Review Article

Human genetics of the metabolic syndrome

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Genetic studies of metabolic syndrome provide a means to identify key pathways that predispose individuals to various phenotypes of the metabolic diseases and risk factors to type 2 diabetes and cardiovascular disease. Both genome wide linkage and association studies have been attempted to answer this issue. In this minireview, I will address genetic studies in Chinese in both family and population samples. The works of genome scan of were reported from the SAPPHIRe cohort as an example to address the linkage approaches to unraveling genetics of various traits composing the metabolic syndrome. In addition, some of the important biological candidate genes were also discussed. Finally, the success of finding genes through genome wide association for the metabolic syndrome remains to be explored.

Key Words: metabolic syndrome, genetic factors, linkage mapping, candidate genes

INTRODUCTION

Metabolic syndrome is defined with a cluster of multiple complex traits including central obesity, glucose/insulin disturbance, dyslipidemia, and high blood pressure.[1] Although the underlying mechanism is not fully understood, insulin resistance appears to be one of the important determinants.[2,3] The metabolic syndrome is accompanied by an increased risk for type 2 diabetes mellitus and cardiovascular disease.

However, the genetic susceptibility factors for insulin resistance and metabolic syndrome remain to be further studied, due to a limited success in gene finding for the multifactorial diseases in general.[4,5] Since the complex nature of the metabolic syndrome, a large collection of families of different ethnic individuals would provide a very unique resource of human genetic studies. Therefore, in an attempt to identify genetic factors of hypertension, there appears a NIH-sponsored Family Blood Pressure Program (FBPP) involving four networks of GenNet, GENOA, HyperGEN and SAPPHIRe The Stanford Asian Pacific Program of Hypertension and Insulin Resistance (SAPPHIRe) among of the 4 different networks was designed to study the genetic factors of hypertension and insulin resistance as intermediate phenotypes in Chinese and Japanese populations. Importantly, genome screening was completed using the same set of 387 highly polymorphic microsatellite markers in African Americans, Hispanics, Caucasians, Chinese and Japanese populations render comparisons among different ethnic groups possible.

On the other hand, association study using candidate gene approach or genome wide association (GWA) by use of hundred thousands single nucleotide polymorphisms covering whole human genome have been shown to be feasible to identify significant genes that contribute to complex disorders.

In this review, we discuss genetic studies in a large collection of families with hypertensive probands whose metabolic phenotypes have been characterized in detail. Linkage mappings of specific phenotype and some of the biological candidate genes are discussed.

STUDY DESIGN AND ANALYSES

Two different designs have been employed to study genetics of complex disorders, namely association study either in case control design or family-based association study and linkage mapping in pedigrees recruited for family members with and without disease of interest.

The SAPPHIRe (Stanford-Asian Pacific Program in Hypertension and Insulin Resistance) cohort, as network of the FBPP, included both concordant sib-pairs (both sibs with high blood pressure, defined as systolic blood pressure (SBP) $\geqq$160 mmHg or diastolic blood pressure (DBP) $\geqq$95 mmHg, or taking two medications for high blood pressure, or taking one medication for high blood pressure with either SBP$\geqq$140 or DBP $\geqq$90 mmHg) and discordant sibs (one with high blood pressure and one with low blood pressure, defined as BP in the bottom 30% of the age- and sex-adjusted BP distribution) of either Chinese or Japanese descent.

The microsatellite markers were typed by the Mammalian Genotyping Service (MGS) in Marshfield, WI, which has an average heterozygosity of ~80%, an average

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inter-marker distance of 10 cM, and covers ~95% of the human genome.

Selected SNPs of certain candidate genes were genotyped for association studies.

LINKAGE ANALYSIS FOR HYPERTENSION

Using genome-wide linkage analyses, we found no chromosomal regions showed significant linkage to hypertension in SAPPHIRe cohort.[6] A meta-analysis has been performed with data obtained from all networks of the FBPP also showed negative,[7] demonstrating a lack of power of combined analyses as for such a complex genetics of hypertension.

LINKAGE ANALYSIS OF SINGLE METABOLIC TRAIT

To study genetic contribution of various metabolic phenotypes, we examined heritability for each of individual traits in Chinese population. We found a high heritability (*h*2), ranging from 0.43 to 0.63, for different metabolic variables.[8]

To map the potential loci for these different traits, residuals of the log-transformed quantitative traits were analyzed in multipoint linkage analysis using a variance-components approach. We demonstrated that the most significant QTL for fasting insulin, which coincides with the QTL for homeostasis model assessment of insulin resistance, was located at 37 cM on chromosome 20, with a maximum empirical LOD score of 3.01 when adjusted for age, sex, BMI, and other environmental factors. There were other loci with maximum empirical LOD scores>1.29 located on chromosomes 1q, 2p, 5q, 7p, 9q, 10p, 14q, 18q, and 19q for different diabetes-related traits. The genes located at these loci may contribute to glucose homeostasis.[9]

A meta-analysis of the genome scans of the metabolic traits has been studied. There are some evidence suggestive of linkage for certain metabolic phenotypes such as glucose, insulin, HOMA-IR, and metabolic syndrome. The most significant evidence of linkages was mapped on chromosome 7q36 at 163 cM, with a logarithm of odds (LOD) score of 3.21 for HOMAIR, and on chromosome 19q13 at 88 cM, with a LOD score of 3.33 for fasting glucose.[10] Further follow-up dense mapping and association studies were suggested.

BIVARIATE LINKAGE ANALYSES

Since hypertension, obesity, dysglycemia and dyslipidemia cluster together more often than expected by chance alone, there is a possibility that pleiotropic effects from a common set of genes that might influence more than one trait simultaneously. We therefore conducted bivariate linkage analyses for those highly correlated traits, aiming to dissect the genetic architecture affecting these traits. We confirmed the pleiotropic effects of the locus at 37 cM on chromosome 20 on the following pairs: (1) fasting insulin and insulin AUC; (2) fasting insulin and homeostasis model assessment of beta cell function (HOMA-beta); and (3) HOMA of insulin resistance (IR) and HOMA-beta.[11] More strikingly, the peak LOD scores of linkage between a chromosomal locus and a trait for the pair fasting insulin and HOMA-IR rose to 5.10 from 3.67 and 3.42 respectively for these two traits in univariate analysis. Additional significant linkage evidence, not shown in single-trait analysis, can be further identified, e.g. at 45 cM on chromosome 16 for the pair 1 h insulin and the AUC for insulin, with a LOD score of 4.29. This new locus might harbour some common gene(s) that regulate these two traits.[11]

FACTOR ANALYSES AND LINKAGE MAPPING

Using factor analysis, it has been found that the main factor loaded obesity (OBS) and blood pressure (BP) in African Americans; OBS and insulin (INS) in Hispanics, in Japanese, and in Whites; and OBS alone in Chinese. In Hispanics, Whites, and Japanese, BP loaded as a separate factor. Lipids in combination with INS also loaded in a separate factor. These data indicate an ethnic difference for metabolic syndrome.[12]

To advance our knowledge of genetic loci for the latent factors of the metabolic syndrome, linkage analyses have been carried out in these populations.[13] Indeed, different QTLs have been identified in different ethnic groups, one of them linked to the obesity and insulin factor with a lod score of 3.94 located on chromosome 18p11.21 in GENOA black, the other linked to the blood pressure factor with a lod score of 3.22 located on chromosome 17q23.1 for Hispanics.[13]

CANDIDATE GENE APPROACH OF METABOLIC SYNDROME

Since obesity has been considered as the most important factor, the genes involved in adipocyte differentiation have been considered biological candidates. One of the major players of adipocyte differentiation is peroxisome proliferators activated receptor γ (PPARγ). In addition, the adiponectin (*APM1*) has been demonstrated under regulation of PPARγ. Using SAPPHIRe cohort, we provide evidence of involvement of genetic variations of these two genes in insulin sensitivity.[14,15] More interestingly, using family-based association study, we found that there was an interaction of *PPARγ* and *APM1* on insulin sensitivity,[16] supporting presence of geneto- gene interaction on insulin resistance and complex disorders.

Among other potential biological pathways, insulin receptor signalling apparently plays a pivotal role in insulin action. Upon insulin stimulation, there is a rapid phosphorylation on tyrosine residues of the insulin receptor and insulin receptor substrate (IRS) proteins. One of the protein tyrosine phosphatases, *PTPN1*, has been shown to involve in downregulation of receptor phosphorylation and attenuation of insulin action. The single nucleotide polymorphism (SNP) haplotypes have been found to associate with many features of the metabolic syndrome in our population.[17] Another signalling protein, the sorbin homology containing SH3 domain protein (*SORBS1*), is also involved in insulinstimulated glucose uptake which is independent of phosphatidylinositol 3'-kinase (PI3K). In preliminary analyses, we found genetic association of *SORBS1* with obesity and type 2 diabetes.[18] The association of this gene with other aspects of metabolic syndrome remains to be replicated.

IS GENOME WIDE ASSOCIATION (GWA) A FINAL SOLUTION?

Upon completion of the HapMap project, millions of SNPs are evaluated and made available for use in genome wide association studies.[19] Not until recently, GWA has been considered as one of the most powerful strategies for finding DNA variations that confer an increased risk for diabetes, heart disease, cancer, and other common complex genetic disorders.[20] Among these independent studies, one of the most consistently identified T2D gene is *TCF7L2* gene.[21] One of the SNP (rs790316) has been shown associated with type 2 diabetes in almost all the ethnic groups studied.[22] Instead of SNP rs790316, we demonstrated different SNP on the different LD block of the *TCF7L2* gene was associated with type 2 diabetes in Chinese,[23] indicating a caution of utilizing similar subset of SNPs for GWA studies across different ethnic populations.

In this review, we provide an overview of the evidence in support of an inherited contribution to the metabolic syndrome and the search for causative genomic regions that contribute to the multifactorial diseases like metabolic syndrome. Follow-up dense mapping and association studies of those mapped regions for various phenotypes are warranted. In addition, future genomewide SNP association study might be another strategy for elucidating the genetic variations that have only small effect on the variation of complex disease traits. Issues of the complex interactions between inherited factors and the environment in determining individual's susceptibility to type 2 diabetes mellitus and related syndromes will be resolved in the future.

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AUTHOR DISCLOSURES

Lee-Ming Chuang, no conflicts of interest.

REFERENCES

1. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006;23: 469-80.
2. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988;37:1595-1607.
3. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin resistance syndrome (Syndrome X). Diabetes. 992;41:715-22.
4. Groop L. Genetics of the metabolic syndrome. Br J Nutr. 2000;83(Suppl 1):S39-S48.
5. Stern MP. Strategies and prospects for finding insulin resistance genes. J Clin Invest. 2000;106:323-327.
6. Ranade K, Hinds D, Hsiung CA, Chuang LM, Chang MS, Chen YT, Pesich R, Hebert J, Chen YD, Dzau V, Olshen R, Curb D, Botstein D, Cox DR, Risch N. A genome scan for hypertension susceptibility loci in populations of Chinese and Japanese origins. Am J Hypertens. 2003;16:158-62.
7. Province MA, Kardia SLR, Ranade K, Rao DC, Thiel BA, Cooper RS, Risch N, Turner ST, Cox DR, Hunt SC, Weder AB, Boerwinkle E. A Meta-Analysis of Genome-Wide Linkage Scans for Hypertension: The National Heart, Lung and Blood Institute Family Blood Pressure Program. Am J Hypertens. 2003;16:144-47.
8. Wu KD, Hsiao CF, Ho LT, Sheu WHH, Pei D, Chuang LM, Curb D, Chen YDI, Tsai HJ, Dzau VJ, Cox D, Tai TY. Clustering and Heritability of Insulin Resistance in Chinese and Japanese Hypertensive Families: A SAPPHIRe Sib Study. Hypertens Res. 2002;25:529-36.
9. Chiu YF, Chuang LM, Hsiao CF, Hung YJ, Lin MW, Chen YT, Grove J, Jorgenson E, Quertermous T, Risch N, Hsiung CA. An autosomal genome-wide scan for loci linked to pre-diabetic phenotypes in non-diabetic Chinese from the SAPPHIRe family study. Diabetes. 2005;54:1200-6.
10. An P, Freedman BI, Hanis CL, Chen YDI, Weder AB, Schork NJ, Boerwinkle E, Province MA, Hsiung CA, Wu X, Quertermous T, Rao DC. Genome-wide Linkage Scans for Fasting Glucose, Insulin, and Insulin Resistance in the National Heart, Lung, and Blood Institute Family Blood Pressure Program. Evidence of Linkages to Chromosome 7q36 and 19q13 From Meta-Analysis. Diabetes. 2005;54: 909-14.
11. Chiu YF, Chuang LM (equal first author), Kao HY, Ho LT, Ting CT, Hung YJ, Chen I, Donlon T, Curb D, Quertermous T, Hsiung CA and the SAPPHIRe Study Group. Bivariate genome-wide scan for metabolic phenotypes in non-diabetic Chinese subjects from the Stanford Asia-Pacific program of hypertension and insulin resistance family study. Diabetologia. 2007;50:1631-40.
12. Kraja AT, Rao DC, Weder AB, Mosley TH, Turner ST, Hsiung CA, Quertermous T, Cooper R, Curb JD, Province MA. An evaluation of the metabolic syndrome in a large multi-ethnic study: the Family Blood Pressure Program. BMC Nutrition & Metabolism. 2005, 2:17.
13. Kraja AT, Rao DC, Weder AB, Cooper R, Curb JD, Hanis CL, Turner ST, de Andrade M, Hsiung CA, Quertermous T, Zhu X, Province MA. Two Major QTLs and Several Others Relate to Factors of Metabolic Syndrome in the Family Blood Pressure Program. Hypertension. 2005;46:751-58.
14. Chuang LM , Hsiung CA, Chen YDI, Ho, Sheu WHH, Pei D, Nakatsuka CH, Cox D, Pratt RE, Lei HH, Tai TY, and the SAPPHIRe Study Group. Sibling-based association study of the PPARγ2 Pro12Ala polymorphism and metabolic variables in Chinese and Japanese hypertension families: a SAPPHIRe study. J Mol Med. 2001;79:656-64.
15. Yang WS, Tsou PL, Lee WJ, Tseng DL, Chen CL, Peng CC, Lee KC, Chen MJ, Huang CJ, Tai TY, Chuang LM. Allele-specific differential expression of a common adiponectin gene polymorphism related to obesity. J Mol Med. 2003;81:428-34.
16. Yang WS, Hsiung CA, Ho LT, Chen YT, He CT, Curb JD, Grove J, Quertermous T, Chen YDI, Kuo SS, Chuang LM for the SAPPHIRe Study Group. Genetic Epistasis of Adiponectin and PPARγ2 Genotypes in Modulation of Insulin Sensitivity: a Family-based Association Study. Diabetologia. 2003;46:977-83.
17. Olivier M, Hsiung CA, Chuang LM, Ho LT, Ting CT, Bustos VI, Lee TM, De Witte A, Chen YD, Olshen R, Rodriguez B, Wen CC, Cox DR. Single nucleotide polymorphisms in protein tyrosine phosphatase 1 (PTPN1) are associated with essential hypertension and obesity. Hum Mol Genet. 2004;13:1885-92.
18. Lin WH, Chiu KC, Chang HM, Lee KC, Tai TY, Chuang LM. Molecular scanning for the human sorbin and SH3 domain containing 1 (*SORBS1*) gene: A positive association of the T228A polymorphism with obesity and type 2 diabetes. Hum Mol Genet. 2001;10:1753-60.

19. International HapMap. Consortium. The International HapMap Project. Nature. 2003;426:789-96.
20. Couzin J, Kaiser J. Closing the Net on Common Disease Genes. Science. 2007;316:820-22.
21. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006;38:320-23.
22. Cauchi S, Achhab YEI, Choquet H, Dina C, Krempler F, Weitgasser R, Nejjari C, Patsch W, Chikri M, Meyre D, Froguel P. TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. J Mol Med. 2007;85:777-82.
23. Chang YC, Chang TJ, Jiang YD, Kuo SS, Lee KC, Chiu KC, Chuang LM. Association Study of the Genetic Polymorphisms of the Transcription Factor7- like 2 (*TCF7L2*) Gene and Type 2 Diabetes in the Chinese Population. Diabetes. 2007; 56:2631-7.