler, I, Zaboli, G, Axenovich, T, Peters, A, Schreiber, S, Wichmann, H, Schunkert, H, Hastie, N, Oostra, B, Wild, S, Meitinger, T, Gyllensten, U, van Duijn, C, Wilson, J, Wright, A, Schmitz, G, and Campbell, H. Genetic determinants of circulating sphingolipid concentrations in European populations. *PLoS.Genet.* 2009:5(10), e1000672.
53. Lee, S, van der Werf, J, Hayes, B, Goddard, M, and Visscher, P. Predicting unobserved phenotypes for complex traits from whole-genome SNP data. *PLoS.Genet.* 2008:4(10), e1000231.
54. Tanaka, T, Shen, J, Abecasis, G, Kisiailiou, A, Ordovas, J, Guralnik, J, Singleton, A, Bandinelli, S, Cherubini, A, Arnett, D, Tsai, M, and Ferrucci, L. Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. *PLoS.Genet.* 2009:5(1), e1000338.
55. Goring, H, Curran, J, Johnson, M, Dyer, T, Charlesworth, J, Cole, S, Jowett, J, Abraham, L, Rainwater, D, Comuzzie, A, Mahaney, M, Almasy, L, MacCluer, J, Kissebah, A, Collier, G, Moses, E, and Blangero, J. Discovery of expression QTLs using large-scale transcriptional profiling in human lymphocytes. *Nat.Genet.* 2007:39(10), 1208–1216.
56. Emilsson, V, Thorleifsson, G, Zhang, B, Leonardson, A, Zink, F, Zhu, J, Carlson, S, Helgason, A, Walters, G, Gunnarsdottir, S, Mouy, M, Steinthorsdottir, V, Eiriksdottir, G, Bjornsdottir, G, Reynisdottir, I, Gudbjartsson, D, Helgadottir, A, Jonasdottir, A, Jonasdottir, A, Styrkarsdot-

- tir, U, Gretarsdottir, S, Magnusson, K, Stefansson, H, Fossdal, R, Kristjansson, K, Gislason, H, Stefansson, T, Leifsson, B, Thorsteinsdottir, U, Lamb, J, Gulcher, J, Reitman, M, Kong, A, Schadt, E, and Stefansson, K. Genetics of gene expression and its effect on disease. *Nature* 2008: 452(7186), 423–428.
57. Manolio, T, Collins, F, Cox, N, Goldstein, D, Hindorff, L, Hunter, D, McCarthy, M, Ramos, E, Cardon, L, Chakravarti, A, Cho, J, Guttmacher, A, Kong, A, Kruglyak, L, Mardis, E, Rotimi, C, Slatkin, M, Valle, D, Whittemore, A, Boehnke, M, Clark, A, Eichler, E, Gibson, G, Haines, J, Mackay, T, McCarroll, S, and Visscher, P. Finding the missing heritability of complex diseases. *Nature* 2009:461(7265), 747–753.
  58. Maher, B. Personal genomes: The case of the missing heritability. *Nature* 2008:456(7218), 18–21.
  59. Manolio, T. Genomewide association studies and assessment of the risk of disease. *N.Engl.J.Med.* 2010:363(2), 166–176.
  60. Donnelly, P. Progress and challenges in genome-wide association studies in humans. *Nature* 2008:456(7223), 728–731.
  61. Visscher, PM, Yang, J, and Goddard, ME. A commentary on ‘common SNPs explain a large proportion of the heritability for human height’ by Yang et al. (2010). *Twin Res.Hum.Genet.* 2010:13(6), 517–524.
  62. Yang, J, Benyamin, B, McEvoy, BP, Gordon, S, Henders, AK, Nyholt, DR, Madden, PA, Heath, AC, Martin, NG, Montgomery, GW, Goddard, ME, and Visscher, PM. Common SNPs explain a large proportion of the heritability for human height. *Nat.Genet.* 2010:42(7), 565–569.
  63. Manolio, T, Brooks, L, and Collins, F. A HapMap harvest of insights into the genetics of common disease. *J.Clin.Invest.* 2008:118(5), 1590–1605.
  64. Sebastiani, P, Timofeev, N, Dworkis, D, Perls, T, and Steinberg, M. Genome-wide association studies and the genetic dissection of complex traits. *Am.J.Hematol.* 2009:84(8), 504–515.
  65. Clarke, A and Cooper, D. GWAS: heritability missing in action? *Eur.J.Hum.Genet.* 2010:18(8), 859–861.
  66. Hardy, J and Singleton, A. Genomewide association studies and human disease. *N.Engl.J.Med.* 2009:360(17), 1759–1768.
  67. Bourgain, C, Genin, E, Cox, N, and Clerget-Darpoux, F. Are genome-wide association studies all that we need to dissect the genetic component of complex human diseases? *Eur.J.Hum.Genet.* 2007:15(3), 260–263.
  68. Thomas, D. Gene-environment-wide association studies: emerging approaches. *Nat.Rev.Genet.* 2010:11(4), 259–272.
  69. Martin, N, Boomsma, D, and Machin, G. A twin-pronged attack on complex traits. *Nat.Genet.* 1997:17(4), 387–392.
  70. Fischer, K, Bot, A, Zwaan, B, and Brakefield, P. Genetic and environmental sources of egg size variation in the butterfly *Bicyclus anynana*. *Heredity* 2004:92(3), 163–169.
  71. van der Greef, J, Davidov, E, Verheij, E, Vogels, J, van der Heijden, R, Adourian, A, Oresic, M, Marple, E, and Naylor, S. The role of metabolom-

- ics in systems biology. In Harrigan, G and Goodacre, R, editors, *Metabolic profiling: its role in biomarker discovery and gene function analysis*, chapter 11, pages 171–198. Kluwer Academic Publishers, Boston: 2004.
72. Nanki, T, Kohsaka, H, Mizushima, N, Ollier, W, Carson, D, and Miyasaka, N. Genetic control of T cell receptor BJ gene expression in peripheral lymphocytes of normal and rheumatoid arthritis monozygotic twins. *J.Clin.Invest.* 1996:98(7), 1594–1601.
  73. German, J, Roberts, M, and Watkins, S. Personal metabolomics as a next generation nutritional assessment. *J.Nutr.* 2003:133(12), 4260–4266.
  74. Koek, M, Muilwijk, B, van der Werf, M, and Hankemeier, T. Microbial metabolomics with gas chromatography/mass spectrometry. *Anal.Chem.* 2006:78(4), 1272–1281.
  75. Murphy, D. The biogenesis and functions of lipid bodies in animals, plants and microorganisms. *Prog.Lipid.Res.* 2001:40(5), 325–438.
  76. Baur, L, O'Connor, J, Pan, D, Wu, B, O'Connor, M, and Storlien, L. Relationships between the fatty acid composition of muscle and erythrocyte membrane phospholipid in young children and the effect of type of infant feeding. *Lipids* 2000:35(1), 77–82.
  77. Swift, RW. The effects of low environmental temperature upon metabolism: II. The influence of shivering, subcutaneous fat, and skin temperature on heat production. *J.Nutr.* 1932:5, 227–249.
  78. Dodds, P. Incorporation of xenobiotic carboxylic acids into lipids. *Life Sci.* 1991:49(9), 629–649.
  79. Tew, D, Southan, C, Rice, S, Lawrence, M, Li, H, Boyd, H, Moores, K, Gloger, I, and Macphee, C. Purification, properties, sequencing, and cloning of a lipoprotein-associated, serine-dependent phospholipase involved in the oxidative modification of low-density lipoproteins. *Arterioscler.Thromb.Vasc.Biol.* 1996:16(4), 591–599.
  80. Elstad, M, Stafforini, D, McIntyre, T, Prescott, S, and Zimmerman, G. Platelet-activating factor acetylhydrolase increases during macrophage differentiation. A novel mechanism that regulates accumulation of platelet-activating factor. *J.Biol.Chem.* 1989:264(15), 8467–8470.
  81. Quinn, M, Parthasarathy, S, and Steinberg, D. Lysophosphatidylcholine: a chemotactic factor for human monocytes and its potential role in atherogenesis. *Proc.Natl.Acad.Sci.USA* 1988:85(8), 2805–2809.
  82. Glomset, J. The plasma lecithins:cholesterol acyltransferase reaction. *J.Lipid Res.* 1968:9(2), 155–167.
  83. Kern, H, Volk, T, Knauer-Schiefer, S, Mieth, T, Rustow, B, Kox, W, and Schlame, M. Stimulation of monocytes and platelets by short-chain phosphatidylcholines with and without terminal carboxyl group. *Biochim.Biophys.Acta* 1998:1394(1), 33–42.
  84. Coleman, R. Biochemistry of bile secretion. *Biochem.J.* 1987:244(2), 249–261.
  85. Zachowski, A. Phospholipids in animal eukaryotic membranes: transverse asymmetry and movement. *Biochem.J.* 1993:294 ( Pt 1), 1–14.

86. McKeone, B, Patsch, J, and Pownall, H. Plasma triglycerides determine low density lipoprotein composition, physical properties, and cell-specific binding in cultured cells. *J.Clin.Invest.* 1993:91(5), 1926–1933.
87. Sigal, Y, McDermott, M, and Morris, A. Integral membrane lipid phosphatases/phosphotransferases: common structure and diverse functions. *Biochem.J.* 2005:387(Pt 2), 281–293.
88. Veldhuizen, R, Nag, K, Orgeig, S, and Possmayer, F. The role of lipids in pulmonary surfactant. *Biochim.Biophys.Acta* 1998:1408(2-3), 90–108.
89. Acton, S, Rigotti, A, Landschulz, K, Xu, S, Hobbs, H, and Krieger, M. Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science* 1996:271(5248), 518–520.
90. Boomsma, D, de Geus, E, Vink, J, Stubbe, J, Distel, M, Hottenga, J, Posthuma, D, van Beijsterveldt, T, Hudziak, J, Bartels, M, and Willemsen, G. Netherlands Twin Register: from twins to twin families. *Twin.Res.Hum.Genet.* 2006:9(6), 849–857.
91. Hoekstra, R, Bartels, M, and Boomsma, D. Longitudinal genetic study of verbal and nonverbal IQ from early childhood to young adulthood. *Learning and individual differences* 2007:17, 97–114.
92. R Development Core Team. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria, 2005. ISBN 3-900051-07-0.
93. Vandeginste, B, Massart, D, Buydens, L, de Jong, S, Lewi, P, and Smeyers-Verbeke, J. *Handbook of chemometrics and qualimetrics: part B*. Elsevier, Amsterdam, 1998.
94. Barnes, R, Dhanoa, M, and Lister, S. Standard normal variate transformation and de-trending of near-infrared diffuse reflectance spectra. *Applied spectroscopy* 1989:43, 772–777.
95. Sokal, R. Distance as a measure of taxonomic similarity. *Systematic zoology* 1961:10, 70–79.
96. Young, G and Householder, A. Discussion of a set of points in terms of their mutual distances. *Psychometrika* 1938:3, 19–22.
97. Kruskal, WH and Wallis, W. Use of ranks in one-criterion variance analysis. *Journal of the American Statistical Association* 1952:47(260), 583–621.
98. Hochberg, Y and Tamhane, A. *Multiple comparison procedures*. John Wiley & Sons, New York, 1987.
99. Sokal, R and Rohlf, F. The comparison of dendrograms by objective methods. *Taxon* 1962:11(2), 33–40.
100. Sneath, P and Sokal, R. *Numerical taxonomy: the principles and practice of numerical classification*. W.H. Freeman & Co., New York, 1973.
101. Suzuki, R and Shimodaira, H. Pvcust: an R package for assessing the uncertainty in hierarchical clustering. *Bioinformatics* 2006:22(12), 1540–1542.
102. Damian, D, Orešič, M, Verheij, E, Meulman, J, Friedman, J, Adourian, A, Morel, N, Smilde, A, and van der Greef, J. Applications of a new subspace

- clustering algorithm (COSEA) in medical systems biology. *Metabolomics* 2007:3, 629–649.
103. Tan, Q, Christensen, K, Christiansen, L, Frederiksen, H, Bathum, L, Dahlgaard, J, and Kruse, T. Genetic dissection of gene expression observed in whole blood samples of elderly Danish twins. *Hum.Genet.* 2005: 117(2-3), 267–274.
  104. Omori-Inoue, M, Fukata, H, Komiyama, M, Todaka, E, Osada, H, Aburatani, H, and Mori, C. The contamination levels of organochlorines and the pattern of gene expressions in human umbilical cords from intra-pairs of twins at delivery. *Reprod.Toxicol.* 2007:23(3), 283–289.
  105. Zhou, X, Tan, F, Xiong, M, Arnett, F, and Feghali-Bostwick, C. Monozygotic twins clinically discordant for scleroderma show concordance for fibroblast gene expression profiles. *Arthritis Rheum.* 2005:52(10), 3305–3314.
  106. Matigian, N, Windus, L, Smith, H, Filippich, C, Pantelis, C, McGrath, J, Mowry, B, and Hayward, N. Expression profiling in monozygotic twins discordant for bipolar disorder reveals dysregulation of the WNT signalling pathway. *Mol.Psychiatry* 2007:12(9), 815–825.
  107. Teuffel, O, Betts, D, Dettling, M, Schaub, R, Schafer, B, and Niggli, F. Prenatal origin of separate evolution of leukemia in identical twins. *Leukemia* 2004:18(10), 1624–1629.
  108. Tsang, T, Huang, J, Holmes, E, and Bahn, S. Metabolic profiling of plasma from discordant schizophrenia twins: correlation between lipid signals and global functioning in female schizophrenia patients. *J.Proteome Res.* 2006:5(4), 756–760.
  109. Pietiläinen, K, Sysi-Aho, M, Rissanen, A, Seppanen-Laakso, T, Yki-Jarvinen, H, Kaprio, J, and Orešič, M. Acquired obesity is associated with changes in the serum lipidomic profile independent of genetic effects – a monozygotic twin study. *PLoS ONE* 2007:2, e218.
  110. Hastie, T, Tibshirani, R, and Friedman, J. *The elements of statistical learning; data mining, inference, and prediction.* Springer, New York, 2001.
  111. Iselius, L. Analysis of family resemblance for lipids and lipoproteins. *Clin.Genet.* 1979:15(4), 300–306.
  112. Snieder, H, van Doornen, L, and Boomsma, D. Dissecting the genetic architecture of lipids, lipoproteins, and apolipoproteins: lessons from twin studies. *Arterioscler.Thromb.Vasc.Biol.* 1999:19(12), 2826–2834.
  113. Boomsma, D, Kempen, H, Gevers Leuven, J, Havekes, L, de Knijff, P, and Frants, R. Genetic analysis of sex and generation differences in plasma lipid, lipoprotein, and apolipoprotein levels in adolescent twins and their parents. *Genet.Epidemiol.* 1996:13(1), 49–60.
  114. Cohn, J, McNamara, J, Cohn, S, Ordovas, J, and Schaefer, E. Post-prandial plasma lipoprotein changes in human subjects of different ages. *J.Lipid Res.* 1988:29(4), 469–479.
  115. Steinmetz, V, Sévilla, F, and Bellon-Maurel, V. A methodology for sensor



- fusion design: application to fruit quality assessment. *J.Agric.Engng.Res.* 1999:74, 21–31.
116. Smilde, A, van der Werf, M, Bijlsma, S, van der Werff-van der Vat BJ, and Jellema, R. Fusion of mass spectrometry-based metabolomics data. *Anal.Chem.* 2005:77(20), 6729–6736.
  117. Zelena, E, Dunn, W, Broadhurst, D, Francis-McIntyre, S, Carroll, K, Begley, P, O'Hagan, S, Knowles, J, Halsall, A, Wilson, I, and Kell, D. Development of a robust and repeatable UPLC-MS method for the long-term metabolomic study of human serum. *Anal.Chem.* 2009:81(4), 1357–1364.
  118. Feudale, R, Woody, N, Tan, H, Myles, A, Brown, S, and Ferré, J. Transfer of multivariate calibration models: a review. *Chemom.Intell.Lab.Syst.* 2002:64, 181–192.
  119. Alam, T, Alam, M, McIntyre, S, Volk, D, Neerathilingam, M, and Luxon, B. Investigation of chemometric instrumental transfer methods for high-resolution NMR. *Anal.Chem.* 2009:81(11), 4433–4443.
  120. Keun, H, Ebbels, T, Antti, H, Bollard, M, Beckonert, O, Schlotterbeck, G, Senn, H, Niederhauser, U, Holmes, E, Lindon, J, and Nicholson, J. Analytical reproducibility in <sup>1</sup>H NMR-based metabonomic urinalysis. *Chem.Res.Toxicol.* 2002:15(11), 1380–1386.
  121. Dumas, M, Maibaum, E, Teague, C, Ueshima, H, Zhou, B, Lindon, J, Nicholson, J, Stamler, J, Elliott, P, Chan, Q, and Holmes, E. Assessment of analytical reproducibility of <sup>1</sup>H NMR spectroscopy based metabolomics for large-scale epidemiological research: the INTERMAP Study. *Anal.Chem.* 2006:78(7), 2199–2208.
  122. Sangster, T, Major, H, Plumb, R, Wilson, A, and Wilson, I. A pragmatic and readily implemented quality control strategy for HPLC-MS and GC-MS-based metabonomic analysis. *Analyst* 2006:131(10), 1075–1078.
  123. Gika, H, Theodoridis, G, Wingate, J, and Wilson, I. Within-day reproducibility of an HPLC-MS-based method for metabonomic analysis: application to human urine. *J.Proteome.Res.* 2007:6(8), 3291–3303.
  124. Theodoridis, G, Gika, H, and Wilson, I. LC-MS-based methodology for global metabolite profiling in metabonomics/metabolomics. *Trends in Analytical Chemistry* 2008:27(3), 251–260.
  125. Burton, L, Ivosev, G, Tate, S, Impey, G, Wingate, J, and Bonner, R. Instrumental and experimental effects in LC-MS based metabolomics. *J.Chrom.B* 2008:871, 227–235.
  126. Dunn, W, Broadhurst, D, Brown, M, Baker, P, Redman, C, Kenny, L, and Kell, D. Metabolic profiling of serum using Ultra Performance Liquid Chromatography and the LTQ-Orbitrap mass spectrometry system. *J.Chrom.B* 2008:871, 288–298.
  127. Bijlsma, S, Bobeldijk, I, Verheij, E, Ramaker, R, Kochhar, S, Macdonald, I, van Ommen, B, and Smilde, A. Large-scale human metabolomics studies: a strategy for data (pre-) processing and validation. *Anal.Chem.* 2006:78(2), 567–574.

128. van der Kloet, F, Jellema, R, Verheij, E, and Bobeldijk, I. Analytical error reduction using single point calibration for accurate and precise metabolomic phenotyping. *J Proteome Res.* 2009:8(11), 5132–5141.
129. Kolen, M and Jarjoura, D. Analytic smoothing for equipercenile equating under the common item nonequivalent populations design. *Psychometrika* 1987:52(1), 43–59.
130. Van der Linden, W. A test-theoretic approach to observed-score equating. *Psychometrika* 2000:65(4), 437–456.
131. Wagner, S, Scholz, K, Sieber, M, Kellert, M, and Voelkel, W. Tools in metabonomics: an integrated validation approach for LC-MS metabolic profiling of mercapturic acids in human urine. *Anal.Chem.* 2007:79(7), 2918–2926.
132. Vogels, J, Tas, A, Venekamp, J, and van der Greef, J. Partial linear fit: a new NMR spectroscopy preprocessing tool for pattern recognition applications. *J.Chemometrics* 1996:10, 425–438.
133. Hendriks, M, Smit, S, Akkermans, W, Reijmers, T, Eilers, P, Hoefsloot, H, Rubingh, C, de Koster, C, Aerts, J, and Smilde, A. How to distinguish healthy from diseased? Classification strategy for mass spectrometry-based clinical proteomics. *Proteomics.* 2007:7(20), 3672–3680.
134. Bolstad, B. Probe level quantile normalization of high density oligonucleotide array data. <http://bmbolstad.com/stuff/qnorm.pdf>, 2001.
135. Bolstad, B, Irizarry, R, Astrand, M, and Speed, T. A comparison of normalization methods for high density oligonucleotide array data based on variance and bias. *Bioinformatics* 2003:19(2), 185–193.
136. Cleveland, W. *The elements of graphing data.* Hobart Press, Summit, N.J., 2nd edition, 1994.
137. Wilk, M and Gnanadesikan, R. Probability plotting methods for analysis of data. *Biometrika* 1968:55(1), 1–17.
138. Cawley, S, Bekiranov, S, Ng, H, Kapranov, P, Sekinger, E, Kampa, D, Piccolboni, A, Sementchenko, V, Cheng, J, Williams, A, Wheeler, R, Wong, B, Drenkow, J, Yamanaka, M, Patel, S, Brubaker, S, Tammana, H, Helt, G, Struhl, K, and Gingeras, T. Unbiased mapping of transcription factor binding sites along human chromosomes 21 and 22 points to widespread regulation of noncoding RNAs. *Cell* 2004:116(4), 499–509.
139. Kim, J, Tchernyshyov, I, Semenza, G, and Dang, C. HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. *Cell Metab.* 2006:3(3), 177–185.
140. Chen, H, Yu, S, Chen, C, Chang, G, Chen, C, Yuan, A, Cheng, C, Wang, C, Terng, H, Kao, S, Chan, W, Li, H, Liu, C, Singh, S, Chen, W, Chen, J, and Yang, P. A five-gene signature and clinical outcome in non-small-cell lung cancer. *N.Engl.J.Med.* 2007:356(1), 11–20.
141. Higgs, R, Knierman, M, Gelfanova, V, Butler, J, and Hale, J. Comprehensive label-free method for the relative quantification of proteins from biological samples. *J.Proteome.Res* 2005:4(4), 1442–1450.
142. Angoff, W. Scales, norms, and equivalent scores. In Thorndike, R, editor,

- Educational measurement*, pages 562–600. American Council on Education, Washington, D.C., 2nd edition: 1971.
143. Gentleman, R, Carey, V, Bates, D, Bolstad, B, Dettling, M, Dudoit, S, Ellis, B, Gautier, L, Ge, Y, Gentry, J, Hornik, K, Hothorn, T, Huber, W, Iacus, S, Irizarry, R, Leisch, F, Li, C, Maechler, M, Rossini, A, Sawitzki, G, Smith, C, Smyth, G, Tierney, L, Yang, J, and Zhang, J. Bioconductor: open software development for computational biology and bioinformatics. *Genome Biol.* 2004:5(10), R80.
  144. R Development Core Team. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria, 2008. ISBN 3-900051-07-0.
  145. Jouan-Rimbaud, D, Massart, D, Saby, C, and Puel, C. Determination of the representativity between two multidimensional data sets by a comparison of their structure. *Chemom.Intell.Lab.Syst.* 1998:40, 129–144.
  146. Frisby, J and Clatworthy, J. Learning to see complex random-dot stereograms. *Perception* 1975:4, 173–178.
  147. Deprez, S, Sweatman, B, Connor, S, Haselden, J, and Waterfield, C. Optimisation of collection, storage and preparation of rat plasma for <sup>1</sup>H NMR spectroscopic analysis in toxicology studies to determine inherent variation in biochemical profiles. *J.Pharm.Biomed.Anal.* 2002:30(4), 1297–1310.
  148. Mehr, K, John, B, Russell, D, and Avizonis, D. Electronic referencing techniques for quantitative NMR: pitfalls and how to avoid them using amplitude-corrected referencing through signal injection. *Anal.Chem.* 2008:80(21), 8320–8323.
  149. Lauridsen, M, Hansen, S, Jaroszewski, J, and Cornett, C. Human urine as test material in <sup>1</sup>H NMR-based metabonomics: recommendations for sample preparation and storage. *Anal.Chem.* 2007:79(3), 1181–1186.
  150. Srinivasan, R and Stewart, R. The catalysis of proton exchange in creatinine by general acids and general bases. *Can.J.Chem.* 1975:53, 224–231.
  151. Mackay, T. The genetic architecture of quantitative traits. *Annu.Rev.Genet.* 2001:35, 303–339.
  152. Eaves, L. Putting the ‘human’ back in genetics: modeling the extended kinships of twins. *Twin Res.Hum.Genet.* 2009:12(1), 1–7.
  153. Hu, C, van der Heijden, R, Wang, M, van der Greef, J, Hankemeier, T, and Xu, G. Analytical strategies in lipidomics and applications in disease biomarker discovery. *Journal of Chromatography B* 2009:877, 2836–2846.
  154. Vrije Universiteit - Nederlands Tweelingen Register. <http://www.tweelingenregister.org/>. Accessed 27-March-2011.
  155. Draisma, H, Reijmers, T, Bobeldijk-Pastorova, I, Meulman, J, Estourgie-Van Burk, G, Bartels, M, Ramaker, R, van der Greef, J, Boomsma, D, and Hankemeier, T. Similarities and differences in lipidomics profiles among healthy monozygotic twin pairs. *OMICS* 2008:12(1), 17–31.
  156. Draisma, H, Reijmers, T, van der Kloet, F, Bobeldijk-Pastorova, I, Spies-Faber, E, Vogels, J, Meulman, J, Boomsma, D, Van der Greef, J, and Han-

- kemeier, T. Equating, or correction for between-block effects with application to body fluid LC-MS and NMR metabolomics data sets. *Anal.Chem.* 2010:82(3), 1039–1046.
157. Willemsen, G, de Geus, E, Bartels, M, van Beijsterveldt, C, Brooks, A, Estourgie-Van Burk, G, Fugman, D, Hoekstra, C, Hottenga, J, Klufft, K, Meijer, P, Montgomery, G, Rizzu, P, Sondervan, D, Smit, A, Spijker, S, Suchiman, H, Tischfield, J, Lehner, T, Slagboom, P, and Boomsma, D. The Netherlands Twin Register biobank: a resource for genetic epidemiological studies. *Twin Res.Hum.Genet.* 2010:13(3), 231–245.
158. R Development Core Team. *R: A language and environment for statistical computing.* R Foundation for Statistical Computing, Vienna, Austria, 2009. ISBN 3-900051-07-0.
159. Clyne, B and Olshaker, J. The C-reactive protein. *J.Emerg.Med.* 1999: 17(6), 1019–1025.
160. Scriver, C. Garrod’s foresight; our hindsight. *J.Inherit.Metab Dis.* 2001: 24(2), 93–116.
161. Shah, S, Hauser, E, Bain, J, Muehlbauer, M, Haynes, C, Stevens, R, Wenner, B, Dowdy, Z, Granger, C, Ginsburg, G, Newgard, C, and Kraus, W. High heritability of metabolomic profiles in families burdened with premature cardiovascular disease. *Mol.Syst.Biol.* 2009:5, 258.
162. Vaidyanathan, S, Harrigan, G, and Goodacre, R. Introduction. In Vaidyanathan, S, Harrigan, G, and Goodacre, R, editors, *Metabolome analyses: strategies for systems biology*, chapter 1, pages 1–8. Springer Science+Business Media, Inc., New York, NY: 2005.
163. van der Greef, J, Martin, S, Juhasz, P, Adourian, A, Plasterer, T, Verheij, E, and McBurney, R. The art and practice of systems biology in medicine: mapping patterns of relationships. *J.Proteome.Res.* 2007:6(4), 1540–1559.
164. Carey, G. Inference about genetic correlations. *Behav.Genet.* 1988:18(3), 329–338.
165. Schmitz, S, Cherny, S, and Fulker, D. Increase in power through multivariate analyses. *Behav.Genet.* 1998:28(5), 357–363.
166. Posthuma, D and Boomsma, D. A note on the statistical power in extended twin designs. *Behav.Genet.* 2000:30(2), 147–158.
167. Schmitt, J, Lenroot, R, Wallace, G, Ordaz, S, Taylor, K, Kabani, N, Greenstein, D, Lerch, J, Kendler, K, Neale, M, and Giedd, J. Identification of genetically mediated cortical networks: a multivariate study of pediatric twins and siblings. *Cerebral Cortex* 2008:18, 1737–1747.
168. Schmitt, J, Lenroot, R, Ordaz, S, Wallace, G, Lerch, J, Evans, A, Prom, E, Kendler, K, Neale, M, and Giedd, J. Variance decomposition of MRI-based covariance maps using genetically informative samples and structural equation modeling. *Neuroimage.* 2009:47(1), 56–64.
169. Boker, S, Neale, M, Maes, H, Wilde, M, Spiegel, M, Brick, T, Spies, J, Estabrook, R, Kenny, S, Bates, T, Mehta, P, and Fox, J. OpenMx: an open source extended structural equation modeling framework. *Psychometrika* : advance online publication 6 January 2011; doi:

- 10.1007/S11336-010-9200-6.
170. Nadder, T, Silberg, J, Eaves, L, Maes, H, and Meyer, J. Genetic effects on ADHD symptomatology in 7- to 13-year-old twins: results from a telephone survey. *Behav.Genet.* 1998:28(2), 83–99.
  171. Neale, M and Miller, M. The use of likelihood-based confidence intervals in genetic models. *Behav.Genet.* 1997:27(2), 113–120.
  172. Giedd, J, Schmitt, J, and Neale, M. Structural brain magnetic resonance imaging of pediatric twins. *Hum.Brain Mapp.* 2007:28(6), 474–481.
  173. Baaré, W, Hulshoff Pol, H, Boomsma, D, Posthuma, D, de Geus, E, Schnack, H, van Haren, N, van Oel, C, and Kahn, R. Quantitative genetic modeling of variation in human brain morphology. *Cerebral Cortex* 2001: 11, 816–824.
  174. Atchley, W, Plummer, A, and Riska, B. Genetics of mandible form in the mouse. *Genetics* 1985:111(3), 555–577.
  175. Eyler, L, Prom-Wormley, E, Fennema-Notestine, C, Panizzon, M, Neale, M, Jernigan, T, Fischl, B, Franz, C, Lyons, M, Stevens, A, Pacheco, J, Perry, M, Schmitt, J, Spitzer, N, Seidman, L, Thermenos, H, Tsuang, M, Dale, A, and Kremen, W. Genetic patterns of correlation among subcortical volumes in humans: Results from a magnetic resonance imaging twin study. *Hum.Brain Mapp.* : advance online publication 22 June 2010; doi: 10.1002/hbm.21054.
  176. Pilia, G, Chen, W, Scuteri, A, Orru, M, Albai, G, Dei, M, Lai, S, Usala, G, Lai, M, Loi, P, Mameli, C, Vacca, L, Deiana, M, Olla, N, Masala, M, Cao, A, Najjar, S, Terracciano, A, Nedorezov, T, Sharov, A, Zonderman, A, Abecasis, G, Costa, P, Lakatta, E, and Schlessinger, D. Heritability of cardiovascular and personality traits in 6,148 Sardinians. *PLoS.Genet.* 2006:2(8), e132.
  177. Voet, D, Voet, J, and Pratt, C. Synthesis and degradation of lipids. In *Principles of biochemistry*, chapter 20, pages 677–731. John Wiley & Sons, Hoboken,NJ, 3rd edition: 2008.
  178. Nicholson, J and Lindon, J. Systems biology: Metabonomics. *Nature* 2008:455(7216), 1054–1056.
  179. Fenger, M, Benyamin, B, Schousboe, K, Sørensen, T, and Kyvik, K. Variance decomposition of apolipoproteins and lipids in Danish twins. *Atherosclerosis* 2007:191(1), 40–47.
  180. Beekman, M, Heijmans, B, Martin, N, Pedersen, N, Whitfield, J, DeFaire, U, van Baal, G, Snieder, H, Vogler, G, Slagboom, P, and Boomsma, D. Heritabilities of apolipoprotein and lipid levels in three countries. *Twin Res.* 2002:5(2), 87–97.
  181. Kullo, I, de Andrade, M, Boerwinkle, E, McConnell, J, Kardia, S, and Turner, S. Pleiotropic genetic effects contribute to the correlation between HDL cholesterol, triglycerides, and LDL particle size in hypertensive sibships. *Am.J.Hypertens.* 2005:18(1), 99–103.
  182. Mathias, R, Deepa, M, Deepa, R, Wilson, A, and Mohan, V. Heritability of quantitative traits associated with type 2 diabetes mellitus in large

- multiplex families from South India. *Metabolism* 2009:58(10), 1439–1445.
183. Benyamin, B, Sørensen, T, Schousboe, K, Fenger, M, Visscher, P, and Kyvik, K. Are there common genetic and environmental factors behind the endophenotypes associated with the metabolic syndrome? *Diabetologica* 2007:50, 1880–1888.
  184. Rahman, I, Bennet, A, Pedersen, N, de Faire, U, Svensson, P, and Magnusson, P. Genetic dominance influences blood biomarker levels in a sample of 12,000 Swedish elderly twins. *Twin Res.Hum.Genet.* 2009:12(3), 286–294.
  185. Rahmioglu, N and Ahmadi, K. Classical twin design in modern pharmacogenomics studies. *Pharmacogenomics* 2010:11(2), 215–226.
  186. Demetrashvili, M, Kron, K, Pethe, V, Bapat, B, and Briollais, L. How to deal with batch effect in sequential microarray experiments? *Molecular Informatics* 2010:29, 387–393.
  187. Sims, A, Smethurst, G, Hey, Y, Okoniewski, M, Pepper, S, Howell, A, Miller, C, and Clarke, R. The removal of multiplicative, systematic bias allows integration of breast cancer gene expression datasets – improving meta-analysis and prediction of prognosis. *BMC Med.Genomics* 2008:1, 42.
  188. Benito, M, Parker, J, Du, Q, Wu, J, Xiang, D, Perou, C, and Marron, J. Adjustment of systematic microarray data biases. *Bioinformatics* 2004: 20(1), 105–114.
  189. Jiang, H, Deng, Y, Chen, H, Tao, L, Sha, Q, Chen, J, Tsai, C, and Zhang, S. Joint analysis of two microarray gene-expression data sets to select lung adenocarcinoma marker genes. *BMC Bioinformatics* 2004:5, 81.
  190. Kim, K, Ki, D, Jeong, H, Jeung, H, Chung, H, and Rha, S. Novel and simple transformation algorithm for combining microarray data sets. *BMC Bioinformatics* 2007:8, 218.
  191. Johnson, W, Li, C, and Rabinovic, A. Adjusting batch effects in microarray expression data using empirical Bayes methods. *Biostatistics* 2007: 8(1), 118–127.
  192. Scherer, A, editor. *Batch effects and noise in microarray experiments*. John Wiley & Sons, Ltd., Chichester, West Sussex, UK, 1st edition, 2009.
  193. Shabalin, A, Tjelmeland, H, Fan, C, Perou, C, and Nobel, A. Merging two gene-expression studies via cross-platform normalization. *Bioinformatics* 2008:24(9), 1154–1160.
  194. Begley, P, Francis-McIntyre, S, Dunn, W, Broadhurst, D, Halsall, A, Tseng, A, Knowles, J, Goodacre, R, and Kell, D. Development and performance of a gas chromatography-time-of-flight mass spectrometry analysis for large-scale nontargeted metabolomic studies of human serum. *Anal.Chem.* 2009:81(16), 7038–7046.
  195. Fiehn, O, Kristal, B, van Ommen, B, Sumner, L, Sansone, S, Taylor, C, Hardy, N, and Kaddurah-Daouk, R. Establishing reporting standards for metabolomic and metabonomic studies: a call for participation. *OMICS*. 2006:10(2), 158–163.

196. Fiehn, O, Robertson, D, Griffin, J, Van der Werf, M, Nikolau, B, Morrison, N, Sumner, L, Goodacre, R, Hardy, N, Taylor, C, Fostel, J, Kristal, B, Kaddurah-Daouk, R, Mendes, P, van Ommen, B, Lindon, J, and Sansone, S. The metabolomics standards initiative (MSI). *Metabolomics* 2007:3, 175–178.
197. Sumner, L, Amberg, A, Barrett, D, Beale, M, Beger, R, Daykin, C, Fan, T, Fiehn, O, Goodacre, R, Griffin, J, Hankemeier, T, Hardy, N, Harnly, J, Higashi, R, Kopka, J, Lane, A, Lindon, J, Marriott, P, Nicholls, A, Reily, M, Thaden, J, and Viant, M. Proposed minimum reporting standards for chemical analysis. *Metabolomics* 2007:3, 211–221.
198. Searls, D. Data integration: challenges for drug discovery. *Nature Reviews Drug Discovery* 2005:4, 45–58.
199. Redestig, H, Fukushima, A, Stenlund, H, Moritz, T, Arita, M, Saito, K, and Kusano, M. Compensation for systematic cross-contribution improves normalization of mass spectrometry based metabolomics data. *Anal.Chem.* 2009:81(19), 7974–7980.
200. Frazier, P, Tix, A, and Barron, K. Testing moderator and mediator effects in counseling psychology research. *Journal of Counseling Psychology* 2004: 51, 115–134.
201. Scriver, C. Homeostasis, complexity, and monogenic phenotypes: the view from phenylketonuria. In Valle, D, Beaudet, A, Vogelstein, B, Kinzler, K, Antonarakis, S, Ballabio, A, Scriver, C, Sly, W, Childs, B, Bunz, F, Gibson, K, and Mitchell, G, editors, *Scriver's OMMBID*, 77S1. McGraw-Hill, New York, NY: 2010.

