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GENOTYPE ANNOUNCEMENT IN A GENETIC POLYMORPHISM STUDY FOR HEALTH CHECKUP EXAMINEES AT NAGOYA UNIVERSITY HOSPITAL

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ABSTRACT

On June 9, 2003, we started free genetic tests of eight polymorphisms for health checkup examinees who attended a basic course at Nagoya University Hospital. They were informed of their genotypes within four weeks after blood donation for research purposes. The genotypes 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. In the first three months, 227 (89.4%) out of 254 examinees participated in the free tests, having been informed of the research aims, after which they consented to our use of research data. To date, there have been no complaints from the participants, indicating that the announcement of polymorphism genotypes may be accepted differently from that of hereditary disease genotypes.

Key Words: Health Checkup, Genetic Polymorphisms

INTRODUCTION

The application of polymorphism genotypes to health checkup screening is quite controversial in terms of its usefulness for disease prevention as well as for addressing the issue of ethical data management. We are aware of the differences in the responses to hazardous agents among individuals with different genetic traits, which are largely determined through genetic polymorphisms.[1-3] To date, many polymorphisms have been found to have associations with disease risk.[4-6] There is no doubt that tens or even hundreds of polymorphisms will be accepted as useful tools to predict the disease risk, generally or specifically, to hazardous agents.

At the present time, many epidemiologists, however, take a skeptical view on genetic tests, especially those conducted under commercial auspicies. Although such concerns are biologically plausible, the majority of polymorphisms so far reported have only a limited strength of association across genetically diverse populations. The effectiveness of adopting genetic tests of

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polymorphisms has not been documented on either individual or social levels, so that charging a fee for genotyping at health checkups is not considered.

Ethical considerations also make us hesitate to undertake such genetic tests, because the genotypes cannot be changed and the resulting information is regarded as highly private. The responses to such information may vary among informed individuals and among societies. In addition, the information relates to pedigree, which may cause 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.

Aware of this social context, we started a project to inform health checkup examinees of their genotypes on June 9, 2003. This article describes the study design and participation, procedure, with the aim of making the study outline accessible to the public.

SUBJECTS AND METHODS

Subjects were health checkup examinees aged 20 years or over at the Nagoya University Hospital. Those attending "a basic health checkup" course with blood tests were invited to participate in our polymorphism study, in which a free genotype announcement was provided to the participants if they so wished. The course costs 41,286 yen, but participation in the study was free.

The details of the invitation and informed consent process were as follows. 1) A written informed consent form as well as a sheet describing the study outline and a free-genotype announcement were enclosed in a health checkup registration confirmation letter. 2) On the day of the checkup, the staff explained the contents of the study and the availability of a free genotype announcement to the eligible examinees before the routine drawing of blood for the checkup. 3) Each examinee's consent was individually confirmed regarding study participation, the genotype announcement and the use of blood for future studies. 4) A copy of the informed consent form was handed to each participant, as well as an 8-page color-printed booklet (Fig. 1) and a note listing the name, telephone number and address of the person in charge of genotype announcements, in order to enhance their understanding and to help us better respond to whatever unanticipated problems may arise. 5) Additional peripheral blood for research purposes was sampled with a 5-ml EDTA-Na tube (a 7-ml tube in the first two weeks). Blood samples were numbered at Department of Preventive Medicine/Biostatistics and Medical Decision Making by the staff, none of whom were privy to details provided by using the informed consent form. 6) In addition, a genotype report enclosed in a sealed envelope was sent to each participant.

The announced genotypes 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. The associations between these polymorphisms and disease risk were reviewed in a separate document.

The participation rates were compared by a Fisher's exact test using STATA version 7.0 statistical software (STATA Corporation Inc., College Station, TX). This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine in 2003 (Approval number 52).

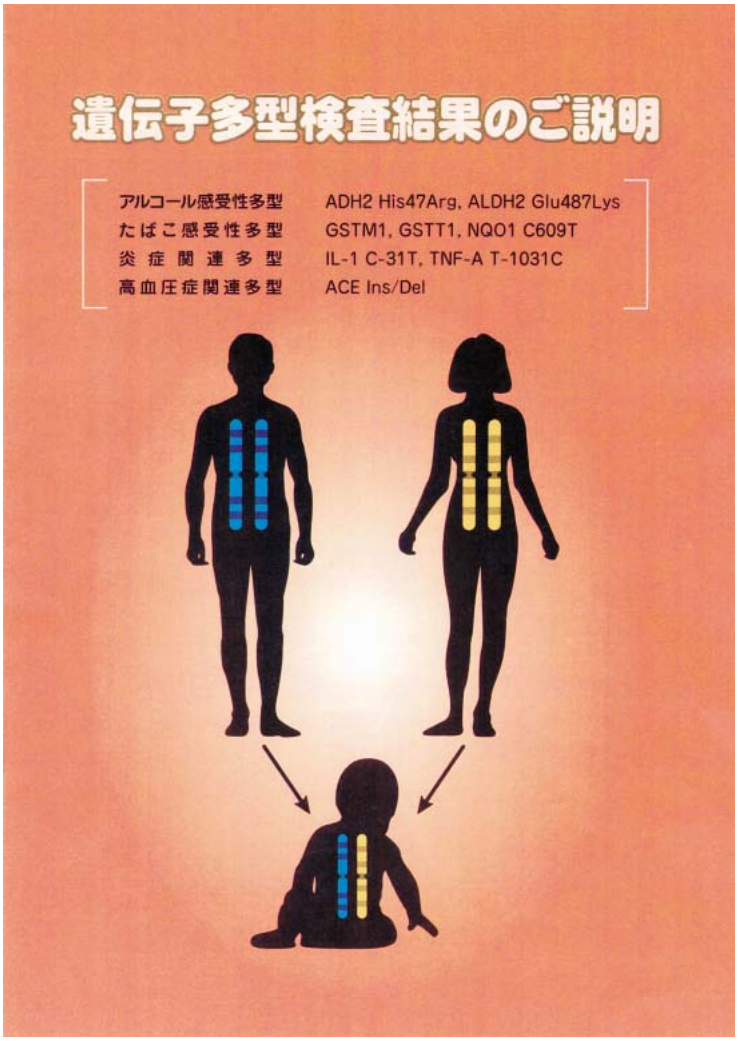

Fig. 1 Cover page of the booklet used for explaining indications of eight polymorphism genotypes; *alcohol dehydrogenase 2* (*ADH2*) Arg47His, *aldehyde dehydrogenase 2* (*ALDH2*) Glu487Lys, *NAD(P)H: quinone oxidoreductase* (*NQO1*) C609T, *glutathione S transferase M1* (*GSTM1*), *glutathione S-transferase T1* (*GSTT1*), *interleukin-1B* (*IL-1B*) C-31T, and *tumor necrosis factor A* (*TNF-A*) T-1031C, *angiotensin-converting enzyme* (*ACE*) Ins/Del.

RESULTS

In the first three months, 227 (89.4%) out of 254 examinees participated in this study. All the participants desired or agreed to be informed of their genotypes. As shown in Table 1, the participation rate varied little according to the month of enrollment. However, there was a statistically significant difference ($p<0.05$) in the rate between males (92.8%) and females (84.2%). Although the participation rate for those aged 70 years or over was slightly lower than that for the other age groups, the difference was not significant.

Table 1 Participation in free genotype tests among health checkup examinees at Nagoya University Hospital

Characteristics	Examinees	Participants*	(%)	p
June 9 to 30	48	44	91.7	
July 1 to 31	120	107	89.2	
August 1 to 31	86	76	88.4	0.896
Males	153	142	92.8	
Females	101	85	84.2	0.037
Age –39	60	55	91.7	
40–49	62	54	87.1	
50–59	72	66	91.7	
60–69	45	41	91.1	
70–	15	11	73.3	0.297
Total	254	227	89.4	

*All participants agreed to be informed of their genotypes.

DISCUSSION

Informing participants of their genotypes is a delicate task, because 1) disseminating information on individuals is becoming a sensitive issue, as exemplified by Privacy Information Protection Act issued in 2003, 2) the public has not yet clearly understood the differences in interpretation between genotypes of hereditary diseases and of polymorphisms, 3) the benefits of knowing of their polymorphism genotypes are not always appreciated by participants, 4) companies may profit from the business of genetic tests at the expense of uneducated consumers, and 5) there may be unanticipated problems in dealing with genotype announcements. What we know at present of this matter is that 1) the frequencies of minor alleles tested are not generally low, so the public may accept the genotypes as a routine matter, 2) polymorphism genotypes are not determinitive of disease onset, and lifestyle changes can be recommended considered to modify the risk of disease among those with high-risk genotypes, 3) ABO blood type tests (nearly equivalent to genotyping tests) have not given rise to invasion of privacy or discrimination problems, 4) we have already had experience in dealing with *L-myc* genotype announcements for more than 200 smokers in a complex project conducted at the Aichi Cancer Center, and encountered no problems.

Through the enrollment of the present study with a participation rate of 89.4%, we learned that only a small percentage of individuals declined to know their own genotypes, while the great majority were eager to do so. Refusals were significantly more frequent in females than in males. Some examinees expressed a vague anxiety about privacy, probably influenced by their past experiences. Other examinees showed a strong curiosity about their own genotypes, which could be used as an opportunity to make needed lifestyle changes or to reform a current harmful habit such as drinking or smoking. As a matter of fact, one study showed that genotype announcements were effective in efforts to quit smoking.[7)]

Since the attitude to genotype information varies among individuals, the informed consent process was essential to confirm a participant choice. The present polymorphism study for health checkup examinees at the Nagoya University Hospital aimed to examine the association between biomarkers collected at the checkup and genotypes, rather than to measure the impact of genotype announcements. The free genotype announcement was used to provide examinees an incentive to participate in the polymorphism study. As of the end of September, no claims

were received concerning the announcement of genotypes, suggesting that informed consent is effective for avoiding subsequent problems.

In summary, this article reported 1) the design of a polymorphism study for health checkup examinees at the Nagoya University Hospital, in which the informed consent process was properly conducted, and 2) the participation rate was a high 89.4%, indicating that the great majority willingly agreed to the genotype announcement. Our experience with genotype announcements will provide fundamental information for the routine introduction of genotype tests at health checkups.

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REFERENCES

1) Bartsch, H., Nair, U., Risch, A., Rojas, M., Wikman, H. and Alexandrov, K.: Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. *Cancer Epidemiol. Biomarkers Prev.*, 9, 3–28 (2000).
2) Ingelman-Sundberg, M.: Polymorphism of cytochrome P450 and xenobiotic toxicity. *Toxicology*, 181–182, 447–452 (2002).
3) Lazarus, R., Vercelli, D., Palmer, L.J., Klimecki, W.J., Silverman, E.K., Richter, B., Riva, A., Ramoni, M., Martinez, F.D., Weiss, S.T. and Kwiatkowski, D.J.: Single nucleotide polymorphisms in innate immunity genes: abundant variation and potential role in complex human disease. *Immunol. Rev.*, 190, 9–25 (2002).
4) Houlston, R.S.: Glutathione S-transferase M1 status and lung cancer risk: a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.*, 8, 675–682 (1999).
5) Goode, E.L., Ulrich, C.M. and Potter, J.D.: Polymorphisms in DNA repair genes and associations with cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, 11, 1513–1530 (2002).
6) Mitrunen, K. and Hirvonen, A.: Molecular epidemiology of sporadic breast cancer. The role of polymorphic genes involved in oestrogen biosynthesis and metabolism. *Mutat Res*., 544, 9–41 (2003).
7) McBride, C. M., Bepler, G., Lipkus, I. M., Lyna, P., Samsa, G., Albright, J., Datta, S. and Rimer, B.K.: Incorporating genetic susceptibility feedback into a smoking cessation program for African-American smokers with low income. *Cancer Epidemiol. Biomarkers Prev.*, 11, 521–528 (2002).