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REGULAR ARTICLE

Factors in genetic susceptibility in a chemical sensitive population using QEESI

Saeko Fujimori · Mizue Hiura · Cui Xiao Yi · Lu Xi · Takahiko Katoh

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Abstract
Objectives Inherited impairment of xenobiotic metabolism is a postulated mechanism underlying environmentally associated pathogeneses such as multiple chemical sensitivity (MCS). Using the Quick Environmental Exposure and Sensitivity Inventory (QEESI), we defined people who have a strong response to chemical substances as "chemical sensitive populations (CSP)." The aim of this study is to evaluate the condition of subjects sensitive to chemicals and to analyze their genotypes in order to identify susceptibility factors in CSPs in Japanese populations.
Methods A total of 1,084 employees of Japanese companies were surveyed using the QEESI, history of MCS, and sick house syndrome. The common genotypes of the participants were analyzed for *glutathione S-transferase* (*GST*) *M1*, *GSTT1*, *aldehyde dehydrogenase2* (*ALDH2*), and *paraoxonase1* (*PON1*) in order to identify factors in the susceptibility to sensitivity to chemicals.
Results Four subjects had history of diagnosis of MCS; no subjects had diagnosis of sick house syndrome. The subjects were divided into four levels according to scores of 0, 1–19, 20–39, and 40 or more on three of the QEESI subscales. In addition, we used the MCS criteria by Hojo to differentiate between cases (CSP) and controls. No significant differences in the allelic distribution of genetic polymorphisms in the *GSTM1*, *GSTT1*, *ALDH2* or *PON1* genes were found among the four levels of each subscale, or between cases and controls.
Conclusions Our findings suggest that the common genotypes of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* are of little importance to CSP in a Japanese population.

Keywords Genetic susceptibility · Multiple chemical sensitivity (MCS) · Idiopathic environmental intolerance (IEI) · Quick Environmental Exposure and Sensitivity Inventory (QEESI) · Logistic regression analysis

Introduction

Multiple chemical sensitivity (MCS), also known as idiopathic environmental intolerance [1], has been described as disabling multi-organ symptoms triggered by multiple exposures to chemicals. A number of hypotheses concerning the etiology and pathophysiology of MCS have been proposed [2], including impaired ability to metabolize toxic chemicals [3] and psychological mechanisms [4].

There is no widely accepted instrument to measure general chemical intolerance, and no objective criteria for identification of chemicals contributing to MCS, but Miller and Prihoda [5, 6] developed the Quick Environmental Exposure and Sensitivity Inventory (QEESI), which has its origins in the Environment Exposure and Sensitivity Inventory [7]. The QEESI is a reliable and valid screening instrument for chemical intolerance that consists of five subscales: chemical sensitivity, other chemical sensitivity, symptom severity, life impact, and masking index. The Japanese version of the QEESI was translated by Ishikawa and Miyata in 1999 [8].

The present study was designed to determine whether the results of the QEESI reveal a genetic difference for

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S. Fujimori · M. Hiura · C. X. Yi · L. Xi · T. Katoh (✉)
Department of Public Health, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjou, Kumamoto 860-8556, Japan
e-mail: katoht@gpo.kumamoto-u.ac.jp

specific enzymes, primarily those possibly associated with chemical detoxification: glutathione *S*-transferase (GST) M1, GSTT1, aldehyde dehydrogenase 2 (ALDH2), and paraoxonase 1 (PON1).

The GSTs are a family of multifunctional enzymes and play a central role in detoxification of toxic and carcinogenic electrophiles. The polymorphic GSTs catalyze conjugation of glutathione to a variety of electrophilic compounds, including formaldehyde. Absence of activity of GSTM1, a μ class enzyme which detoxifies the reactive metabolites of benzo[*a*]pyrene and other polycyclic aromatic hydrocarbons, is due to homozygous deletion of the gene [9]. A similar polymorphism of the *GSTT1* gene, encoding the θ class enzymes, has been described [10]. GSTT1 metabolizes various potential carcinogens, such as monohalomethanes, which are widely used as methylating agents, pesticides, and solvents [9].

Although GSTs are presumed to be involved in the first step of formaldehyde metabolism, it is still not clear which GST molecular species is responsible for formaldehyde metabolism. In addition, GST cytosolic activity in olfactory epithelium, the highest among extrahepatic tissues [11], is of particular interest in MCS, where the role of odorous triggers is important.

Acetaldehyde is one of the important chemicals that induce sick house syndrome and MCS [12]. Approximately half of the Japanese population lack ALDH2 activity because of a structural point mutation in the *ALDH2* gene. This genetic polymorphism, which is seen in Asians, including Japanese, but not in Caucasians, results in catalytic deficiency of aldehyde metabolism [13]. However, there are few studies regarding MCS and genetic polymorphism among Asians.

PON1 is known to be polymorphic in humans, with two isoforms displaying distinct hydrolyzing activities. The Arg192 isoform hydrolyzes paraoxon rapidly, whereas the Gln192 isoform acts slowly [14]. *PON1* genes were associated with Gulf War Syndrome [15], and PON1 reacts with toxic organophosphorus compounds [16].

Methods

Subjects

The present study was conducted from August to October 2003 at two companies (company A, an integrated circuit manufacturing company; company B, a paper pulp producing company) in Kyushu, in the south of Japan. The participants numbered 1,310 people from company A (males 936, females 374) and 891 from company B (males 778, females 113). Those who replied to the questionnaires (90.2%) and furthermore agreed to give genetic samples (52.2%) were included. Finally, a total of 1,084 subjects (49.3%) who had purified DNA in good condition, including 502 subjects from company A (males 390, females 112) and 582 from company B (males 579, females 3), were eligible for this study (Table 1).

Table 1 Demographic characteristics of the subjects

	All subjects
Sex	
Male	969 (89.4%)
Female	115 (10.6%)
Total	1,084
Average age (range), years	
Male	42.2 ± 8.9 (19–63)
Female	32.3 ± 6.3 (23–67)
Total	41.2 ± 9.1 (19–67)
Smoking (>once/week)	
Male	572 (59.0%)
Female	31 (27.0%)
Total	603 (55.6%)
Drinking (>once/week)	
Male	742 (76.6%)
Female	43 (37.4%)
Total	785 (72.4%)
History of diagnosis	
Multiple chemical sensitivity	
Male	2 (0.2%)
Female	2 (0.2%)
Total	4[a] (0.3%)
Sick house syndrome	
Male	0 (0%)
Female	0 (0%)
Total	0 (0%)
Allergic disease	
Male	212 (21.9%)
Female	47 (40.9%)
Total	259[a] (23.9%)
Chemical sensitivity ≥40	
Male	60 (6.2%)
Female	8 (7.0%)
Total	77 (7.1%)
Other chemical sensitivity ≥25	
Male	29 (3.0%)
Female	5 (4.3%)
Total	34 (3.1%)
Symptom severity ≥40	
Male	68 (7.0%)
Female	6 (5.2%)
Total	74 (6.8%)

[a] Three subjects had both multiple chemical sensitivity and allergy disease

Instruments

We used the QEESI (Japanese version) [8] for the survey described above. The QEESI consists of five subscales: the chemical sensitivity subscale measures the extent to which certain odors or exposures make one sick, the other chemical sensitivity subscale measures the extent to which a variety of other exposures make one sick, the symptom severity subscale refers to the extent to which one experiences certain symptoms, the life impact subscale measures the extent to which the sensitivity affects certain aspects of life, and the masking index measures whether there are ongoing exposures from routinely used products. Unlike other studies in which the subjects were patients, the participants in our study were collected from the general population. We selected 3 of the subscales, eliminating life impact and masking index. Each subscale has ten questions, and each question has a possible score of 0–10. Therefore, the total possible score was 0–100. All study subjects completed a self-reporting questionnaire which covered history of MCS, sick house syndrome, and allergic disease, drinking history, and smoking history.

As defined by Miller and Prihoda [5, 6], scores on the QEESI reveal three levels of symptom: low, medium, and high. The criteria for chemical sensitivity and symptom severity are low = 0–19, medium = 20–39, and high = 40–100. The criteria for other chemical sensitivity are low = 0–11, medium = 12–24, and high = 25–100. It has been reported that these three subscales can distinguish individuals with high susceptibility and a control group using cutoff values [5].

Hojo et al. [17] designed a study to establish a new cutoff value for Japanese using the QEESI for screening of MCS patients. According to that study, one difference from patients in America was that in Japanese patients the other chemical sensitivity subscale had low sensitivity and low specificity. They concluded that the other chemical sensitivity subscale should be excluded when applying the QEESI to evaluate subjective symptoms in Japan. The new cutoff values for Japanese subjects were determined to be $\geq$40 for the chemical sensitivity subscale, $\geq$20 for the symptom severity subscale, and $\geq$10 for the life impact subscale. Using their criteria, we divided our subjects into two groups according to the score achieved (Table 2). Individuals with chemical sensitivity score $\geq$40 and symptom severity score $\geq$20 were defined as chemical sensitive population (CSP) (cases), while individuals with moderate or no symptoms were classified as nonsensitive (controls, chemical sensitivity score <39 or symptom severity score <19).

Table 2 Demographic characteristics of cases and controls defined by QEESI score

	Cases (CSP)[a] (n = 47)	Controls (n = 1,037)	P value
Sex			
Male	41 (87.2%)	928 (89.5%)	
Female	6 (12.8%)	109 (10.5%)	0.62[b]
Average age, years			
Mean ± SD	44.2 ± 8.8	41.1 ± 9.1	0.69[c]
Median (range)	44 (30–59)	41 (19–67)	
Smoking status (>once/week)	18 (38.3%)	585 (56.4%)	0.01[b]
Drinking status (>once/week)	32 (68.1%)	753(72.6%)	0.50[b]

Cases (chemical sensitive population, CSP): chemical sensitivity score $\geq$40 and symptom severity score $\geq$20. Controls: chemical sensitivity score $\leq$39 or symptom severity score $\leq$19

[a] Classification in cases and controls according to Hojo et al. [17]

[b] P value, chi-square test. $P < 0.05$, difference significant

[c] P value, Student's t-test. $P < 0.05$, difference significant

Genotyping

Genomic DNA was isolated from peripheral leukocytes by proteinase K digestion, phenol/chloroform extraction, and ethanol precipitation. A multiplex polymerase chain reaction (PCR) method was used to detect the presence or absence of *GSTM1*and *GSTT1* [18].

Absence of *GSTM1* and *GSTT1* is due to homozygous deletion of these hereditary genes, termed the null genotype. The genotypes of *ALDH2* (rs671) were identified by the method of Harada and Zhang [13] as the homozygous genotype of normal *ALDH2* (**1/*1*), the homozygous genotype of inactive *ALDH2* (**2/*2*), and the heterozygous genotype of normal and inactive *ALDH2* (**1/*2*). The genotype of the Gln192Arg (rs662) polymorphism of the *PON1* gene was determined essentially as described previously [19].

Statistical analysis

Relative associations between the CSP and controls were assessed by calculating crude odds ratios (ORs) from contingency tables. Corresponding chi-square tests were carried out on the cases and controls. In logistic regression analysis, ORs with corresponding 95% confidence intervals (CI) were calculated. P values smaller than 0.05 were considered significant. Statistical analysis was carried out using SPSS version 19.

Statistical power calculations were performed using Epistat (Finnish Institute of Occupational Health). This study sample size had at least 80% power (two-sided test significant, α of 0.05) to detect an OR of at least 2.5, following the calculations used in previous studies [18–20]. We used the dominant model for *GSTM1* and *GSTT1* and the recessive model for *ALDH2* and *PON1* in the test analysis.

Ethical considerations

The Ethics Review Board of Miyazaki University (no. 82, April 9, 2003) and Kumamoto University (no. 168, May 11, 2011) approved this study, following the ethical guidelines for human genome research. All participants were given full explanations of informed consent and the full protection of their personal data in written form.

Results

Table 1 presents the frequency of MCS, sick house syndrome, and allergic diseases such as asthma, allergic coryza, and atopic dermatitis. Four subjects reported history of diagnosis of MCS, three of whom also had history of allergy. The QEESI score and genotypes of these 4 subjects were as follows: (1) Q1 (27), Q2 (15), Q3 (36), *GSTM1 null*, *GSTT1 null*, *ALDH2*1/*1* and *PON1 Arg/Arg*; (2) Q1 (38), Q2 (5), Q3 (14), *GSTM1 null*, *GSTT1 null*, *ALDH2*1/*1* and *PON1 Arg/Arg*; (3) Q1 (27), Q2 (30), Q3 (78), *GSTM1 non-null*, *GSTT1 non-null*, *ALDH2*1/*1* and *PON1 Arg/Arg*; and (4) Q1 (9), Q2 (12), Q3 (23), *GSTM1 non-null*, *GSTT1 null*, *ALDH2*1/*2* and *PON1 Arg/Arg*. No subjects in this study population had diagnosis of sick house syndrome.

Chemical sensitivity was estimated by high cutoff values in the three subscales of chemical sensitivity ($\geq$40), other chemical sensitivity ($\geq$25), and symptom severity ($\geq$40). The percentage of subjects to whom high cutoff values were applied for the subscales of chemical sensitivity, other chemical sensitivity, and symptom severity were 7.1%, 3.1%, and 6.8%, respectively. The risks for chemical sensitivity as defined by Miller and Prihoda, estimated by high cutoff values on two subscales or three subscales, were 2.9% ($n = 31$) and 0.7% ($n = 8$), respectively.

When Hojo et al. [17] confirmed that the QEESI is effective for screening Japanese MCS patients, they suggested that the cutoff values for Japanese subjects should be chemical sensitivity score $\geq$40 and symptom severity score $\geq$20. In our study population, 4.3% ($n = 47$) of the subjects met that criteria and were defined as the cases (Table 2). There was a significant difference between the cases and controls in smoking status. However, no significant differences between the two groups in drinking status were observed.

Next we examined the association between genetic variants in *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* and chemical sensitivity in the total population and the case–control population. The frequencies of genotypes for all examined gene variants by chemical sensitivity subscale score are presented in Table 3. On the chemical sensitivity subscale, 32.7% scored 0, 42.7% scored from 1 to 19, 17.5% scored from 20 to 39, and 7.1% scored 40 or higher. On the other chemical sensitivity subscale, 26.6% scored 0, 67.9% scored from 1 to 19, 5.0% scored from 20 to 39, and 0.5% scored 40 or higher (Electronic Supplementary Table S1). On the symptom severity subscale, 15.5% scored 0, 54.9% scored from 1 to 19, 22.8% scored from 20 to 39, and 6.8% scored 40 or higher (Electronic Supplementary Table S2). No significant difference in frequency was found for any gene variant between any levels in the total population or on any subscale of the QEESI. Similarly, there were no significant differences between the QEESI scores of genetic variants in *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* (Table 3, Electronic Supplementary Tables S1 and S2).

The genotype data were also analyzed in the case–control design using logistic regression analyses with chemical sensitive status (cases: chemical sensitivity score $\geq$40 and symptom severity score $\geq$20) as outcome variables and genotype as the predictor variable, as presented in Table 4. No categorical predictor variable reached statistical significance. To check the effect of the genes in combination with smoking status, we calculated the OR for data classified by smoking status and by gene genotypes. The summarized data and ORs are presented in Table 5 together with 95% CIs. None of the distributions of genotypes showed any significant differences from the controls.

Discussion

This study focused on gene polymorphisms as a factor of chemical sensitivity, and analyzed *GSTM1*, *GSTT1*, *ALDH2*, and *PON1*.

Schnakenberg et al. [21] observed that the *GSTM1* and *GSTT1* gene deletion genotype occurred significantly more often in those individuals in German populations who reported chemical-related hypersensitivity. On the other hand, the allele and genotype frequencies of *GSTM1* and *GSTT1* were similar in Italian MCS patients and control populations [22]. In our study, no significant differences between the genotype frequency of *GSTT1* and *GSTM1* were found for any severity of three QEESI subscales or in the case–control study. The contradictory results are

Table 3 Association of QEESI chemical sensitivity subscale score with variants of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1*

Gene	Genotype	QEESI score					
		0 *n* (%) 354 (32.7)	1–19 *n* (%) 463 (42.7)	20–39 *n* (%) 190 (17.5)	40–100 *n* (%) 77 (7.1)	Total *n* (%) 1,084 (100)	*P* value[a]
GSTM1	*Non-null*	152 (42.9)	213 (46.0)	95 (50.0)	36 (46.8)	496 (45.8)	
	Homozygous-null	202 (57.1)	250 (54.0)	95 (50.0)	41 (53.2)	588 (54.2)	0.47
GSTT1	*Non-null*	199 (56.2)	257 (55.5)	99 (52.1)	48 (62.3)	603 (55.6)	
	Homozygous-null	155 (43.8)	206 (44.5)	91 (47.9)	29 (37.7)	481 (44.4)	0.49
ALDH2	**1/*1*	222 (62.7)	276 (59.6)	113 (59.5)	54 (70.1)	665 (61.3)	
	**1/*2*	109 (30.8)	166 (35.9)	66 (34.7)	20 (26.0)	361 (33.3)	
	**2/*2*	23 (6.5)	21(4.5)	11 (5.8)	3 (3.9)	58 (5.4)	
	**1/*2* or **2/*2*	131 (37.3)	187 (40.4)	77 (40.5)	23 (29.9)	419 (38.7)	0.30[b]
PON1	*Arg/Arg*	147 (41.5)	178 (38.5)	81 (42.6)	33 (42.8)	439 (40.5)	
	Arg/Gln	185 (52.3)	253 (54.6)	91(47.9)	38 (49.4)	567 (52.3)	
	Gln/Gln	22 (6.2)	32 (6.9)	18 (9.5)	6 (7.8)	78 (7.2)	
	Arg/Gln or *Gln/Gln*	207 (58.5)	285 (61.5)	109 (57.4)	44 (57.2)	645 (59.5)	0.68[c]

[a] *P* value, chi-square test. $P < 0.05$, difference significant

[b] **1/*2* or **2/*2* against **1/*1*

[c] *Arg/Gln* or *Gln/Gln* against *Arg/Arg*

Table 4 Association of cases and controls defined by QEESI score with the variants of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1*

Gene	Genotype	Cases (CSP) $n = 47$ (%)	Controls $n = 1037$ (%)	Crude OR[a]	*P* value[b]	Adjusted OR[b,c]
GSTM1	*Non-null*	20 (42.6)	476 (45.9)	1		1
	Homozygous-null	27 (57.4)	561 (54.1)	1.15 (0.61–2.15)	0.62	1.16 (0.64–2.10)
GSTT1	*Non-null*	31 (66.0)	572 (55.2)	1		1
	Homozygous-null	16 (34.0)	465 (44.8)	0.63 (0.33–1.22)	0.12	0.61 (0.33–1.13)
ALDH2	**1/*1*	32 (68.1)	633 (61.0)	1		1
	**1/*2*	13 (27.7)	348 (33.6)			
	**2/*2*	2 (4.2)	56 (5.4)			
	**1/*2* or **2/*2*	15 (31.9)	404 (39.0)	0.73 (0.37–1.42)	0.18[d]	0.63 (0.32–1.24)[d]
PON1	*Arg/Arg*	19 (40.4)	420 (40.5)	1		1
	Arg/Gln	25 (53.2)	542 (52.3)			
	Gln/Gln	3 (6.4)	75 (7.2)			
	Arg/Gln or *Gln/Gln*	28 (59.6)	617 (59.5)	1.00 (0.53–1.88)	0.85[e]	1.06 (0.58–1.94)[e]

[a] Odds ratio (OR) and 95% confidence interval (95% CI)

[b] *P* value, chi-square test. $P < 0.05$, difference significant

[c] ORs were adjusted for age (continuous), gender, smoking, and drinking

[d] **1/*2* or **2/*2* against **1/*1*

[e] *Arg/Gln* or *Gln/Gln* against *Arg/Arg*

mainly due to the inclusion criteria adopted by the different studies.

Our study is the first to analyze the association between *ALDH2* variants and chemical sensitivity, and no significant association was observed in our Japanese population. This result suggests that the *ALDH2* variants may not be involved in CSP.

PON1 plays a major role in biodegradation of various organophosphates that can function as potent cholinesterase inhibitors. Previous studies suggested that the polymorphic site in *PON1* was related to an increased risk of MCS [23] and Gulf War Syndrome, which is an MCS-related syndrome [15]. However, no significant association between the Gln192Arg polymorphism and *PON1* was

Table 5 Odds ratio for genotypes related to CSP by smoking status

Gene	Genotype	Nonsmokers, OR (95% CI)[a] $n = 481$ (44.6%)	Smokers (>once/week), OR (95% CI)[a] $n = 603$ (55.6%)
GSTM1	*Homozygous-null* versus *non-null* genotype	1.49 (0.69–3.23)	0.78 (0.30–2.01)
GSTT1	*Homozygous-null* versus *non-null* genotype	1.18 (0.36–3.92)	0.85 (0.32–2.23)
ALDH2	**1/*2* or **2/*2* versus **1/*1*	1.21 (0.37–4.00)	0.50 (0.15–1.67)
PON1	*Arg/Gln* or *Gln/Gln* versus *Arg/Arg*	1.24 (0.38–4.09)	1.08 (0.41–2.85)

[a] ORs were adjusted for age (continuous), gender, and drinking

obtained in our study. This trend in the MCS case–control design was reversed in the general population samples, perhaps reflecting that the *PON1* polymorphism played a minor or no role in the development of MCS in our population. In support of our study, Wiesmuller et al. [24] failed to detect an association between *PON1* polymorphism and self-reported MCS in a population sample.

On the other hand, we tried to define chemical sensitivity cases by Miller and Prihoda and estimated the risk for the genetic variants of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1*, respectively. However, no case–control differences were observed in each genotype of the 4 genes.

Smoking status was significantly lower in the cases than in the controls. Several reports suggest that MCS patients who are aware of their chemical intolerance avoid exogenous chemicals such as those from smoking [23, 24]. Tobacco smoke contains many kinds of chemicals, including formaldehyde and acetaldehyde [25]. For these reasons, we hypothesize that the genotypes of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* might contribute to development of CSP in smokers. However, among the smokers there were no significant differences between CSP and controls in the *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* genotypes.

In the present study, no significant differences between sequence variations of *GSTM1*, *GSTT1*, *ALDH2*, and *PON1* were found between the CSPs and controls. One possible weakness of our study design is a lack of assessments of environmental exposure to chemicals metabolized by the examined enzymes. It is plausible that gene–environment interactions exist, and the genetic variations of metabolic enzymes may either confer protection against or increase risk from harmful effects of chemical exposure. A second problem is the possibility that the subject sample we defined, following the QEESI protocols, was not a correct sampling of MCS. Our survey included the other chemical sensitivity subscale, but not life impact. Extrapolating from the results of Hojo et al., our defined cases whose scores exceeded the two cutoff values of chemical sensitivity ≥ 40 and symptom severity ≥ 20 were considered to be equivalent to 65% of the patients suspected to have MCS and 7% of the healthy controls. This screening criteria means that detecting the condition has sensitivity of 65% and specificity of 93%. It is unlikely that sensitivity, specificity, positive predictive value, and negative predictive value are influenced by the prevalence of the disease. As a result of that, we might not have been able to find the effect of important genotypes. A future strategy could be to subgroup patients according to symptoms, which may be genetically more homogeneous that a patient population as whole.

In conclusion, an association between risks for CSP-related MCS and genetic variation in biologically plausible candidate genes was not observed. Additionally, our results suggest that an exact case criterion is required to determine the actual importance to MCS of genetic variants in genes that encode metabolic enzymes.

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Conflict of interest No conflicts of interest.

References

1. American Academy of Allergy, Asthma, and Immunology. Idiopathic environmental intolerances. J Allergy Clin Immunol. 1999;103:36–40.
2. Winder C. Mechanisms of multiple chemical sensitivity. Toxicol Lett. 2002;128:85–97.
3. Cullen MR. The worker with multiple chemical sensitivities: an overview. Occup Med. 1987;2:655–61.
4. Labarge AS, McCaffrey RJ. Multiple chemical sensitivity: a review of the theoretical and research literature. Neuropsychol Rev. 2000;10:183–211.
5. Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. Toxicol Ind Health. 1999;15:370–85.
6. Miller CS, Prihoda TJ. A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity. Toxicol Ind Health. 1999;15:386–97.
7. Ashford NA, Miller CS. Appendix C: environmental exposure and sensitivity inventory. In: Chemical exposures: low levels and high stakes. 2nd ed. New York: Wiley; 1998. p. 371–84.

8. Ishikawa S, Miyata M. Multiple chemical sensitivity-criteria and test methods for diagnosis. Allergol Immunol. 1999;6:990–8.
9. Hayes JD, Pulford DJ. The glutathione *S*-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit Rev Biochem Mol Biol. 1995;30:445–600.
10. Pemble S, Schroeder KR, Spencer SR, Meyer DJ, Hallier E, Bolt HM, et al. Human glutathione *S*-transferase Theta (GSTT1): cDNA cloning and the characterization of a genetic polymorphism. Biochem J. 1994;300:271–6.
11. Ben-Arie N, Khen M, Lancet D. Glutathione *S*-transferases in rat olfactory epithelium: purification, molecular properties and odorant biotransformation. Biochem J. 1993;292:379–84.
12. Saito M, Kumano H, Yoshiuchi K, Kokubo N, Ohashi K, Yamamoto Y, et al. Symptom profile of chemical sensitivity in actual life. Psychosom Med. 2005;67:318–25.
13. Harada S, Zhang S. New strategy for detection of ALDH2 mutant. Alcohol Alcohol Suppl. 1993;1A:11–3.
14. Smolen A, Eckerson HW, Gan KN, Hailat N, La Du BN. Characteristics of the genetically determined allozymic forms of human serum paraoxonase/arylesterase. Drug Metab Dispos. 1991;19:107–12.
15. Haley RW, Billecke S, La Du BN. Association of low PON1 type Q (type A) arylesterase activity with neurologic symptom complexes in Gulf War veterans. Toxicol Appl Pharmacol. 1999;157:227–33.
16. La Du BN, Aviram M, Billecke S, Navab M, Primo-Parmo S, Sorenson RC, et al. On the physiological role(s) of the paraoxonases. Chem Biol Interact. 1999;119–120:379–88.
17. Hojo S, Sakabe K, Ishikawa S, Miyata M, Kumano H. Evaluation of subjective symptoms of Japanese patients with multiple chemical sensitivity using QEESI((c)). Environ Health Prev Med. 2009;14:267–75.
18. Katoh T, Nagata N, Kuroda Y, Itoh H, Kawahara A, Kuroki N, et al. Glutathione *S*-transferase M1 (GSTM1) and T1 (GSTT1) genetic polymorphism and susceptibility to gastric and colorectal adenocarcinoma. Carcinogenesis. 1996;17:1855–9.
19. Yamasaki Y, Sakamoto K, Watada H, Kajimoto Y, Hori M. The Arg192 isoform of paraoxonase with low sarin-hydrolyzing activity is dominant in the Japanese. Hum Genet. 1997;101:67–8.
20. Takeshita T, Morimoto K, Mao X, Hashimoto T, Furuyama J. Characterization of the three genotypes of low Km aldehyde dehydrogenase in a Japanese population. Hum Genet. 1994;94:217–23.
21. Schnakenberg E, Fabig KR, Stanulla M, Strobl N, Lustig M, Fabig N, et al. A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug-metabolizing enzymes. Environ Health. 2007;6:6.
22. De Luca C, Scordo MG, Cesareo E, Pastore S, Mariani S, Maiani G, et al. Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. Toxicol Appl Pharmacol. 2010;248:285–92.
23. McKeown-Eyssen G, Baines C, Cole DE, Riley N, Tyndale RF, Marshall L, et al. Case–control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR. Int J Epidemiol. 2004;33:971–8.
24. Wiesmüller GA, Niggemann H, Weissbach W, Riley F, Maarouf Z, Dott W, et al. Sequence variations in subjects with self-reported multiple chemical sensitivity (sMCS): a case–control study. J Toxicol Environ Health A. 2008;71:786–94.
25. Pang X, Lewis AC. Carbonyl compounds in gas and particle phases of mainstream cigarette smoke. Sci Total Environ. 2011;409:5000–9.