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原发性高血压全基因组关联研究进展

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摘要 原发性高血压是一种由遗传与环境因素共同导致的复杂疾病, 具有高度的遗传异质性。自2007年首个高血压全基因组关联研究(Genome-wide association studies , GWAS)报道以来, 许多GWAS相继开展。文章首先对2007年1月至2011年9月期间报道的24篇血压/高血压易感基因的GWAS按人种与染色体位置对其结果进行汇总, 经统计位点rs17249754、rs1378942和rs11191548报道频数最多。其次介绍了GWAS方法学的研究进展, 包括选择高质量的数量表型和选择多阶段研究设计来增加研究发现阳性关联的机会。统计分析方面, 除强调了已经报道过的多重比较和重复(验证)研究等问题外, 文章还介绍了通过Meta分析对GWAS数据进行深度发掘, 并应用基因型填补法对缺失数据进行填补可以提高全基因组遗传标记的覆盖率的方法。尽管GWAS发现了许多我们未知的基因与疾病表型的关联, 为了解高血压的发病机制提供了更多线索, 但是目前GWAS发现的血压/高血压相关变异多为对人群血压的影响极其微弱的常见变异。因此今后的研究中可加强深度功能学研究对易感基因精细定位和外显子组测序技术的应用, 结合GWAS的成果进行生物信息学通路分析和表观遗传学机制研究等, 逐步揭示高血压的遗传机制。

关键词: 原发性高血压 血压 全基因组关联研究 易感基因

Abstract: Since the first genome-wide association study was reported in 2007, hypertension has attracted numerous studies to identify its genetic basis. The first part of the current review summarizes the genetic loci associated with blood pressure/ hypertension identified by genome-wide association studies (GWAS) from January 2007 to September 2011, by race and chromosomal location. In the second part, we stress several important points in GWAS methodology, for example, selecting high-quality phenotypes and using multi-stage study design to increase the power studies to identify loci with minor effect. For statistical analysis, besides multiple testing correction and replication of the GWAS that have been introduced in previous reviews, computer-based genotype imputation has been described for its advantages in compensating GWAS genotyping failures. Although GWAS identifies many unknown genetic variants and improves our understanding for the pathogenesis of hypertension, the loci related to blood pressure / hypertension are common sequence variations with minor effect. The association studies are difficult to be replicated in different populations. Further studies are expected including extensive functional studies and fine mapping using advanced techniques, such as whole genome exon sequencing and pathway analysis, as well as epigenetic study to elucidate the etiology of human essential hypertension.

Keywords: essential hypertension, blood pressure, genome-wide association study, susceptibility gene

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[1] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. *Lancet*, 2005, 365(9455): 217-223.

[2] Lawes CMM, Hoorn SV, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet*, 2008, 371 (9623): 1513-1518.

[3] Feinleib M, Garrison RJ, Fabsitz R, Christian JC, Hrubec Z, Borhani NO, Kannel WB, Rosenman R, Schwartz JT, Wagner JO. The NHLBI twin study of cardiovascular disease risk factors: Methodology and summary of results. *Am J Epidemiol*, 1977, 106(4): 284-285.

[4] Hunt SC, Hasstedt SJ, Kuida H, Stults BM, Hopkins PN, Williams RR. Genetic heritability and common environmental components of resting and stressed blood pressures, lipids, and body mass index in Utah pedigrees and twins. *Am J Epidemiol*, 1989, 129(3): 625-638.

[5] Pearson TA, Manolio TA. How to interpret a genome-wide association study. *JAMA J Am Med Assoc*, 2008, 299(11): 1335-1344.

[6] Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, Kwiatkowski DP, McCarthy MI, Ouwehand WH, Samani NJ. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*, 2007, 447(7145): 661-678.

[7] Levy D, Larson MG, Benjamin EJ, Newton-Cheh C, Wang TJ, Hwang SJ, Vasan RS, Mitchell GF. Framingham heart study 100K project: Genome-wide associations for blood pressure and arterial stiffness. *BMC Med Genet*, 2007, 8(Suppl. 1): S3.

[8] Ehret GB, Morrison AC, O'Connor AA, Grove ML, Baird L, Schwander K, Weder A, Cooper RS, Rao DC, Hunt SC, Boerwinkle E, Chakravarti A. Replication of the wellcome trust genome-wide association study of essential hypertension: The family blood pressure program. *Eur J Hum Genet*, 2008, 16(12): 1507-1511.

[9] Wang Y, O'Connell JR, McArdle PF, Wade JB, Dorff SE, Shah SJ, Shi XL, Pan L, Rampersaud E, Shen HQ, Kim JD, Subramanya AR, Steinle NI, Parsa A, Ober CC, Welling PA, Chakravarti A, Weder AB, Cooper RS, Mitchell BD, Shuldiner AR, Chang YPC. Whole-genome association study identifies *STK39* as a hypertension susceptibility gene. *Proc Natl Acad Sci USA*, 2009, 106(1): 226-231.

[10] Org E, Eyheramendy S, Juhanson P, Gieger C, Lichtner P, Klopp N, Veldre G, Döring A, Viigimaa M, Sõber S, Tomberg K, Eckstein G, Kelgo P, Rebane T, Shaw- Hawkins S, Howard P, Onipinla A, Dobson RJ, Newhouse SJ, Brown M, Dominiczak A, Connell J, Samani N, Farrall M, Caulfield MJ, Munroe PB, Illig T, Wichmann HE, Meitinger T, Laan M. Genome-wide scan identifies *CDH13* as a novel susceptibility locus contributing to blood pressure determination in two european populations. *Hum Mol Genet*, 2009, 18(12): 2288-2296.

[11] Roslin NM, Hamid JS, Paterson AD, Beyene J. Genome-wide association analysis of cardiovascular-related quantitative traits in the framingham heart study. *BMC Proc*, 2009, 3(Suppl. 7): S117.

[12] Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Köttgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo XQ, Arking DE, Mitchell GF, Mattace-Raso FUS, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJG, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JCM, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet*, 2009, 41(6): 677-687.

[13] Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Eyheramendy S, Papadakis K, Voight BF, Scott LJ, Zhang F, Farrall M, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet*, 2009, 41(6): 666-676.

[14] Zhu XF, Young JH, Fox E, Keating BJ, Franceschini N, Kang S, Tayo B, Adeyemo A, Sun YV, Li YL, Morrison A, Newton-Cheh C, Liu K, Ganesh SK, Kutlar A, Vasan RS, Dreisbach A, Wyatt S, Polak J, Palmas W, Musani S, Taylor H, Fabsitz R, Townsend RR, Dries D, Glessner J, Chiang CWK, Mosley T, Kardia S, Curb D, Hirschhorn JN, Rotimi C, Reiner A, Eaton C, Rotter JI, Cooper RS, Redline S, Chakravarti A, Levy D. Combined admixture mapping and association analysis identifies a novel blood pressure genetic locus on 5p13: Contributions from the care consortium. *Hum Mol Genet*, 2011, 20(11): 2285-2295.

[15] Ho JE, Levy D, Rose L, Johnson AD, Ridker PM, Chasman DI. Discovery and replication of novel blood pressure genetic loci in the Women's Genome Health Study. *J Hypertens*, 2011, 29(1): 62-69.

[16] International Consortium for Blood Pressure Genome- Wide Association Studies. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*, 2011, 478(7367): 103-109.

[17] Adeyemo A, Gerry N, Chen GJ, Herbert A, Doumatey A, Huang HX, Zhou J, Lashley K, Chen YX, Christman M, Rotimi C. A genome-wide association study of hypertension and blood pressure in African americans. *PLoS Genet*, 2009, 5(7): e1000564.

[18] Fox ER, Young JH, Li YL, Dreisbach AW, Keating BJ, Musani SK, Liu K, Morrison AC, Ganes S, Kutlar A, Ramachandran VS, Polak JF, Fabsitz RR, Dries DL, Newton-Cheh C. Association of genetic variation with systolic and diastolic blood pressure among African americans: The candidate gene association resource study. *Hum Mol Genet*, 2011, 20(11): 2273-2284.

[19] Niu WQ, Zhang Y, Ji KD, Gu ML, Gao PJ, Zhu DL. Confirmation of top polymorphisms in hypertension genome wide association study among Han chinese. *Clin Chim Acta*, 2010, 411(19-20): 1491-1495.

[20] Liu C, Li HX, Qi QB, Lu L, Gan W, Loos RJF, Lin X. Common variants in or near FGF5, CYP17A1 and MTHFR genes are associated with blood pressure and hypertension in Chinese Hans. *J Hypertens*, 2011, 29(1): 70-75.

[21] Lin YH, Lai XL, Chen B, Xu Y, Huang BY, Chen ZC, Zhu SH, Yao J, Jiang QQ, Huang HB, Wen JP, Chen G. Genetic variations in CYP17A1, CACNB2 and PLEKHA7 are associated with blood pressure and/or hypertension in She ethnic minority of China. *Atherosclerosis*, 2011, 219(2): 709-714.

[22] Tabara Y, Kohara K, Kita Y, Hirawa N, Katsuya T, Ohkubo T, Hiura Y, Tajima A, Morisaki T, Miyata T, Nakayama T, Takashima N, Nakura J, Kawamoto R, Takahashi N, Hata A, Soma M, Imai Y, Kokubo Y, Okamura T, Tomoike H, Iwai N, Ogihara T, Inoue I, Tokunaga K, Johnson T, Caulfield M, Umemura S, Ueshima H, Miki T. Common variants in the ATP2B1 gene are associated with susceptibility to hypertension: The Japanese Millennium Genome Project. *Hypertension*, 2010, 56(5): 973-980.

[23] Takeuchi F, Isono M, Katsuya T, Yamamoto K, Yokota M, Sugiyama T, Nabika T, Fujioka A, Ohnaka K, Asano H, Yamori Y, Yamaguchi S, Kobayashi S, Takayanagi R, Ogihara T, Kato N. Blood pressure and hypertension are associated with 7 loci in the Japanese population. *Circulation*, 2010, 121(21): 2302-2309.

[24] Miyaki K, Htun NC, Song Y, Ikeda S, Muramatsu M, Shimbo T. The combined impact of 12 common variants on hypertension in Japanese men, considering GWAS results. *J Hum Hypertens*, 2011, doi: 10.1038/jhh.2011.50.

[25] Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, Yoon D, Lee MH, Kim DJ, Park M, Cha SH, Kim JW, Han BG, Min H, Ahn Y, Park MS, Han HR, Jang HY, Cho EY, Lee JE, Cho NH, Shin C, Park T, Park JW, Lee JK, Cardon L, Clarke G, McCarthy MI, Lee JY, Lee JK, Oh B, Kim HL. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nat Gene*, 2009, 41 (5): 527-534.

[26] Park JW, Uhmm SY, Shin C, Cho NH, Cho YS, Lee JY. Genome-wide association analyses on blood pressure using three different phenotype definitions. *Geno Inform*, 2010, 8(3): 108-115.

[27] Hong KW, Go MJ, Jin HS, Lim JE, Lee JY, Han BG, Hwang SY, Lee SH, Park HK, Cho YS, Oh B. Genetic variations in ATP2B1, CSK, ARSG and CSMD1 loci are related to blood pressure and/or hypertension in two Korean cohorts. *J Hum Hypertens*, 2010, 24(6): 367-372.

[28] Hong KW, Lim JE, Oh B. A regulatory SNP in AKAP13 is associated with blood pressure in Koreans. *J Hum Genet*, 2011, 56(3): 205-210.

[29] Kato N, Takeuchi F, Tabara Y, Kelly TN, Go MJ, Sim XL, Tay WT, Chen CH, Zhang Y, Yamamoto K, Katsuya T, Yokota M, Kim YJ, Ong RTH, Nabika T, Gu DF, Chang LC, Kokubo Y, Huang W, Ohnaka K, Yamori Y, Nakashima E, Jaquish CE, Lee JY, Seielstad M, Isono M, Hixson JE, Chen YT, Miki T, Zhou X, Sugiyama T, Jeon JP, Liu JJ, Takayanagi R, Kim SS, Aung T, Sung YJ, Zhang X, Wong TY, Han BG, Kobayashi S, Ogihara T, Zhu D, Iwai N, Wu JY, Teo YY, Tai ES, Cho YS, He J. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. *Nat Genet*, 2011, 43(6): 531-538.

[30] 严卫丽. 复杂疾病全基因组关联研究进展——遗传统计分析. 遗传, 2008, 30(5): 543-549. 浏览

[31] Fox ER, Young JH, Li YL, Dreisbach AW, Keating BJ, Musani SK, Liu K, Morrison AC, Ganesh S, Kutlar A, Ramachandran VS, Polak JF, Fabsitz RR, Dries DL, Newton-Cheh C. Association of genetic variation with systolic and diastolic blood pressure among African Americans: The candidate gene association resource study. *Hum Mol Genet*, 2011, 20(11): 2273-2284.

[32] 权晟, 张学军. 全基因组关联研究的深度分析策略. 遗传, 2011, 33(2): 100-108. 浏览

[33] Westfall PH, Young SS. Resampling-based multiple testing: Examples and methods for p-value adjustment. New York: Wiley-Interscience, 1993.

[34] 顾东风. 常见复杂性疾病的遗传学和遗传流行病学研究: 挑战和对策. 中国医学科学院学报, 2006, 28(2): 115-118.

[35] 陈峰, 柏建岭, 赵杨, 荀鹏程. 全基因组关联研究中的统计分析方法. 中华流行病学杂志, 2011, 32(4): 400-404.

[1] 郑伟 季林丹 邢文华 涂巍巍 徐进.肺结核全基因组关联研究进展[J]. 遗传, 2013,35(7): 823-829

[2] 吴志俊，金玮，张凤如，刘艳.利钠肽家族基因与心血管疾病研究新进展[J]. 遗传, 2012,34(2): 127-133

[3] 李俊燕，谭英姿，冯国鄞，贺林，周里钢，陆灏.糖尿病肾病遗传学研究进展[J]. 遗传, 2012,34(12): 1537-1544

[4] 杨昭庆，褚嘉祐.中国人类遗传多样性研究进展[J]. 遗传, 2012,34(11): 1351-1364

[5] 薛凌，陈红，孟燕子，王燕，卢中秋，吕建新，管敏鑫.高血压相关的线粒体DNA突变[J]. 遗传, 2011,33(9): 911-918

[6] 李宗斌，刘昱圻，李彦华，陈瑞，王琳，朱庆磊，李泱，王士雯.中国汉族原发性高血压患者线粒体tRNA基因突变[J]. 遗传, 2011,33(6): 601-606

[7] 权晟，张学军.全基因组关联研究的深度分析策略[J]. 遗传, 2011,33(2): 100-108

[8] 张子波，于丽军，杨康鹃，徐良慰，盛天昕，郝萍，王玉萍，孟繁平.延边朝鲜族和汉族脂联素启动子SNPs与原发性高血压的相关性[J]. 遗传, 2011,33 (1): 54-59

[9] 韩建文，张学军.全基因组关联研究现状[J]. 遗传, 2011,33(1): 25-35

[10] 曹宗富，马传香，王雷，蔡斌.随机SNP在全基因组关联研究人群分层分析中的应用[J]. 遗传, 2010,32(9): 921-928

[11] 杨英，鲁向锋.冠心病全基因组关联研究进展[J]. 遗传, 2010,32(2): 97-104

[12] 严卫丽.复杂疾病全基因组关联研究进展——遗传统计分析[J]. 遗传, 2008,30(5): 543-549

[13] 严卫丽.复杂疾病全基因组关联研究进展—— 研究设计和遗传标记[J]. 遗传, 2008,30(4): 400-406

[14] 王雅文，朱小泉，宋玉国，孙亮，杨泽.吉林人群强直性脊柱炎6号染色体短臂上的HLA区域遗传易感基因定位研究[J]. 遗传, 2007,29(7): 805-812

[15] 马厚勋，谢正祥，牛永红，李章勇，周平.汉族人群NOS3 A-922G、NOS3 T-786C 与NOS3 G894T SNP的等位基因及其组合分布与高血压的相关性[J]. 遗传, 2006,28(1): 3-10

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