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Letter to the Editor

Paraoxonase-1 Q192R polymorphism and risk of sporadic amyotrophic lateral sclerosis

To the Editor:

Paraoxonase-1 (PON1) is an HDL-associated enzyme which hydrolyzes the oxidized lipids in LDL and organophosphate insecticides, pesticides, and nerve gases. The *PON1* gene is located on chromosome 7q21.3-q22.1. The Q192R polymorphism influences the enzyme activity. Carriers of RR192 genotype present with the lowest ability to protect LDL from oxidation, the lowest hydrolytic activity with diazoxon, soman and sarin, and the highest with paraoxon as compared with QQ genotype carriers (1).

Amyotrophic lateral sclerosis (ALS) is a fatal disorder involving motor neurons. Oxidative stress may play a role in the pathogenesis of sporadic ALS (sALS). The levels of plasma lipid peroxidation are increased in sALS patients compared with those in controls (2). Moreover, epidemiological studies suggest that chronic exposure to environmental chemicals may be a risk factor for sALS (3).

We hypothesize that slower hydrolysis of environmental chemicals or increased oxidized LDL levels in RR genotype carriers may correlate with increased risk of sALS. Therefore, we studied the distribution of PON1 Q192R polymorphism in sALS patients as compared to that in controls.

We included 166 consecutive patients with definite or probable sALS (4) selected in the MND Center, Jagiellonian University, who agreed to participate in the study (87%). Four hundred thirty-seven unrelated individuals, from the population of Krakow, without any neurological disease, excluded by structured questionnaire and neurological examination, served as controls. All cases and the controls were of Caucasian origin and Polish descent. Controls were matched to the cases with respect to the age of the cases' disease onset and sex. The local Ethical Committee approved the study protocol. All individuals gave informed consent before inclusion.

Leukocyte DNA was isolated using a commercial kit (Boehringer Mannheim, Mannheim, Germany). The Q192R genotyping for the *PON1* gene was determined using PCR-RFLP method (5).

Comparison of the genotype or allele frequency between cases and controls was calculated by a χ^2-test. Odds ratios (ORs) were calculated as a measure of association of genotype with sALS under assumptions of additive (assigning scores of 0, 1, and 2 for QQ, QR, and RR, respectively), dominant (score of 0 for QQ and 1 for QR and RR combined), or recessive (score 0 for QQ and QR combined and 1 for RR) mode of inheritance. A p-value of <0.05 was considered statistically significant.

The patients and the controls were of similar age and sex distribution (Table 1). The Q192R genotypes of *PON1* gene in both groups were in Hardy–Weinberg equilibrium.

No difference in genotype distribution was seen between cases and controls ($\chi^2_{2df} = 5.482$, $p = 0.065$). R alleles were overrepresented in the cases ($\chi^2_{1df} = 4.703$, $p = 0.03$) (Table 1).

Logistic regression analysis carried out under assumption of an additive (OR = 1.36,

Table 1. Demographic data, genotype, and allele distribution in patients with sporadic amyotrophic lateral sclerosis (sALS) and controls

	Cases ($n = 166$)	Controls ($n = 437$)	p-value
Age (years)	56.2 ± 13.1	57.9 ± 17.7	0.25[a]
Sex (female)	79 (47.6%)	222 (50.8%)	0.44[b]
Genotypes			
QQ	79 (47.6%)	240 (54.9%)	0.065[b]
QR	67 (40.4%)	167 (38.2%)	
RR	20 (12.0%)	30 (6.9%)	
Alleles			
Q	225 (67.8%)	647 (74.0%)	0.03[b]
R	107 (32.2%)	227 (26.0%)	

[a]Student's *t*-test.
[b]χ^2-test for a 2 × k contingency table.

95%CI = 1.03–1.78, p = 0.034) or recessive mode of inheritance (OR = 1.86, 95%CI = 1.02–3.38, p = 0.04) showed a significant association between phenotype and genotype with the R allele.

Our study results suggest that Q192R polymorphism of the *PON1* gene influences the risk of sALS in a Polish population. No correlation was found between the Q192R polymorphism and the age of sALS onset, the type of the disease (bulbar *vs* limb onset), or its progression.

Chronic exposure to organophosphate compounds in R allele carriers of *PON1* gene may result in their slower hydrolysis and, in consequence, loss of vulnerable neuronal populations such as motor neurons.

It cannot be excluded that slower hydrolysis of nerve gases in R allele carriers may be responsible for the increased risk of sALS in Gulf War veterans (6). This hypothesis can be supported by the significantly higher prevalence of the R allele of the Q192R polymorphism in Gulf War veterans with different neurological symptom complexes (7).

It is also possible that the imbalance between the antioxidant defense system and free radical production, due to lower PON1 activity and resultant increased levels of oxidized LDL, increases the risk of sALS.

In our study, RR genotype carriers have 1.3 (additive model) and 1.8-fold (recessive model) higher risk of sALS. This relation, however, does not reach the suggested $p < 0.01$ for genetic association studies. Our study results should be interpreted with caution and it will be important to replicate our finding in different populations.

The relation between exposure to different environmental toxins and the levels of oxidized LDL in ALS patients with respect to their PON1 Q192R genotypes should be investigated. Our findings may provide a new direction for research and generate new insights into ALS pathogenesis.

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