Worldwide Distribution of Four SNPs in X-Ray and Repair and Cross-Complementing Group 1 (XRCC1)

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Abstract

Purpose: X-ray repair cross-complementing group 1 (XRCC1) repairs single-strand breaks in DNA. Several reports have shown the association of single nucleotide polymorphisms (SNPs) (*Arg194Trp*, *Pro206Pro*, *Arg280His*, *Arg399Gln*) in *XRCC1* to diseases. Limited population data are available regarding SNPs in *XRCC1*, especially in African populations. In this study, genotype distributions of four SNPs in worldwide populations were examined and compared with those reported previously.

Materials and Methods: Four SNPs (*Arg194Trp*, *Pro206Pro*, *Arg280His*, *Arg399Gln*) in *XRCC1* from genomic DNA samples of 10 populations were evaluated by using polymerase chain reaction followed by restriction fragment length polymorphism analysis.

Results: The frequency of the minor allele corresponding to the *Trp* allele of *XRCC1Arg194Trp* was higher in Asian populations than in African and Caucasian populations. As for *XRCC1Pro206Pro*, Africans showed higher minor allele frequencies than did Asian populations, except for Tamils and Sinhalese. *XRCC1 Arg280His* frequencies were similar among Africans and Caucasians but differed among Asian populations. Similarly, lower mutant *XRCC1 Arg399Gln* frequencies were observed in Africans.

Conclusions: This study is the first to show the existence of a certain genetic heterogeneity in the worldwide distribution of four SNPs in *XRCC1*. Clin Trans Sci 2015; Volume 8: 347–350

Keywords: x-ray repair cross-complementing group 1 (XRCC1), DNA repair, ethnic differences, single nucleotide polymorphisms (SNP), base excision repair (BER)

Introduction

There are two main DNA repair pathways: base excision repair (BER) and nucleotide excision repair.[1,2] Among genes in the BER pathway, human 8-oxoguanine DNA glycosylase (hOGG1), apurinic/apyrimidinic endonuclease (APE1), and x-ray repair cross-complementing group 1 (XRCC1) have been especially well studied. 8-hydroxy-2′-deoxyguanosine (8-OHdG) is a byproduct of ROS damage to DNA: 8-OHdG genes are repaired by hOGG1 in combination with APE1.[3] XRCC1, a multidomain protein, repairs single-strand breaks in DNA that result from either the BER process itself or damage to deoxyribose.[4,5]

Single nucleotide polymorphisms (SNPs) in the genes involved in DNA repair pathways could influence susceptibility to oxidative damage. Variants in three genes, *hOGG1 Ser326Cys* (rs1052133), *APE1 Asp148Glu* (rs3136820), and *XRCC1 Arg399Gln* (rs25487), have been shown to reduce the capacity to repair oxidative damage.[6] In addition, we have previously reported that individuals with *hOGG1 326Cys/Cys* showed significantly higher urinary 8-OHdG concentrations than did those with *326Ser/Cys* and *326Ser/Ser*. As for *APE1 Asp148Glu*, heterozygous subjects showed significantly higher urinary 8-OHdG concentrations than did those homozygous for Asp/Asp, suggesting that the *Cys* allele of *hOGG1 Ser326Cys* and the *Glu* allele of *APE1 Asp148Glu* might reduce the capacity to repair oxidative damage, as compared with the counterpart allele of each SNP.[7] The most studied SNPs in the XRCC1 gene are *Arg194Trp* on exon 6, *Arg280His* on exon 9, and *Arg399Gln* on exon 10.[8] A previous study reported that only the *XRCC1 Arg280His* variant protein is defective in its efficient localization to a damaged site in the chromosome, thereby reducing cellular BER efficiency.[9] The *399Gln* allele has been reported to be associated with higher mutagen sensitivity and higher levels of DNA adducts.[10,11] Several reports have shown the association of SNPs (*Arg194Trp*, *Pro206Pro*, *Arg280His*, *Arg399Gln*) in *XRCC1* to diseases.[12–20]

As described above, DNA repair capacity is influenced by SNPs in BER genes, and several studies have showed the association of XRCC1 polymorphisms to diseases. Data accumulation of SNPs in XRCC1 genes is important for elucidating the interindividual differences in capacity for repairing oxidative damage and susceptibility to disease. However, to our knowledge, limited population data are available regarding SNPs in *XRCC1*, especially in African populations. Therefore, we have performed global ethnic comparisons of the allelic frequencies of the four SNPs in *XRCC1* in 10 different populations with previous reported data.

Biological samples

Genomic DNA was extracted from blood or bloodstain samples randomly collected from the following healthy subjects: 191 Ovambos (Bantusin, Namibia), 121 Ghanaians (Accra, Ghana), 104 Xhosas (Cape Town, South Africa), 144 Mongolians (Ulaanbaatar, Mongol), 53 Tamangs (Kotyang, Nepal), 178 Tibetans (Katmandu, Nepal), 56 Tamils and 53 Sinhalese (Kandy, Sri Lanka), 100 Vietnamese (Ha Nam Province, Vietnam), and 37 Uyghurs (Urumqi of China). Informed consent was obtained from each participant. Genomic DNA was extracted from blood or bloodstain samples randomly collected from healthy subjects using the QIAamp DNA Mini Kit (QIAGEN Inc., Chatsworth, CA, USA). The study was approved by the Ethical Committees of the institutes.

Genotyping method

SNP genotyping of *XRCC1 Arg194Trp*(C/T) at exon 6 (rs1799782), *Pro206Pro* (A/G) at exon 7 (rs915927), *Arg280His* (G/A) at exon 9, and *Arg399Gln* (G/A) at exon 10 (rs25487) were analyzed

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SNPs		Primer sequence	Restriction enzyme
Arg194Trp	Sense antisense	5′-GCCCCGTCCCAGGTA-3′ 5′-AGCCCCAAGACCCTTTCACT-3′	*MspI*
Pro206Pro	Sense antisense	5′-GTCCCATAGATAGGAGTGAAAG-3′ 5′-CCCTAGGACACAGGAGCACA-3′	*MspI*
Arg399Gln	Sense antisense	5′-GGACTGTCACCGCATGCGTCGG-3′ 5′-GGCTGGGACCACCTGTGTT-3′	*MspI*
Arg280His	Sense antisense	5′-CCAGTGGTGCTAACCTAATC-3′ 5′-CACTCAGCACCAGTACCACA-3′	*RsaI*

Table 1. Primer sequence, and restriction enzymes for PCR-based genotyping of the SNPs in this study.

by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis. Primers for the specific amplification of the DNA fragments encompassing a substitution site corresponding to the SNPs (*Arg194Trp* and *Pro206Pro*) were newly designed on the basis of the nucleotide sequence (*Table 1*). Primers for *Arg280His* and *Arg399Gln* were the same as in our previous study.[7] Amplification was performed with a 10-μL reaction mixture containing GoTaq® Green

Populations	*Arg194Trp* (C to T)			*Pro206Pro* (A to G)		*Arg280His* (G to A)		*Arg399Gln* (G to A)		
	N	C	T	A	G	G	A	G	A	Reference
Ovambo	191	0.907	0.093	0.628	0.372	0.992	0.008	0.936	0.064	This study
Ghanaians	121	0.909	0.091	0.632	0.368	0.983	0.017	0.908	0.092	This study
Xhosans	104	0.965	0.035	0.767	0.233	0.973	0.027	0.906	0.094	This study
African American	682	0.930	0.070			0.960	0.040	0.861	0.139	Pachkowski et al. (2006)[28]
Mongolian	144	0.844	0.156	0.917	0.083	0.970	0.030	0.723	0.277	This study
Tamangs	53	0.736	0.264	0.896	0.104	0.922	0.078	0.736	0.264	This study
Tibetans	178	0.665	0.335	0.819	0.181	0.948	0.052	0.829	0.171	This study
Tamils	56	0.853	0.147	0.724	0.276	0.780	0.220	0.698	0.302	This study
Sinhalese	53	0.880	0.120	0.685	0.315	0.852	0.148	0.685	0.315	This study
Vietnamese	100	0.750	0.250	0.910	0.090	0.870	0.130	0.560	0.440	This study
Uygur	37	0.794	0.213	0.838	0.162	0.955	0.045	0.784	0.216	This study
Japanese	222	0.723	0.277			0.950	0.050	0.671	0.329	Weng et al. (2008)[29]
Taiwanese	283					0.760	0.240	0.537	0.463	Cho et al. (2003)[30]
Turks	93					0.900	0.100	0.670	0.330	Paridar-Karpuzoğlu et al. (2008)[31]
Kazakhstan	123	0.874	0.126			0.854	0.146	0.785	0.215	Chacko et al. (2005)[32]
Iran	707	0.909	0.091					0.661	0.339	Mohamadynejad et al. (2008)[33]
Pashtuns (Afghanistan)	257	0.928	0.072					0.638	0.362	Saify et al. (2013)[34]
Tajiks (Afghanistan)	217	0.915	0.085					0.622	0.378	Saify et al. (2013)[34]
Hazaras (Afghanistan)	120	0.892	0.108					0.704	0.296	Saify et al. (2013)[34]
Uzbeks (Afghanistan)	62	0.855	0.145					0.766	0.234	Saify et al. (2013)[34]
Whites	1135	0.939	0.061			0.970	0.070	0.665	0.335	Pachkowski et al. (2006)[28]
Italy	324	0.910	0.090	0.483	0.517			0.628	0.372	Matullo et al. (2005)[35]
Spain	1096	0.939	0.061			0.927	0.073	0.621	0.379	Figueroa et al. (2007)[36]
Poland	124	0.912	0.088					0.609	0.391	Kowalski et al. (2009)[37]
France	413	0.931	0.069					0.641	0.359	Duell et al. (2000)[38]
Norway	377	0.952	0.048			0.960	0.040	0.624	0.376	Zienolddiny et al. (2006)[39]
Finland	223	0.973	0.027					0.679	0.321	Frosina et al. (2004)[40]
England	178	0.937	0.063					0.522	0.478	Seedhouse et al (2002)[41]
Belgium	110	0.923	0.077					0.651	0.349	De Ruyck et al. (2007)[42]

Table 2. Genotype distribution of four XRCC1 SNPs in worldwide populations.

Master Mix (Promega, Madison, WI, USA). The PCR products were digested with each restriction enzyme (New England Biolabs, Beverly, MA, USA; *Table 1*). The digests were separated in an 8% polyacrylamide gel, and the patterns on the gels were visualized by silver staining, as described previously. Nucleotide sequences of the representative subjects were confirmed by the dideoxy chain-terminating method with the BigDye Terminator Cycle Sequencing Kit using a 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

A chi-square-analysis was performed to evaluate the Hardy–Weinberg equilibrium. Using the chi-square test for RxC contingency tables, genotype distributions were compared between the populations.

Results and discussion

In this study, the PCR-RFLP method was newly developed for use in genotyping *Arg194Trp* and *Pro206Pro* polymorphisms, and *Arg280His* and *Arg399Gln* were genotyped according to our previous method.[7] We used a mismatched PCR amplification method for genotyping *Arg194Trp* and *Pro206Pro*. Incorporation of a deliberate mismatch close to the 3′-terminus of a PCR primer allowed the creation of each enzyme recognition site. A DNA fragment containing a substitution site was separately amplified using a set of PCR primers and was subjected to digestion with each enzyme (*Table 1*). The validity of the genotyping results obtained by these methods was confirmed by the sequencing analysis of genomic DNA derived from several representative subjects.

The allele frequencies of the four SNPs in the XRCC1 gene of Ovambos, Ghanaians, Xhosas, Mongolian, Tamangs, Tibetans, Tamils, Sinhalese, Vietnamese, and Uyghurs, as well as those in populations studied previously,[28–42] are shown in *Table 2*. The genotype distributions of these 10 populations were found to be within the Hardy–Weinberg equilibrium (data not shown). The allele frequencies differed among populations. The frequency of the minor allele corresponding to the *Trp* allele of *XRCC1Arg194Trp* was higher in Asian populations than in African and Caucasian populations: African and Caucasian populations showed lower mutant allele frequencies (<0.1). As for *XRCC1Pro206Pro*, genotype distributions were different among the populations: Africans showed higher minor allele frequencies than did Asian populations, except for Tamils and Sinhalese. *XRCC1 Arg280His* frequencies were similar among Africans and Caucasians but differed among Asian populations. Similarly, lower mutant *XRCC1 Arg399Gln* frequencies were observed in Africans. In this study, genotype distributions were similar among Caucasians and Asians, while those of Africans were different.

Recent studies have shown that *XRCC1 Arg194Trp* is a risk factor for differentiated thyroid carcinoma,[13] head and neck cancer,[18] and breast cancer.[16] Yin et al. (2007) suggested that the *XRCC1 Pro206Pro* polymorphism may contribute to genetic susceptibility for lung cancer in the population of northeastern China.[12] Mahjabeen et al. (2013) suggested that *XRCC1 Pro206Pro* may be related to susceptibility to head and neck cancers in the Pakistani population.[15] Liu et al. (2013) suggested that *XRCC1 Arg280His* polymorphisms were risk factors for increasing bladder cancer in Asian populations.[14] Salimi et al. (2014) have shown that the *XRCC1 399Arg/Gln* heterozygous genotype plays a protective role in systemic lupus erythematosus susceptibility.[17] Zhang et al. (2014) suggested that *XRCC1 Arg399Gln* polymorphism may increase hepatocellular carcinoma risk, especially among Asians, but may play a protective role against hepatocellular carcinoma among Caucasians.[20] In the American population, *XRCC1 Arg399Gln* polymorphism has been suggested to be related to breast cancer.[19] Previous studies have shown lower prevalence of breast cancer in South Asian and Black women than in White women, both in the United Kingdom[21–24] and in the United States.[25–27] In this study, XRCC1 *Arg399Gln* mutant frequencies were lower in Africans and Asians as compared to Caucasians. Further study is needed to clarify the relevance of *XRCC1* polymorphism to the disease.

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