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. Although the underlying mechanism is not fully understood, insulin resistance appears to be one of the important determinants. 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. 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) ≥160 mmHg or diastolic blood pressure (DBP) ≥95 mmHg, or taking two medications for high blood pressure, or taking one medication for high blood pressure with either SBP ≥140 or DBP ≥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...
inter-marker distance of 10 cM, and covers ~95% of the human genome.

Selected SNPs of certain candidate genes were geno-
typed for association studies.

LINKAGE ANALYSIS FOR HYPERTENSION
Using genome-wide linkage analyses, we found no chro-
mosomal regions showed significant linkage to hyperten-
sion in SAPPHIRE cohort. A meta-analysis has been per-
formed with data obtained from all networks of the
FBPP also showed negative, demonstrating a lack of
power of combined analyses as for such a complex genet-
ics of hypertension.

LINKAGE ANALYSIS OF SINGLE METABOLIC
TRAIT
To study genetic contribution of various metabolic pheno-
types, 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.

To map the potential loci for these different traits, re-
siduals 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.

A meta-analysis of the genome scans of the metabolic
traits has been studied. There are some evidence sugges-
tive of linkage for certain metabolic phenotypes such as
glucose, insulin, HOMA-IR, and metabolic syndrome.

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 homeo-

stasis model assessment of beta cell function (HOMA-
beta); and (3) HOMA of insulin resistance (IR) and
HOMA-beta. 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 univari-
ate 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.

FACTOR ANALYSES AND LINKAGE MAPPING
Using factor analysis, it has been found that the main fac-
tor loaded obesity (OBS) and blood pressure (BP) in Af-

rican 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.

To advance our knowledge of genetic loci for the latent
factors of the metabolic syndrome, linkage analyses have
been carried out in these populations. 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.

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 pro-
vide evidence of involvement of genetic variations of
these two genes in insulin sensitivity. More
interestingly, using family-based association study, we found that
there was an interaction of PPARγ and APM1 on insulin
sensitivity, supporting presence of geneto- gene interac-
tion on insulin resistance and complex disorders.

Among other potential biological pathways, insulin re-
ceptor signalling apparently plays a pivotal role in insulin
action. Upon insulin stimulation, there is a rapid phos-
phorylation on tyrosine residues of the insulin receptor
and insulin receptor substrate (IRS) proteins. One of the
protein tyrosine phosphatases, PTPN11, 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 as-
sociate with many features of the metabolic syndrome in
our population. 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. The associa-
tion of this gene with other aspects of metabolic syn-
drome 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.20 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.21 Among these independent studies, one of the most consistently identified T2D gene is TCF7L2 gene.22 One of the SNP (rs790316) has been shown associated with type 2 diabetes in almost all the ethnic groups studied.23 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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Lee-Ming Chuang, no conflicts of interest.

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