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# *XRCC1* Arg194Trp and *XRCC1* Arg399Gln Polymorphisms Affect Clinical Features and Prognosis of Myelodysplastic Syndromes

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#### Article Information

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### **Backgrounds & Aims**

X-ray repair cross-complementing group 1 (*XRCC1*) plays an important role in base excision repair (BER) system, which is critical for genome maintenance. Polymorphisms in *XRCC1* that result alteration of DNA repair capacity are reportedly associated with cancer risk and treatment response. However, whether these polymorphisms alter the susceptibility and clinical outcomes of patients with myelodysplastic syndromes (MDS) is unknown. The aim of this study was to evaluate the association of two polymorphisms, *XRCC1* Arg194Trp and *XRCC1* Arg399Gln, with susceptibility to and clinical outcome of MDS.

#### Methods

Our study included 119 patients with MDS or chronic myelomonocytic leukemia [median 67.9 years, range 17.1-86.5 years; male/female 81/38] and 202 healthy control subjects. Genotypes were determined via PCR-restriction fragment length polymorphism (PCR-RFLP).

## Results

Differences in allele or genotype frequencies for *XRCC1* Arg194Trp or *XRCC1* Arg399Gln between patients with MDS and the control group were not significant. However, *XRCC1* 399 non-Arg/Arg genotypes were significantly associated with previous history of radio-therapy and multiple cancers. Furthermore, *XRCC1* 194 non-Arg/Arg genotypes and *XRCC1* 399 Arg/Arg genotype were each significantly associated with poor prognosis for patients with MDS.

#### Conclusions

Our studies suggest that *XRCC1* polymorphisms affected clinical features of MDS and may be useful prognostic marker for MDS.

#### References

- 1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours, Volume 2 IARC WHO Classification of Tumours, No.2 IARC.
- 2. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic

syndromes. Blood 1997; 91: 2079-2088.

- 3. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 2014; 28: 241-247.
- 4. Berwick M, Vineis P. Markers of DNA repair and susceptibility to cancer in humans: an epidemiologic review. J Natl Cancer Inst 2000; 92: 874-897.
- 5. Przybylowska-Sygut K, Stanczyk M, Kusinska R, et al. Association of the Arg194Trp and the Arg399Gln polymorphisms of the *XRCC1* gene with risk occurrence and the response to adjuvant therapy among Polish women with breast cancer. Clin Breast Cancer 2013; 13: 61-68.
- 6. Parsons JL, Dianov GL. Co-ordination of base excision repair and genome stability. DNA Repair 2013; 12: 326-333.
- Audebert M, Salles B, Calsou P. Involvement of poly (ADPribose) polymerase-1and *XRCC1*/DNA ligase III in an alternative route for DNA double-strand breaks rejoining. J Biol Chem 2004; 279: 55117-55126.
- 8. Thompson LH, West MG. *XRCC1* keeps DNA from getting stranded. Mutat Res 2000; 459: 11-18.
- 9. Hu Z, Ma H, Chen F, et al. *XRCC1* polymorphisms and cancer risk: a meta-analysis of 38 case-control studies. Cancer Epidemiol Biomarkers Prev 2005; 14: 1810-1818.
- Schneider J, Classen V, Helmig S. XRCC1 polymorphism and lung cancer risk. Expert Rev Mol Diagn 2008; 8: 761-780.
- 11. Mateuca RA, Roelants M, Iarmarcovai G, et al. hOGG1 (326), *XRCC1*(399) and *XRCC3*(241) polymorphisms influence micronucleus frequencies in human lymphocytes in vivo. Mutagenesis 2008; 23: 35-41.
- Weng H, Weng Z, Lu Y, et al. Effects of cigarette smoking, *XRCC1* genetic polymorphisms, and age on basal DNA damage in human blood mononuclear cells. Mutat Res 2009; 679: 59-64.
- Alter BP, Giri N, Savage SA, et al. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. Br J Haematol 2010; 150: 179-188.
- Palodetto B, de Melo Campos P, Benites BD, et al. MDR-1 and GST polymorphisms are involved in myelodysplasia progression. Leuk Res 2013; 37: 970-973.
- Jankowska AM, Gondek LP, Szpurka H, et al. Base excision repair dysfunction in a subgroup of patients with myelodysplastic syndrome. Leukemia 2008; 22: 551-558.
- Stern MC, Siegmund KD, Conti DV, et al. XRCC1, XRCC3, and XPD polymorphisms as modifiers of the effect of smoking and alcohol on colorectal adenoma risk. Cancer Epidemiol Biomarkers Prev 2006; 15: 2384-2390.
- El-Khamisy SF, Masutani M, Suzuki H, et al. A requirement for PARP-1 for the assembly or stability of *XRCC1* nuclear foci at sites of oxidative DNA damage. Nucleic Acids Res 2003; 31: 5526-5533.
- Hu JJ, Smith TR, Miller MS, et al. Amino acid substitution variants of APE1 and XRCC1 genes associated with ionizing radiation sensitivity. Carcinogenesis 2001; 22: 917-922.
- 19. El-Khamisy SF, Masutani M, Suzuki H, et al. A requirement for PARP-1 for the assembly or stability of *XRCC1* nuclear foci at sites of oxidative DNA damage. Nucleic Acids Res 2003; 31: 5526-5533.
- 20. Wang Y, Spitz MR, Zhu Y, et al. From genotype to

phenotype: correlating *XRCC1* polymorphisms with mutagen sensitivity. DNA Repair 2003; 2: 901-908.

- 21. Tuimala J, Szekely G, Wikman H, et al. Genetic polymorphisms of DNA repair andxenobiotic-metabolizing enzymes: effects on levels of sister chromatid exchanges and chromosomal aberrations. Mutat Res 2004; 554: 319-333.
- 22. Brem R, Hall J. *XRCC1* is required for DNA single-strand break repair in human cells. Nucleic Acids Res 2005; 33: 2512-2520.
- 23. Abdel-Rahman SZ, El-Zein RA. The 399Gln polymorphism in the DNA repair gene *XRCC1* modulates the genotoxic response induced in human lymphocytes by the tobacco-specific nitrosamine NNK. Cancer Lett 2000; 159: 63-71.
- 24. Weng H, Weng Z, Lu Y, et al. Effects of cigarette smoking, *XRCC1* genetic polymorphisms, and age on basal DNA damage in human blood mononuclear cells. Mutat Res 2009; 679: 59-64.
- 25. Saadat M. Haplotype analysis of *XRCC1* (at codons 194 and 399) and susceptibilityto breast cancer, a meta-analysis of the literatures. Breast Cancer Res Treat 2010; 124: 785-789.
- Zhang H, Liu H, Jiang G. Genetic polymorphisms of *XRCC1* and leukemia risk: a meta-analysis of 19 case-control studies. PLoS One 2013; 8: e80687.
- 27. Sorour A, Ayad MW, Kassem H. The genotype distribution of the *XRCC1*, *XRCC3*, and XPD DNA repair genes and their role for the development of acute myeloblastic leukemia. Genet Test Mol Biomarkers 2013; 17: 195-201.
- Bănescu C, Duicu C, Trifa AP, et al. XRCC1 Arg194Trp and Arg399Gln polymorphisms are significantly associated with shorter survival in acute myeloid leukemia. Leuk Lymphoma 2014; 55: 365-370.
- 29. Ron E. Ionizing radiation and cancer risk from epidemiology. Radiation Res 1998; 150, S40-S41.
- Seedhouse C, Bainton R, Lewis M, et al. The genotype distribution of the XRCC1 gene indicates a role for base excision repair in the development of therapy-related acute myeloblastic leukemia. Blood 2002, 100: 3761-3766.
- 31. Liddiard K, Hills R, Burnett AK, et al. OGG1 is a novel prognostic indicator in acute myeloid leukaemia. Oncogene 2010; 29: 2005-2012.
- 32. Moreno V, Gemignani F, Landi S, et al. Polymorphisms in genes of nucleotide and base excision repair: risk and prognosis of colorectal cancer. Clin Cancer Res 2006; 12: 2101-2108.
- 33. Jaremko M, Justenhoven C, Schroth W, et al. Polymorphism of the DNA repair enzyme XRCC1 is associated with treatment prediction in anthracycline and cyclophosphamide/ methotrexate/5-fluorouracil-based chemotherapy of patients with primary invasive breast cancer. Pharmacogenet Genomics 2007; 17: 529-538.
- Li H, You Y, Lin C, et al. XRCCl codon 399Gln polymorphism is associated with radiotherapy-induced acute dermatitis and mucositis in nasopharyngeal carcinoma patients. Radiat Oncol 2013; 8: 31.
- 35. Zhang Y, Wang M, Gu D, et al. Association of *XRCC1* gene polymorphisms with the survival and clinicopathological characteristics of gastric cancer. DNA Cell Biol 2013; 32: 111-118.