[16:30 - 17:00]

ABC Transporters and Tailored Medicine

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Introduction

ATP-binding cassette (ABC) transporters constitute a superfamily of membrane proteins found in all organisms examined to date. The ABC proteins provide nutrients to the cells, protect them from a wide range of toxic compounds, and regulate basic biologic processes of essential organs such as alimentary tract, liver, lung and immune system.[1-3] Consequently, mutations affecting ABC-transporters have been found to be the underlying causes for a large number of human inherited diseases. Currently, 49 ABC transporter genes were identified in human genome and classified into 7 subfamilies according to their sequence homologies; MDR/TAP, ALD, MRP/CFTR, ABC1, White, OABP, and GCN20.[4] Among them, we tried to identify mutations in CFTR, MDR, and MRP in Korean population, since the function of these transporters are relatively well-characterized and the genetic variations of these transporters may induce the alteration of drug response profile in addition to inherited diseases.[5-8]

Cystic fibrosis transmembrane conductance regulator (CFTR)

Aberrant membrane transport caused by mutations in CFTR gene is associated with a wide spectrum of respiratory and digestive diseases as well as cystic fibrosis.[5-6] Using a gene scanning method, we found 11 polymorphisms and mutations of the *CFTR* gene in the Korean population. Individual variations at these loci were analyzed by conventional DNA screening in 117 control and 75 patients having bronchiectasis or

chronic pancreatitis. In a haplotype determination based on Bayesian algorithm, fifteen haplotypes were assembled in the 192 individuals tested. Several haplotypes, especially with Q1352H, IVS8 T_5, and E217G were found to have disease associations in a case-control study. Notably, a common polymorphism of M470V appears to affect the intensity of the disease association. These findings provide evidence for the importance of CFTR mutations in the Asian population. In addition, the results also reveal that interactions between multiple genetic variations in a *cis*-gene affect the final function of the gene products.[6)]

Muti-drug resistance (MDR) and Multi-drug resistance related protein (MRP).

The multi-drug resistance 1 gene (*MDR1*) was originally identified as a gene that confers multi-drug resistance to cancer cells. The MRPs were discovered as a second type of drug pump in caner cells exhibiting multi-drug resistance not caused by *MDR1*. However, recently it was accepted that they are the native exporters having physiological role of protecting organism from various toxic substances including commonly prescribed medications.[9)] Thus, identifying the individual genetic variations of these transporters carries significant meaning in pharmacotherapy of post-genomic era, since such genetic variants are likely to be an important source for the inter-individual variability in toxicity and response of many drugs.[7, 8)] For example, recently we found an association between the genetic variations of MRP2 and drug-induced toxic hepatitis[10)].

Multidrug resistance protein 2 (MRP2, ABCC2) plays an important role in the biliary clearance of a wide variety of endogenous and exogenous toxic compounds. Therefore, polymorphisms and mutations in the MRP2 gene may affect individual susceptibility to hepatotoxic reactions. Using a gene scanning method, 12

polymorphisms and mutations were found in the MRP2 gene in a Korean population. Individual variation at these sites was analyzed by conventional DNA screening in 110 control subjects and 94 patients with toxic hepatitis induced mostly by herbal remedies. When haplotypes were identified, over 85% of haploid genes belonged to the five most common haplotypes. Among these, a haplotype containing the g.-1774delG polymorphism showed a strong association with cholestatic- or mixed-type hepatitis, and a haplotype containing the g.-1549G>A, g.-24C>T, c.334-49C>T, and c.3972C>T variations was associated with hepatocellular-type hepatitis. A comprehensive functional study of these sites revealed that genetic variations in the promoter of this gene are primarily responsible for the susceptibility to toxic liver injuries. These results suggest that genetic variations of MRP2 are an important predisposing factor for herbal- or drug-induced toxic liver injuries.

Future prospectives

To date, we have identified 220 genetic variations of 13 drug transporter genes in the Korean population (Table 1). Preliminary results of association studies between these transporter genetic variations and clinical outcomes of various pharmacotherapies revealed that genetic variations of MRPs are associated with the drug response and toxicity of antidepressants, antiepileptics and cardiovascular agents. Further identification of the functional genetic variations on MDR and MRPs in conjunction with clinical pharmacokinetic and pharmacodynamic studies will improve the predictive value of genetic tests for tailored drug therapy.

References

1. Hung LW, Wang IX, Nikaido K, et al. Nature. 1998; 396:703-707.

2. Welsh MJ, Robertson AD, Ostedgaard LS. Nature. 1998; 396:623-624.

3. Holland IB, Blight MA. J Mol Biol. 1999;293:381-399.

4. http://www.humanabc.org/

5. Choi JY, Muallem D, Kiselyov K, et al. Nature. 2001; 410:94-97

6. Lee JH, Choi JH, Namkung W, et al. Hum Mol Genet. 2003;12:2321-2332.

7. Hoffmeyer S, Burk O, von Richter O, et al. Proc Natl Acad Sci U S A. 2000;97:3473-3478.

8. Brinkmann U, Roots I, Eichelbaum M. Drug Discov Today. 2001;6:835-839.

9. Kullak-Ublick GA, Beuers U, Paumgartner G. J Hepatol 2000; 32(Suppl 1):3-18.

10. Choi JH et al. Pharmacogenetics and genomics 2006; in press

Table 1. ABC transporter genetic variations found in the Korean population

GENE	Full Name	Cyto map	Ref Seq (NM_#)	SNP No.	Location				Registered	
					5'-flanking	exon	intron	3'-flanking	known	novel
ABCC7	cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7)	Chromosome: 7 (Location: 7q31.2)	genomic seq.(NC_000007) mRNA seq.(NM_000492)	9	1	8	0	0	7	2
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP) member 1	Chromosome: 7 (Location: 7q21.1)	genomic seq.(NC_000007) mRNA seq.(NM_000927)	16	8	5	3	0	16	0
ABCC1	ATP-binding cassette, sub-family C (CFTR/MRP) member 1	Chromosome: 16 (Location: 16p13.1)	genomic seq.(NC_000016) mRNA seq-isoform1(NM_004996)	31	5	8	18	0	13	18
ABCC2	ATP-binding cassette, sub-family C (CFTR/MRP) member 2	Chromosome: 10 (Location: 10q24)	genomic seq.(NC_000010) mRNA seq.(NM_000392)	12	4	4	4	0	10	2
ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP) member 3	Chromosome: 17 (Location: 17q22)	genomic seq.(NC_000017) mRNA seq-isoform3B(NM_020038)	14	4	5	5	0	10	4
ABCC4	ATP-binding cassette, sub-family C (CFTR/MRP) member 4	Chromosome: 13 (Location: 13q32)	genomic seq.(NC_000013) mRNA seq.(NM_005845)	49	8	12	22	7	18	31
ABCC5	ATP-binding cassette, sub-family C (CFTR/MRP) member 4	Chromosome: 3 (Location: 3q27)	genomic seq.(NC_000003) mRNA seq.(NM_005688)	16	6	5	5	0	10	6
SLCO1B1	solute carrier organic anion transporter family member 1B1	Chromosome: 12 (Location: 12p)	genomic seq.(NC_000012) mRNA seq.(NM_006446)	27	6	9	7	5	16	11
SLC22A11	solute carrier family 22 (organic anion/cation transporter) member 11	Chromosome: 11 (Location: 11q13.1)	genomic seq.(NC_000011) mRNA seq.(NM_018484)	3	0	3	0	0	2	1
SLC22A8	solute carrier family 22 (organic anion transporter) member 8	Chromosome: 11 (Location: 11q11)	genomic seq.(NC_000011) mRNA seq.(NM_004254)	2	0	2	0	0	2	0
SLC22A2	solute carrier family 22 (organic cation transporter)	Chromosome: 6 (Location: 6q26)	genomic seq.(NC_000006) mRNA seq-isoformb(NM_153191)	11	4	6	1	0	11	0
SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter)	Chromosome: 6 (Location: 6q26-q27)	genomic seq.(NC_000006) mRNA seq.(NM_021977)	10	6	3	1	0	10	0
ABCG2	ATP-binding cassette, sub-family G (WHITE) member 2	Chromosome: 4 (Location: 4q22)	genomic seq.(NC_000004) mRNA seq.(NM_004827)	20	5	5	10	0	18	2
				220	57	75	76	12	143	77