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# Human Genomics and Personalized Medicine

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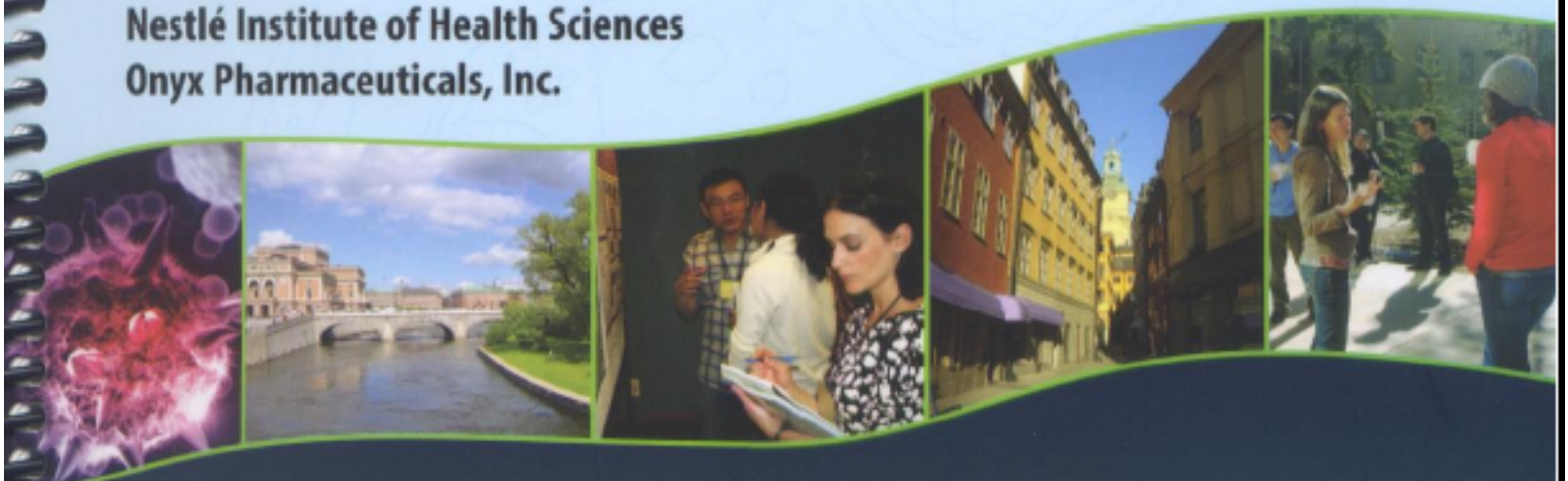

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## 1017 Differential genetic influences of common variants on the TG/HDLC ratio according to Sasang constitutional types

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The ratio of triglycerides to HDL cholesterol (TG/HDLC) predicts the risk of cardiovascular disease (CVD). In Sasang constitutional medicine (Korean traditional tailored medicine), one constitutional type characterized by insulin resistance, hypertension, diabetes mellitus, and metabolic syndrome represents the risk for CVD.
In this study, we aimed to investigate the common genetic variants influencing the TG/HDLC ratio in Koreans and to estimate whether the genetic influences differed according to Sasang constitutional types.
Therefore, we performed a genome-wide association study (GWAS) in Korean cohorts (n = 5,781) and in tertiles of the probability values for discriminating the constitutional types with CVD risks.
In the GWAS, we found several variants near the *apolipoprotein A-V* gene, representing strong associations with the TG/HDLC ratio ($p < 10^{-7}$–$10^{-14}$). In a top tertile presenting the constitutional type with high CVD risks, a variant near the *nerve growth factor* gene showed a significant signal ($p < 10^{-6}$)—the signal was higher than that shown by the *apolipoprotein A-V* variant. Interestingly, the above two genes are related with CVD risks. On the other hand, the TG/HDLC ratio was significantly associated with a variant near the *5-hydroxytryptamine (serotonin) receptor 5A* gene ($p < 10^{-10}$), previously known to affect TG levels, in the bottom tertile presenting the constitutional type with low CVD risks.
These results showed that the variants associated with the TG/HDLC ratio, a predictor of CVD, were different according to Sasang constitutional types, which also have different risks for CVD. We planned to replicate the association with another Korean population (n > 2,000) to confirm the associations from the GWAS analysis.

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## 1018 Proteomic Analysis of Proteins Responsible for the Development of Doxorubicin Resistance in Human Uterine Cancer Cells

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Drug resistance is a common cause of failure in cancer chemotherapy treatments. In this study, we used a pair of uterine sarcoma cancer lines, MES-SA, and the doxorubicin-resistant MES-SA/Dx5 as a model system to examine resistance-dependent cellular responses and to identify potential therapeutic targets. We used two-dimensional differential gel electrophoresis (2D-DIGE) and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF/TOF MS) to examine the global protein expression changes induced by doxorubicin treatment and doxorubicin resistance. A proteomic study revealed that doxorubicin-exposure altered the expression of 87 proteins in MES-SA cells, while no significant response occurred in similarly treated MES-SA/Dx5 cells, associating these proteins with drug specific resistance. By contrast, 37 proteins showed differential expression between MES-SA and MES-SA/Dx5, indicating baseline resistance. Further studies have used RNA interference, cell viability analysis, and analysis of apoptosis against asparagine synthetase (ASNS) and membrane-associated progesterone receptor component 1 (mPR) proteins, to monitor and evaluate their potency on the formation of doxorubicin resistance. The proteomic approach allowed us to identify numerous proteins, including ASNS and mPR, involved in various drug-resistance-forming mechanisms. Our results provide useful diagnostic markers and therapeutic candidates for the treatment of doxorubicin-resistant uterine cancer.

This work was supported by grant (NSC 101-2311-B-007-011) from the National Science Council, Taiwan

## 1019 A male-specific and tumor suppressor like lncRNA in human hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide. Chronic viral infection is one of the most causes in the development of HCC. In recent years, long non-coding RNAs (lncRNAs, > 200-bp) have been shown to have critical regulatory roles in cancer biology, and several lncRNAs have shown a role in the development of HCC. Here, we found an lncRNAs-lncRNA40, which was associated with Chronis hepatitis and gender in 91 HCC patients. Our result showed that lncRNA40 significantly low expression in HCC tumorous compared to paired non-tumorus tissues, suggesting its potential tumor suppressor-like role. Sequence analysis demonstrated that lncRNA40 locates on Y chromosome and specific expresses in human. Knockdown lncRNA40 by using siRNA enhanced HCC cells' proliferation and migration. In addition, we found lncRNA40 direct interaction with proteins of PRC2 complex, DNMT3a, G9a, H3K27me3 by RIP assays. These results suggesting that lncRNA40 is a male specific and tumor suppressor-like lncRNA. The biological function of lncRNA40 is through regulating the inflammation-related genes by recruiting histone modification factors which is related with epigenetic regulation by histone methylation or chromosome remodeling.

## 1020 In search of novel cancer gene in microsatellite-stable *APC*-mutation negative familial colorectal cancer patients

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Colorectal cancer (CRC) is the most frequent cancer and the second leading cause of cancer mortality in Singapore. There are two main autosomal-dominantly inherited CRC, familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). The former is caused mainly by germline mutation in the adenomatous polyposis coli (*APC*) gene and the latter by mismatch repair genes (MMR) characterized by microsatellite instability (MSI). Our ability to exhaustively screen for these genes have enabled us to identify familial CRC patients who are microsatellite-stable and *APC*-mutation negative, suggesting that the underlying defect is in other genes although the clinical manifestation is similar to FAP. We embarked on the search of new genes in one of these families. We first determined whether these patients inherited defects in other known tumor suppressors by the direct sequencing technique. No germline mutations were found in the *MutYH*, *BMPR1A*, *PTEN* and *p53* genes. Next, we performed a genome-wide screen with Affymetrix SNP 6 array on the lymphocytic, and polyp DNA of two affected members of the family and compared their genotypes with that of 88 ethnicity-matched healthy controls. Combined loss of heterozygosity, copy number and allelic-specific copy number analysis uncovered 5 regions of deletions common to both brothers (germline) that were also replicated when their polyp genotypes were compared to the lymphocytic genotypes (somatic). Long-range polymerase chain reaction (PCR) experiments confirmed the 32 kb loss on chromosome 19q. Real-time PCR assays showed the loss of expression of the candidate cancer gene in the polyps compared to the mucosa.