

## ASSOCIATIONS BETWEEN DISEASE RISK AND EIGHT POLYMORPHISMS ADOPTED FOR GENOTYPE ANNOUNCEMENTS AT NAGOYA UNIVERSITY HOSPITAL

KAZUKO NISHIO<sup>1</sup>, SAKURAKO NAKAMURA<sup>2</sup>, YOSHITAKA SEKIDO<sup>2</sup>,  
TOSHIMITSU NIWA<sup>2</sup> and NOBUYUKI HAMAJIMA<sup>2</sup>

<sup>1</sup>*Department of Preventive Medicine/Biostatistics and Medical Decision Making,  
Nagoya University Graduate School of Medicine,*

<sup>2</sup>*Department of Clinical Preventive Medicine, Nagoya University Hospital*

### ABSTRACT

Genetic polymorphisms have the potential to predict disease susceptibility. This may be especially useful among individuals with a high-risk lifestyle, so that the genotyping could be adopted for disease prevention through modifications toward a lower-risk lifestyle. We started a program of free genotype announcements in a polymorphism study among health checkup examinees at the Nagoya University Hospital on June 9, 2003. Since such announcements remain controversial for fear of unexpected harmful effects and counseling system, the accumulated evidence on the association between disease risk and genotypes announcements in our study was reviewed in this article. The genotypes used were those of *alcohol dehydrogenase 2 (ADH2)* Arg47His, *aldehyde dehydrogenase 2 (ALDH2)* Glu487Lys, *NAD(P)H: quinone oxidoreductase (NQO1)* C609T, *glutathione S transferase M1 (GSTM1)*, *glutathione S-transferase T1 (GSTT1)*, *interleukin-1B (IL-1B)* C-31T, and *tumor necrosis factor A (TNF-A)* T-1031C, *angiotensin converting enzyme (ACE)* Ins/Del. Since showed a potential for widespread use in health checkups, the information on the above polymorphisms seems worth documenting. Although there have been no complaints from the participants to date, careful treatments are requested.

Key Words: Health checkup, Genetic polymorphisms, Genotype announcement

### INTRODUCTION

Counseling before and after genotype announcements is essential in cases of hereditary disease as described in the guidelines for Research on the Human Genome issued on March 29, 2001, by collaboration of three Japanese government ministries: the Ministry of Education, Culture, Sports, Science and Technology; the Ministry of Health, Labor and Welfare; and the Ministry of Economy, Trade and Industry. For hereditary diseases, the accumulated information on lifetime cumulative risk (penetrance) and on the limitations of genetic testing have been well documented.

Genetic polymorphisms are defined as those with a low penetrance and a frequency com-

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Address correspondence to Ms. Kazuko Nishio,

Department of Preventive Medicine/Biostatistics and Medical Decision Making,

Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.

Tel.: +81-52-744-2132 Fax.: +81-52-744-2971

monly observed in the general population. Although the associations between disease risk and studied genotypes have often been inconsistent, polymorphisms showing consistent associations with disease risk have been reported, as well as those interacting with environmental factors.<sup>1-6)</sup> There is no doubt that dozens of polymorphisms will be accepted in the near future as useful tools to predict the disease risk, generally or specifically, to hazardous agents.

At present, however, the announcement of polymorphism genotypes for health checkup examinees is quite controversial. Ethical considerations make us hesitate to use such genetic test, because of the permanent and private nature of genotypes. The responses to such announcements are considered to vary among both informed individuals and societies. In addition, genotype information relates to an individual's pedigree, which may give rise to unexpected objections among family members. Tests conducted without recognizing these potential problems may be considered risky for health care providers, notwithstanding the fact that they regularly deal with even more sensitive information, such as the infection status of patients.

In such a social content, we started a polymorphism study on June 9, 2003, in which free genotype announcements were used as an incentive for study participation. This article briefly describes biological functions, allele/genotype frequencies, reported associations between disease risk and the eight polymorphisms, and presents recommendations. Such a description seems useful not only for our present study, but also for the routine use of researchers or medical practitioners using the eight polymorphisms discussed below.

## SELECTED POLYMORPHISMS

### *1. Alcohol dehydrogenase 2 (ADH2) Arg47His and aldehyde dehydrogenase 2 (ALDH2) Glu487Lys*

The alcohol dehydrogenase  $\beta$  subunit converts ethanol to acetaldehyde, whose gene, *ADH2*, has a functional polymorphism, Arg47His.<sup>7)</sup> Enzyme activity is higher in the 47His allele (*ADH2\*2*) than in the 47Arg allele (*ADH2\*1*).<sup>8)</sup> Aldehyde dehydrogenase coded by *ALDH2* converts acetaldehyde into acetate. The gene has a G-to-A polymorphism at codon 487 (Glu487Lys). The 487Glu (*ALDH2\*1*) allele possesses a full enzyme activity, while the 487Lys allele (*ALDH2\*2*) shows no activity, with the result that individuals with the 487LysLys genotype cannot imbibe a glass of beer without running the risk of acetaldehyde detoxification.

Alcoholism was reported to have associations with *ADH2 47Arg* and *ALDH2 487Glu* in both Chinese<sup>9,10)</sup> and Japanese subjects.<sup>11)</sup> The protective alleles, *ADH2 47His* and *ALDH2 487Lys*, are more prevalent in Orientals than in other ethnic groups;<sup>12,13)</sup> among Japanese the rate is 0.777<sup>14)</sup> for *ADH2 47His*, and 0.265<sup>14)</sup> or 0.278<sup>15)</sup> for *ALDH2 487Lys*.

Those with *ALDH2 487LysLys* (6.8%<sup>14)</sup> of 634 subjects in one study, and 7.9%<sup>15)</sup> of 241 Japanese subjects in another study) are at no risk for alcohol-related diseases because they are all non-drinkers. Drinkers with *ALDH2 487GluLys* (39.4%<sup>14)</sup> of 634 subjects or 38.8%<sup>15)</sup> of 241 Japanese subjects) run a greater risk. After 0.5g/kg ethanol consumption, their acetaldehyde level was reported to be 20 times higher in blood and 2 to 3 times higher in saliva than that of those with 487GluGlu.<sup>16)</sup> In terms of disease prevention, warnings not to overdrink is especially important for drinkers with *ALDH2 487GluLys*. Since drinkers with *ADH2 47ArgArg* (4.9%<sup>14)</sup> of 634 Japanese) are less likely to suffer from a hangover, warning not to drink much for the assurance is provided for them. For the other *ADH2* genotypes, drinking slowly is advised. Informing them of their genotypes would raise awareness of their own physiological limitations, possibly leading to moderate drinking behavior.

## 2. *NAD(P)H:quinone oxidoreductase 1 (NQO1) C609T*

*NAD(P)H:quinone oxidoreductase 1* encoded by *NQO1* is a flavoprotein that plays a role in the detoxification of potentially mutagenic and carcinogenic quinines. It catalyzes the two-electron reduction of potentially toxic quinoid compounds into their reduced form such as hydroquinones.<sup>17)</sup> While the enzyme encoded by the *CC* genotype shows a full activity, that encoded by the *TT* genotype shows none. The enzyme activity of the *CT* genotype occurs between the two genotypes.<sup>18)</sup> Immunohistochemistry demonstrated that *NQO1* was expressed in none of 12 specimens of esophageal squamous cell carcinoma with the *TT* genotype, and in 32 (91.4%) of 36 specimens with the *CC* genotype.<sup>19)</sup>

Several studies have reported the association of the *NQO1 609TT* genotype with the risks of leukaemia,<sup>20-22)</sup> lung cancer,<sup>23)</sup> esophageal cancer,<sup>19)</sup> gastric cardiac carcinoma with family histories of upper gastrointestinal cancer,<sup>24)</sup> colorectal cancer,<sup>17)</sup> bladder cancer,<sup>25)</sup> urological malignancies,<sup>26)</sup> and a possible interaction with smoking for cancers of the lung,<sup>27)</sup> esophagus,<sup>27)</sup> and bladder.<sup>25)</sup> On the other hand, there other studies have reported insignificant, no, or inverse associations for lung cancer,<sup>28-32)</sup> renal cell carcinoma<sup>33)</sup> or bladder cancer.<sup>34)</sup>

The *NQO1 609T* allele was shown to be prevalent in Orientals than in Caucasians, e.g., 0.383 (150 Japanese) by Naoe *et al.*,<sup>21)</sup> 0.421 (214 Japanese) by Hamajima *et al.*,<sup>27)</sup> 0.411 (141 northern Chinese) by Zhang *et al.*,<sup>24)</sup> 0.188 (838 Caucasians in the United Kingdom) by Smith *et al.*,<sup>22)</sup> and 0.141 (252 Caucasians in Germany).<sup>22)</sup>

Epidemiologic findings supported by biological mechanisms indicate that individuals with the *TT* genotype are sensitive to carcinogens. Accordingly, smoking cessation is to be more strongly recommended for sensitive individuals, although smokers with other genotypes should, of course, also be advised to quit smoking.

## 3. *Glutathione S transferases M1 (GSTM1) and T1 (GSTT1)*

*Glutathione S-transferase M1 (GSTM1)* and *glutathione S-transferase T1 (GSTT1)* are considered to be cancer-susceptibility genes because of their ability to regulate the conjugation of carcinogenic compounds to excretable hydrophilic metabolites. Deletion variants lacking in enzyme activity exist in both genes. Individuals with homozygous deletions in the *GSTM1* or *GSTT1* genes may have less ability to metabolically eliminate carcinogenic compounds and may therefore be at an increased cancer risk.<sup>35)</sup> A meta-analysis of lung cancer showed a significantly increased risk for the *GSTM1* null type.<sup>36)</sup> A possible or significant interaction with smoking was reported for lung cancer with *GSTM1*,<sup>37,38)</sup> breast cancer with *GSTT1*,<sup>39)</sup> coronary artery disease with *GSTM1* and *GSTT1*,<sup>40)</sup> atherosclerosis with *GSTT1*,<sup>41)</sup> oral cleft with *GSTT1*,<sup>42)</sup> low birth weight and short gestation with *GSTT1*.<sup>43)</sup> Although a recent meta-analysis of the interaction between smoking and *GSTM1* for lung cancer provided no evidence of such an interaction,<sup>44)</sup> a wide range of both epidemiological and biological findings higher DNA-adduct level for the *GSTM1* null genotype,<sup>45-47)</sup> and inverse associations between serum antioxidant levels and DNA-adduct observed only among those with that genotype,<sup>48)</sup> indicates that *GST* null types are sensitive to hazardous substrates from cigarette smoke.

There is no substantial difference in the null-genotype frequency of *GSTM1* among Japanese (0.510 in 257 subjects,<sup>38)</sup> Koreans (0.559 in 220,<sup>49)</sup> Chinese (0.508 in 417,<sup>50)</sup> and Caucasians (0.531 in 10,514,<sup>51)</sup> while the *GSTT1* null genotype is more common in Japanese (0.520 in 200<sup>52)</sup>), Koreans (0.459 in 220<sup>49)</sup>) and Chinese (0.456 in 417<sup>50)</sup>) than in Caucasians (0.197 in 5,577.<sup>51)</sup>)<sup>13)</sup>

Similarly for *NQO1 C609T*, those with the *GSTM1* and/or *GSTT1* null types should be strongly recommended to quit smoking.

#### 4. *IL-1B C-31T and tumor necrosis factor A (TNF-A) T-1031C*

Interleukin 1 $\beta$  coded by *IL-1B* has multiple biological effects.<sup>53)</sup> It is 1) a pro-inflammatory cytokine triggering inflammation by inducing other cytokines including tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and itself, and 2) a potent inhibitor of gastric acid secretion.<sup>54)</sup> *IL-1B* is expressed by a transcription factor, nuclear factor  $\kappa$ B (NF- $\kappa$ B), which is activated by many stimuli including bacterial infection. For example, the lipopolysaccharide of the *Helicobacter pylori* cell wall combines with Toll-like receptor 4 on the epithelial cell surface, whose signal is transferred to NF- $\kappa$ B.<sup>55)</sup> *IL-1B* has three major single nucleotide polymorphisms, T-511C, T-31C, and T3954C.<sup>56)</sup> Since -511C and -511T are strongly linked with -31T and -31C, respectively,<sup>57)</sup> there is no need to genotype both. While *IL-1B* T3954C lacks the information indicating functionality, T-31C shows a difference in the binding of transcription factors.<sup>56)</sup> Of 241 outpatients, the *IL-1B* -31T allele was 0.550, and the -31TT genotype was 27.4%.<sup>57)</sup>

TNF- $\alpha$  coded by *TNF-A* is also a pro-inflammatory cytokine with an inhibitory effect on gastric acid secretion.<sup>54)</sup> Since it is expressed by NF- $\kappa$ B, bacterial infection increases the expression of TNF-A as well as IL-1B. TNF-A has several polymorphisms, such as G-238A, G-308A, C-857T, C-863A, and T-1031C.<sup>58)</sup> Since G-238A and G-308A are rare, especially in Japanese, they have only a limited usefulness in research and health checkups. C-862A and T-1031C are almost completely linked to each other, and the haplotypes -857T and -1031C were found to occur very rarely in our data; *TNF-A* -1031T was 0.835 of 1,371 participants, with 69.4% of -1031TT genotype.<sup>59)</sup>

Both the *IL-1B* C-31T and *TNF-A* T-1031C genotypes seem good indicators of genetic traits. To date, a substantial number of papers have been published on their associations with disease risks,<sup>60-63)</sup> including malignant neoplasm, osteoporosis, chronic inflammation, and respiratory, circulatory, neurodegenerative, and autoimmune diseases. Although their indications are rather complicated, *IL-1B* -31TT and *TNF-A* -1031TT generally display inflammatory traits. Subjects with these genotypes should be advised to avoid lifestyles rich in chemical, physical or biological stimuli.

#### 5. *Angiotensin-converting enzyme (ACE)*

Several gene polymorphisms have been reported to be possible determinants of hypertension. The candidate genes includes *AGT*, *ACE*, *Renin*, *AT1*, *Kallikrein*, and *CYP11B2*.<sup>64)</sup> *ACE* is the gene coding angiotensin-converting enzyme, which converts angiotensin I to angiotensin II, a molecule that elevates blood pressure. The *ACE* gene has a 287-bp Ins/Del type of polymorphism within an intron. The serum ACE level was observed to increase with the number of *Del* alleles.<sup>65)</sup> In Japan, the incidence of this genotype among 5,014 residents was 42.2% for *InsIns*, 44.6% for *InsDel*, and 13.1% for *DelDel*.<sup>66)</sup>

In a cross-sectional study in Suita, Japan, a significant association between hypertension and *Del/Del* type was observed, especially for males.<sup>66)</sup> A 9.1-year follow-up study of 678 normotensive subjects living in Northern Belgium found that those with the *Del/Del* genotype ran a significantly higher risk of hypertension.<sup>67)</sup> No such association with hypertension has been reported for Japanese only<sup>68)</sup> or in a multi-ethnic study.<sup>69)</sup> Although the findings on hypertension are not consistent, a meta-analysis of carotid artery wall thickness, a hypertension-related lesion, demonstrated a positive association with the *ACE Del/Del* genotype.<sup>70)</sup>

Since the *Del/Del* type does not always cause hypertension and those with the other genotype could develop hypertension, recommendations of routine blood pressure monitoring and a low-risk lifestyle would be equally beneficial.

## COMMENTS

Polymorphism studies use relative risk as a measure of association, since the cumulative risk is not high even among those with high-risk genotypes. The aims of such genotype testing are to detect high-risk individuals who are candidates for disease prevention, and to induce them to make behavioral changes through genotype announcements. As a matter of fact, a randomized intervention study showed that the cessation rate was higher among smokers informed of a *GSTM1* genotype than among the controls.<sup>71)</sup>

There are no clear criteria concerning the level of evidence needed to justify the genotype announcements during health checkups. That level may differ between checkups for commercial purposes and those for research purposes. This review provides evidence on the current associations with disease risk. Views on genotype announcements as a whole and those specific to polymorphisms may change as new findings on the associations with diseases are accumulated, and public recognition of the value of these announcements evolves.

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