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No association between DNA repair gene *XRCC1* and amyotrophic lateral sclerosis

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Abstract

Reduced DNA repair capacity may play a role in amyotrophic lateral sclerosis (ALS) etiology. We examined the association between ALS risk and single nucleotide polymorphisms (SNPs) in the gene x-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1*) utilizing data from a case-control study and two genome-wide association studies (the Study of Irish Amyotrophic Lateral Sclerosis and the NINDS genome-wide study in Amyotrophic Lateral Sclerosis and Neurologically Normal Controls). Our results did not show any differences in the frequency of *XRCC1* gene polymorphisms between ALS patients and controls free of any neurological disease.

Abnormal capacity to repair DNA damage may play a role in the pathogenesis of amyotrophic lateral sclerosis (ALS) (Bradley and Krasin, 1982). Neurons, especially motor neurons, are sensitive to DNA damage induced by reactive oxygen species ROS. Defects in the base-excision repair (BER) pathway, which counteracts the effects of ROS-induced DNA damage, may thus play a role in ALS. We examined the association of ALS risk to polymorphisms in a key gene in the BER pathway, x-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1*).

Keywords

Amyotrophic lateral sclerosis; DNA repair; *XRCC1*

Materials and Methods

We used data from 108 ALS cases and 39 matched controls from a case-control study conducted in New England in 1993–1996 (Kamel et al., 2002); 95% were white and not Hispanic. We genotyped five SNPs in *XRCC1*: three nonsynonymous SNPs (rs25487 G/A Arg399Gln, rs1799782 C/T Arg194Trp, and rs25489 G/A Arg280His) that have been

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frequently studied, one synonymous SNP (rs915927 A/G Pro206Pro), and one intronic SNP (rs939461 A/C). These five SNPs can distinguish all common haplotypes reconstructed using PHASE 2.0 software on dbSNP data for the European population. DNA was extracted from frozen blood samples using Gentra PUREGENE reagents (Gentra Systems, Minneapolis, MN). SNPs rs939461, rs915927, and rs25489 were genotyped using the MassARRAYTM system (Sequenom, San Diego CA), and SNPs rs25487 and rs1799782 were genotyped using the MasscodeTM system (Qiagen Genomics Inc, Bothell WA). We detected no deviations in Hardy-Weinberg equilibrium ($p > 0.26$ for each locus) using an exact test. For each SNP, we assessed ALS risk among carriers of a specific genotype compared to carriers of the most common homozygotic genotype using exact logistic regression methods to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

We also used publically available GWAS data from two previously described studies, the Study of Irish Amyotrophic Lateral Sclerosis (221 cases and 211 controls with Irish Caucasian ethnicity) (Cronin et al., 2008; dbGAP accession number phs000145.v2.p2) and the NINDS Genome-wide Genotyping in Amyotrophic Lateral Sclerosis and Neurologically Normal Controls Study (276 cases and 271 controls that were white and not Hispanic) (Schymick et al., 2007; dbGAP accession number phs000101.v2.p1). A total of 10 SNPs in *XRCC1* were genotyped in both GWAS and were included in our analysis. We used logistic regression models separately for each study to derive the ORs and 95% CIs for each SNP.

Results and Discussion

In the New England ALS study, a lower risk of ALS was noted among carriers of the variant genotypes for rs25487 and rs939461 (Supplemental material Table 1) but no clear associations were found for the other SNPs. No association between any of the 10 SNPs and ALS risk was noted in the Irish GWAS. An association between rs939461 and ALS risk was noted in the NINDS GWAS, but the estimate was of only borderline statistical significance (Supplemental material Table 2).

DNA damage, possibly due to excessive ROS coupled with defective DNA repair, may be an upstream mechanism for neurodegeneration in ALS. Key genes in the BER pathway are important for repairing oxidative damage to DNA. ALS risk was associated with polymorphisms in two other genes in this pathway, *APEX1* and *OGG1*, in some but not all studies, but to our knowledge, no previous study has investigated the relationship of ALS risk to *XRCC1* polymorphisms. In the present study, single marker analysis did not reveal evidence of a significant association of *XRCC1* variants with ALS risk in this analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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