Null Results in Brief

NAT2 and *NQO1* Polymorphisms Are Not Associated with Adult Glioma[1]

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Introduction

Although various carcinogenic agents (*e.g.*, ionizing radiation, polycyclic aromatic hydrocarbons, *N*-nitroso compounds, dietary nitrosamines, organic solvents, unfiltered cigarettes, and pesticides) have been suggested as possible risk factors for brain cancer, none have emerged as dominant factors. The etiology of most of brain tumors continues to be poorly understood (1). A genetically based difference in susceptibility to carcinogens may play a role in the development of glioma.

Few studies have examined the relationship between genetic polymorphisms of metabolizing enzymes and glioma risk. The finding by Trizna *et al.* (2) of a suggestive, but nonsignificant, elevation in glioma risk for the rapid *NAT2* acetylator genotype suggested that further exploration of this polymorphism might be worthwhile. If aromatic/heterocyclic amines are associated with gliomas, then functional variations in enzymes that metabolize these carcinogens might modify the risk for glioma among exposed individuals. To evaluate this possibility, we examined *NAT2* and *NQO1* polymorphisms in conjunction with smoking history in adult glioma cases and controls.

Materials and Methods

The 159 cases and 163 controls in this study have been described elsewhere (3, 4). DNA samples, obtained from whole blood, were genotyped for *NAT2* with a modification of the PCR-RFLP method of Bell *et al.* (5) that allows classification of individuals as slow *versus* rapid acetylators. *NQO1* has been demonstrated to be polymorphic (C-to-T transition at bp 609), and a 3-fold decrease in reductase activity is associated with this allelic variant. Genotyping for *NQO1* used the PCR method described previously by Wiencke *et al.* (6). Unadjusted ORs[3] and 95% CIs comparing *NAT2* and *NQO1* genotypes and smoking histories of white cases and controls were estimated with unconditional logistic regression analyses. Analyses of smoking history were stratified by genotypes. Analyses also were adjusted for subjects' age and gender.

Results

For *NAT2*, 63% of cases and 54% of controls had the slow acetylator genotype, but this difference was not significantly different ($P > 0.05$). Overall, in both unadjusted and adjusted comparisons, cases were somewhat (40–50%, respectively) more likely than controls to have the *NAT2* slow acetylator genotype (Table 1). Among subjects with fast acetylator genotypes, cases appeared to be more likely than controls to have smoked unfiltered cigarettes, but these results were not significant, and the CI was very wide (case-control OR for having smoked unfiltered cigarettes *versus* never smoked, 3.6; 95% CI, 0.4–36.9). The ORs for smoking filtered cigarettes *versus* never smoking and the ORs for smoking either filtered or unfiltered cigarettes among those subjects with *NAT2* slow acetylator genotypes were all very close to 1. Looked at another way, among subjects who never smoked or who smoked filtered cigarettes, cases were somewhat more likely than controls to have slow acetylator genotypes, whereas among subjects who smoked unfiltered cigarettes, cases were less likely than controls to have slow acetylator genotypes. Almost identical percentages of cases (32%) and controls (34%) were heterozygous for the *NQO1* variant, whereas 4% of both cases and controls were homozygous for this variant. Importantly, all of these findings were compatible with chance.

Statistical Power. With 54% of controls being *NAT2* slow acetylators and 37% of controls being *NQO1* variants, we had ~90% power to detect ~2-fold ORs. Thus, we cannot entirely rule out the possibility of a modest association of *NAT2* slow acetylator genotype and glioma.

Study Limitations. Although adequate power was available to detect an association between genotype and glioma, power may have been insufficient to detect an interaction between *NAT2* and smoking with glioma. In addition, exposure misclassification, selection, and recall bias are concerns in case-control studies and may have influenced the observed results.

In conclusion, these results provide no support for an association of *NQO1* variant genotype and glioma. The results also do not support the hypothesis suggested by Trizna *et al.* (2) that the *NAT2* fast acetylator genotype might increase the risk of gliomas. Trizna *et al.* (2) reported a 1.6-fold (0.84–3.17) elevation in risk for the *NAT2* fast acetylator genotype from a case-control study of 90 cases and 90 controls. In our somewhat larger study, we observed the opposite, a 1.4-fold OR of glioma with the *NAT2* slow acetylator genotype. Although some of the discrepancy between the two studies may be attributable to variations in genotype frequencies in the control populations,

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[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 Gender, age, smoking history, and *NAT2* and *NQO1* genotypes among white glioma cases and controls in the San Francisco Area Adult Glioma Study, 1991–1995

A. Risk Factor

	Genotyped population[a]	
	Case (n = 159)	Control (n = 163)
Gender (%)		
Female	39%	46%
Male	61%	54%
Age (yr, mean)	48.2	53.4
Cigarette smoking (%)		
Never	46%	45%
Former	37%	41%
Current	14%	14%

B. Genotype[b]

	Cases		Controls		OR (95% CI)[c]	OR[d] (95% CI)
	n	(%)	n	(%)		
NAT2						
Rapid	58	(37)	72	(46)	[a]	[a]
Slow	98	(63)	83	(54)	1.5 (0.9–2.3)	1.4 (0.9–2.3)
NQ01						
Wild type	100	(64)	102	(63)	[a]	[a]
Reduced activity	57	(36)	61	(37)	1.0 (0.6–1.5)	1.0 (0.6–1.6)

[a] Referent group.
[b] Not every person was genotyped for each polymorphism.
[c] OR and 95% CI.
[d] OR and 95% CI adjusted for age, gender, and ever smoking.

that variation is unlikely to be solely responsible for the magnitude of difference between the two studies.

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