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Genetic Polymorphism and Personalized Medicine-Application in Metabolic Syndrome

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Abstract: To explore the associations between the phenotypes of metabolic syndrome and several genetic polymorphisms in the people of the Democratic People's Republic of Korea, and to address the basic and practical problems that arise in carrying out the personalized medicine of metabolic syndrome. We analyzed the four phenotypes of metabolic syndrome including hypertension, dyslipidemia, diabetes mellitus and obesity by PCR. And we could select six genetic polymorphisms that are associated with more than three phenotypes (3 of 4 phenotypes including hypertension, dyslipidemia, diabetes mellitus and obesity) of metabolic syndrome; they are CMA (Chymase) A (-1903)G, GNB3(β3 subunit of G protein) C825T and C1429T, eNOS (Nitric oxide synthetase in the endothelium) 4a/4b and G894T, and MTHFR (Methylenetetra hydrofolate reductase) C677T. It shows that these can be the significant markers related with metabolic syndrome in the future. (It recommends future studies to support our conclusion) The typical genes associated with metabolic syndrome in the people of the Democratic People's Republic of Korea will be basic data for the personalized medicine in metabolic syndrome.

Keywords: Metabolic Syndrome, Genes, Personalized Medicine, Polymorphism

1. Introduction

Today's era is not simply the one of personalized preventive medicine but of 4 P medicine, which is predictive, preventive, personalized and participatory [7]. Therefore it assesses the state of the people's health, predict and prevent diseases, and gives the treatment that is efficient for the individual persons. Known that a great number of DNA polymorphism, especially Single Nucleotide Polymorphism (SNP) exists widely in genome [2], the world genetic polymorphism data base is created, added and improved, and this study opens a new era not only for individuality but also for the disease treatment. Today it gives us a chance to choose the drug and therapy, diet and lifestyle that is efficient and without any side effects for each individuals through the test of individual person's biomarkers like genes or proteins. [7]

The metabolic syndrome, a cluster of cardiovascular risk factors, is associated with insulin resistance and obesity, and plays a role in the pathogenesis of diabetes mellitus. However, at least five different phenotypic definitions, including those proposed by the World Health Organization (WHO), the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and most recently the International Diabetes Federation (IDF), have attempted to pin down the essential components of this unique pathophysiological condition. [1] Each definition attempts to provide relatively simple clinical markers that can be used to identify individuals with the complex *bouillabaissen* of metabolic, pro-inflammatory, and pro-thrombotic disturbances that are not routinely measured but which acts as the likely pathogenic agents for CVD. By each definition, metabolic syndrome is a discrete, non-continuous trait. [4]

The practice of clinical medicine teaches us to assess each patient and, on the basis of their symptoms, signs and targeted investigations, to develop a personalized management plan. When we manage patients with metabolic syndrome, it is clear that they represent a very diverse group of people, spanning all ethnicities, the young to the old, the insulin-deficient to the markedly insulin-resistant. As clinicians we try to take into account these differences when developing a personalized

management plan with our patients. This process of personalizing therapy currently is often more of an art than a science. [8]

Study of monogenic forms of metabolic syndrome might help to better understand the common metabolic syndrome. Some very rare patients with certain single gene disorders express clusters of abnormalities that are seen in the common metabolic syndrome. [6]

Although the metabolic syndrome is partially genetically determined, their genetic factors remain mostly unknown. [3] Furthermore, the distribution of genetics polymorphisms are differences with each racial, local and nations.

Recently we found an association between some genetics polymorphisms and the phenotypes of metabolic syndrome. These individuals display the defining features of metabolic syndrome including insulin resistance, dyslipidemia, and hypertension and have markedly increased CVD risk. The purpose of this study was to analyze the distribution of some genetic polymorphisms related with metabolic syndrome in the people of the Democratic People's Republic of Korea and to make basic data for personalized medicine in metabolic syndrome.

2. Subjects and Method

Individuals with diabetes mellitus (n=450), dyslipidemia (n=1506), hypertension (n=817), obesity (n=366) were recruited at the Hospital of the Pyongyang Medical College Kim Il Sung University. This study was approved by the local ethical committee of our hospital. Obesity [5], hypertension, diabetes mellitus [9], hyperlipidemia and metabolic syndrome [10] were determined as previously.

The genotypes were scored using PCR-RFLP analysis and assessed by electrophoresis in agar or polyacrylamide gel [11]. Difference in the distribution among patients and relative healthy people were assessed and then, the genotypes associated with more than three phenotypes of metabolic syndrome were selected.

3. Results

3.1. The Association Between Diabetes Mellitus Type 2 and Genetic Polymorphism

Table 1 shows the genotypes or alleles associated with type 2 diabetes mellitus. CMA A (-1903)G, eNOS G894T and MTHFR C677T polymorphisms are well known to be associated with cardiovascular diseases (CVD) and Calpain-10 I/D, which is associated with regulating the insulin secretion through dislocation of insulin secretory granules, fusion with cellular membranes, and signal conduction pathways, is known to be related with the development of diabetes mellitus. This shows that genetic polymorphisms associated with cardiovascular disease are closely related with diabetes.

Table 1. *Genetic polymorphisms associated with Type 2 diabetes mellitus.*

Genes	Cases	Genotypes			Alleles		Related
CMA A (-1903)G	125	AA	AG	GG	A	G	AG
eNOS G894T	101	GG	GT	TT	G	T	T
Calpain-10 I/D	125	II	ID	DD	D	I	II, I
MTHFR C677T	100	CC	CT	TT	C	T	TT

3.2. The Association Between Obesity and Genetic Polymorphism

Table 2 shows the genotypes or alleles associated with obesity. GNB3 C825T, C1429T, eNOS 4a/4b and ANP (Atrial natriuretic peptide) T2238C polymorphisms are known to be associated with cardiovascular disease, dyslipidemia and hypertension. This means that obesity is the multifactorial phenotype associated with genetic polymorphisms that are related with various diseases.

Table 2. *Genetic polymorphisms associated with obesity.*

Genes	Cases	Genotypes			Alleles		Related
GNB3 C825T	117	CC	CT	TT	C	T	TT, TC, T
C1429T	117	CC	CT	TT	C	T	T
eNOS 4a/4b	101	aa	ab	bb	a	b	a
ANP T2238C	148	TT	TC	CC	T	C	CC

3.3. The Association Between Dyslipidemia and Genetic Polymorphism

Table 3. *Genetic polymorphisms associated with dyslipidemia.*

Genes	Cases	Genotype			Alleles		Related			
							TC	TG	HDL-C	LDL-C
ACE I/D	224	II	ID	DD	I	D			DD	
CMA A (-1903)G	125	AA	AG	GG	A	G	A			
GNB3 C825T	117	CC	CT	TT	C	T			TT, T	
C1429T	117	CC	CT	TT	C	T			T	
ADD1G460W	150	GG	GW	WW	G	W	W			
CYP4A11 T8590C	150	AA	AC	CC	A	C		C		
eNOS 4a/4b	101	aa	ab	bb	a	b			a	
G894T	101	GG	GT	TT	G	T	T		T	
T (-786)C	101	TT	TC	CC	T	C	C			
ADPN T45G	125	TT	TG	GG	T	G	G	G		G
AT1R A1166C	166	AA	AC	CC	A	C	C		C	
LDLR P1/P2	100	P1P1	P1P2	P2P2			P1			P1
ANP T2238C	148	TT	TC	CC	T	C	CC		CC	
MTHFR C677T	100	CC	CT	TT	C	T	TT	TT		TT

TC; total cholesterol, TG; triglyceride, HDL-C; high-density lipoprotein-cholesterol, LDL-C; low-density lipoprotein cholesterol, ADD: Adducin.

Table 3 shows the genotypes or alleles associated with dyslipidemia. Most of the genetic polymorphisms that we have studied are associated with dyslipidemia. This indicates that dyslipidemia is very complicated and has various mechanisms.

3.4. The Association Between Hypertension and Genetic Polymorphism

Table 4 shows the genotypes or alleles associated with hypertension among the ones of genetic polymorphisms. In foreign literatures, the association between these genetic polymorphisms and hypertension is discussed by the differences in the distribution of genetic polymorphisms, races, nations and regions. In our country these genetic polymorphisms are identified to be associated with hypertension and contribute to the development of hypertension in multiple ways.

Table 4. *Genetic polymorphisms associated with hypertension.*

Genes		Genotypes			Alleles		Related
ACE I/D	224	II	ID	DD	I	D	DD, D
CMA A (-1903) G	125	AA	AG	GG	A	G	A
GNB3 C825T	117	CC	CT	TT	C	T	TT, T
C1429T	117	CC	CT	TT	C	T	T
ADD1 G460W	150	GG	GW	WW	G	W	W
CYP4A11 T8590C	150	TT	TC	CC	T	C	C
eNOS 4a/4b	101	aa	ab	bb	a	b	a
G894T	101	GG	GT	TT	G	T	T
MTHFR C677T	100	CC	CT	TT	C	T	TT

3.5. Genetic Polymorphisms Associated with More Than Three Phenotypes of Metabolic Syndrome

Based on the analysis of 4 phenotypes of metabolic syndrome individually, we showed genetic polymorphisms that are associated with more than 3 phenotypes in table 6. Six genetic polymorphisms are selected; CMA A (-1903)G, GNB3 C825T, C1429T, eNOS 4a/4b, G894T and MTHFR C677T. The study shows that these genetic polymorphisms would be the significant items associated with metabolic syndrome in the future.

Table 5. *Genetic polymorphisms associated with more than 3 phenotypes of metabolic syndrome.*

Genes	Cases	DM	Obesity	Hyper-tension	Hyperlipidemia			
					TC	TG	HDL-C	LDL-C
CMA A (-1903)G	125	AG		A	A			
GNB3 C825T	117		TT,TC,T	TT, T			TT, T	
C1429T	117		T	T			T	
eNOS 4a/4b	101		a	a			a	
G894T	101	T		T	T		T	
MTHFR C677T	100	TT		TT	TT	TT		TT

4. Discussion

This is the first report that demonstrates an association between genetic polymorphisms and the phenotypes of metabolic syndrome.

It is necessary to find out the genetic polymorphisms in our county from the point of view that in many previous studies the distribution of genetic polymorphisms varies according to ethnics, nations and cultural and geographical difference. Furthermore, the diagnosis of metabolic syndrome is an important problem in establishing the strategy for prevention and treatment of metabolic syndrome. Several criteria have been introduced so far by the several countries and international organizations through the study and discussion on the diagnosis of metabolic syndrome, but there is no unified criteria, and some degree of disagreement. The fact that there is no unified criteria means that metabolic syndrome differs a lot from region to region, from country to country, and that the criteria for their country should be established based on the study of their nation or population. Based on our finding, we're going to continue to study for the new cut-point in the metabolic syndrome in our country in the future.

The typical genes associated with phenotypes of Metabolic syndrome in our country are CMA A (-1903)G, GNB3 C825T and C1429T, eNOS 4a/4b and G894T.

The practical problems in carrying out the personalized medicine of metabolic syndrome are as follows. Firstly, to select the genetic markers of metabolic syndrome for prediction and assessment of the disease progression. Secondly, to select the genetic markers that show the individual difference in drug and nutritional therapy.

5. Conclusion

The typical genes associated with phenotypes of Metabolic syndrome in our country are CMA A (-1903)G, GNB3 C825T and C1429T, eNOS 4a/4b and G894T.

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