XRCC1 Arg399Gln Gene Polymorphism and the Risk of Systemic Lupus Erythematosus in the Polish Population

Teresa Warchoła,¹ Adriana Mostowska,¹ Margarita Lianeri,¹ Jan K. Łacki,^{2,3} and Paweł P. Jagodziński¹

It has been shown that DNA repair is reduced in patients with systemic lupus erythematosus (SLE) and that the X-ray repair cross-complementing (XRCC1) Arg399Gln (rs25487) polymorphism may contribute to DNA repair. We evaluated the frequency of the XRCC1 Arg399Gln substitution in patients with SLE ($n=265$) and controls ($n=360$) in a sample of the Polish population. The odds ratio (OR) for SLE patients with the Gln/Gln versus Gln/Arg or Arg/Arg genotypes was 1.553 (95% confidence interval [CI]=0.9573–2.520; $p=0.0729$). OR for the Gln/Gln or Gln/Arg versus Arg/Arg genotype was 1.551 (95% CI=1.122–2.144, $p=0.0077$). The OR for the 399 Gln allele in patients with SLE was 1.406 (95% CI=1.111–1.779, $p=0.0045$). There was also a statistically significant p -value of the χ^2 test for the trend observed in the XRCC1 Arg399Gln polymorphism (ptrend=0.0048). We also found a significant contribution of the Gln/Gln or Arg/Gln versus Arg/Arg genotype to the presence of either the malar rash or photosensitivity manifestations of SLE OR=2.241 (1.328–3.781, $p=0.0023$, $p_{\text{corr}}=0.0414$). Moreover, the meta-analysis of Taiwanese Han Chinese, Brazilian, and Polish populations showed that the Gln/Gln or Gln/Arg genotype and Gln allele were associated with SLE incidence. OR for the Gln/Gln or Gln/Arg versus Arg/Arg genotype was 1.440 (95% CI=1.15–1.80, $p=0.0019$) and OR for the Gln allele was 1.27 (95% CI=1.08–1.51, $p=0.0051$). Our studies may confirm that the XRCC1 Arg399Gln polymorphism may increase the risk of incidence of SLE and the occurrence of some SLE manifestations.

Introduction

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is an autoimmune disease, meaning that the body's tissues are attacked by the body's own immune system (Sekigawa *et al.*, 2004). The incidence of this autoimmune disease is nine times greater in women of reproductive age than in men (Sekigawa *et al.*, 2004). The course of this disorder is unforeseeable, with periods of flare-ups occurring between periods of remission (Sekigawa *et al.*, 2004). Patients with SLE display abnormalities in immune cells, including aberrant cytokine production and decreased activity of cytotoxic T cells, changes in CD4⁺ T cell function, and defective B cell activation (Gröndal *et al.*, 2000; Stohl *et al.*, 2003; Crispín *et al.*, 2010).

Genetic studies have demonstrated a strong contribution of many gene variants to SLE incidence and the clinical manifestations of SLE (Wong and Tsao, 2006; Hom *et al.*, 2008; Flesher *et al.*, 2010). Moreover, the induction of SLE development can be initiated by various environmental factors, drugs, chemicals, viral infections, and exposure to ultraviolet (UV) light (Mok and Lau, 2003; Sarzi-Puttini *et al.*, 2005; Jönsen *et al.*, 2007).

An accumulation of breaks in DNA combined with nuclear proteins may generate immunogenic antigens, which induce the production of auto-reactive antibodies (Abs) and an autoimmune response in susceptible individuals (Takeda and Dynan, 2001; Lee *et al.*, 2002). Some studies have shown impaired DNA repair in patients with SLE, which suggests the involvement of various polymorphic variants of genes encoding the proteins responsible for DNA repair (Herrick *et al.*, 1995; McCurdy *et al.*, 1997).

In mammals, DNA is protected from ionizing radiation by proteins encoded by the X-ray repair cross-complementing (XRCC) gene family (Thacker and Zdzienicka, 2004). Some XRCC proteins have demonstrated their role in the incidence of various autoimmune disorders by their presence at DNA damage sites (Takeda and Dynan, 2001; Lee *et al.*, 2002; Tajouri *et al.*, 2003). XRCC1 functions as a platform protein to complex several enzymes responsible repairing DNA breaks (Tudek, 2007). Three single-nucleotide polymorphisms (SNPs) resulting in amino acids changes have been found at the XRCC1 gene (Hong *et al.*, 2005). Recently, it has been reported that the XRCC1Arg399Gln (rs25487) polymorphism

¹Department of Biochemistry and Molecular Biology, Poznan University of Medical Sciences, Poznań, Poland.

²Institute of Rheumatology, Warsaw, Poland.

³Department of Public Health, University of Zielona Góra, Poland.

may play a role in an individual's susceptibility to SLE (Lin *et al.*, 2009). The *XRCC1* Arg399Gln minor allele exhibited relatively high frequency in the Polish population we studied for the distribution of Arg399Gln genotype and allelic frequencies in patients with SLE. As SLE is a heterogeneous disease, we also evaluated the association of these polymorphisms with varied SLE clinical symptoms in this group of patients.

Patients and Methods

Patients and controls

Two hundred sixty-five patients (women only) fulfilling the American College of Rheumatology Classification criteria for SLE (Tan *et al.*, 1982; Hochberg, 1997) were selected randomly at Institute of Rheumatology in Warsaw, Poland (Table 1). The 360 controls consisted of randomly selected unrelated healthy female blood donors and healthy women who had a comprehensive examination at the Institute of Mother and Child in Warsaw, Poland. Both patients and control groups were of Polish Caucasian origin. The protocol of the study was approved by the Local Ethics Committee of Poznań University of Medical Sciences. Written agreement was obtained from all participating individuals. The mean age of SLE patients at diagnosis was 37 ± 12 years, and of controls 36 ± 11 years.

Genotyping

DNA was obtained from peripheral leukocytes using a salting out procedure. The presence of the *XRCC1* Arg399Gln (rs25487) variant was identified by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP). PCR was carried out using primer pair 5' ACCTTGCTGCTTTCTCTGTGTC 3' and 5' TAGTCTGCTGGCTCTGGGCT 3'. The PCR-amplified fragments 509 bp in length containing the *XRCC1* Arg399Gln polymorphism were digested with endonuclease *NciI* (CC/SGG) (New England Biolabs, Ipswich, MA). The *XRCC1* 399 Arg allele was cleaved into 378 bp and 131 bp fragments, whereas the *XRCC1* 399 Gln allele was not cleaved (Fig. 1). The DNA fragments were separated according to size by electrophoresis on 2% agarose gel and observed by ethidium bromide staining. The *XRCC1* Arg399Gln polymorphism was also confirmed by repeated PCR-RFLP analysis and commercial sequencing.

Statistical analysis

The distribution of genotypes in patients and controls was tested for deviation from Hardy–Weinberg equilibrium. Differences in genotypic and allelic distribution between patients and controls and associations between clinical manifestations, production of Abs, and polymorphism

TABLE 1. ASSOCIATION OF THE *XRCC1* ARG399GLN (RS25487) POLYMORPHISM WITH CLINICAL SYMPTOMS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Characteristic	Genotype distribution				OR (95% CI, p^b)	P_{trend}^c
	Arg/Arg (99) ^a	Arg/Gln (127) ^a	Gln/Gln (39) ^a	MAF		
Malar rash	48	77	25	0.42 $p = 0.0485^b$	1.443 (0.7129–2.920, $p = 0.3062$) ^d 1.693 (1.024–2.801, $p = 0.0395$)^e	0.0474
Discoid rash	28	35	16	0.42	1.800 (0.8926–3.629, $p = 0.0973$) ^d 1.125 (0.6502–1.945, $p = 0.6744$) ^e	0.2486
Phototosensitivity	43	69	25	0.43 $p = 0.0201^b$	1.818 (0.8986–3.677, $p = 0.0932$) ^d 1.700 (1.029–2.810, $p = 0.0376$)^e	0.0195
Oral ulcers	46	61	19	0.39	1.057 (0.5352–2.086, $p = 0.8740$) ^d 1.072 (0.6509–1.765, $p = 0.7852$) ^e	0.7838
Arthritis	23	31	9	0.39	0.9556 (0.4270–2.138, $p = 0.9119$) ^d 1.049 (0.5834–1.886, $p = 0.8730$) ^e	0.9556
Serositis	19	26	8	0.40	1.038 (0.4467–2.412, $p = 0.9309$) ^d 1.085 (0.5796–2.029, $p = 0.7995$) ^e	0.8227
Renal	52	68	21	0.39	1.031 (0.5212–2.038, $p = 0.9310$) ^d 1.045 (0.6344–1.720, $p = 0.8635$) ^e	0.8681
Neurologic symptoms	19	26	8	0.40	1.038 (0.4467–2.412, $p = 0.9309$) ^d 1.085 (0.5796–2.029, $p = 0.7995$) ^e	0.8227
Hematologic symptoms	29	42	16	0.43	1.519 (0.7562–3.050, $p = 0.2379$) ^d 1.296 (0.7570–2.220, $p = 0.3437$) ^e	0.2010
Immunologic symptoms	45	62	21	0.41	1.298 (0.6562–2.566, $p = 0.4531$) ^d 1.200 (0.7284–1.977, $p = 0.4738$) ^e	0.3715
Malar rash/ Phototosensitivity	54	91	30	0.43 $p = 0.0033^b$	1.862 (0.8424–4.116, $p = 0.1201$) ^d 2.241 (1.328–3.781, $p = 0.0023$)^e	0.0031
Antinuclear Antibody (ANA)	99	127	39	0.39		

Significant results are highlighted in bold font.

^aRepresents the absolute number of positive patients for Arg/Arg, Arg/Gln, and Gln/Gln genotypes or Gln MAF.

^bSLE was performed by χ^2 test.

^c χ^2 test for trend.

^dGenotype comparison (Gln/Gln vs. Arg/Gln or Arg/Arg) between patients with and patients without clinical manifestations of SLE.

^eGenotype comparison (Gln/Gln or Arg/Gln vs. Arg/Arg) between patients with and patients without clinical manifestations of SLE.

MAF, minor allelic frequency; SLE, systemic lupus erythematosus; CI, confidence interval; OR, odds ratio.

FIG. 1. Representative picture of PCR–restriction fragment length polymorphism analysis of the XRCC1 Arg399Gln polymorphism. The 509 bp PCR-amplified fragments were digested with endonuclease *NciI* (CC/SGG). The XRCC1 399 Gln allele was not cleaved, whereas the XRCC1 399 Arg allele was cleaved into 378 bp and 131 bp fragments. The DNA fragments were separated by electrophoresis on 2% agarose gel and observed by ethidium bromide staining. PCR, polymerase chain reaction.

distribution in patients were determined by χ^2 or Fisher exact test. Bonferroni correction for multiple comparisons was used and both p -values, before (p) and after correction (p_{corr}), were determined. The XRCC1 Arg399Gln polymorphism was tested for association with SLE using the χ^2 test for trend (p_{trend}). The odds ratio (OR) and 95% confidence intervals (95% CI) were also determined. Statistical significance was interpreted as p -value < 0.05 . Power analysis was performed using χ^2 exact test, available at <http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize>

Meta-analysis

The meta-analysis of three independent datasets (Bassi *et al.*, 2008; Lin *et al.*, 2009, and present study) was conducted using the Mantel-Haenszel fixed-effect model. The effect of allele contrast (Gln vs. Arg) and the contrast for the dominant (GlnGln/GlnArg vs. ArgArg) and recessive (GlnGln vs.

GlnArg/ArgArg) models were estimated. The inter- and between-study heterogeneity was tested using the Breslow and Day method. The p -value for significance of association and heterogeneity tests was set to 0.10. All statistical calculations were conducted using the program EasyMA (Cucherat *et al.*, 1997).

Results

Distribution of the XRCC1 Arg399Gln allelic and genotypic variant in SLE patients and controls

Genotype assessment of the XRCC1 Arg399Gln polymorphism did not exhibit significant aberration from the Hardy–Weinberg equilibrium in any group.

The frequency of the XRCC1 399 Gln/Gln genotype was approximately 1.5-fold times higher in SLE patients than in the controls, and reached 0.15 and 0.10 in those groups, respectively (Table 2). The prevalence of the XRCC1 399 Gln/Arg heterozygous genotype was also increased in individuals with SLE as compared to controls, and frequencies reached 0.48 and 0.42, respectively (Table 2). The OR for SLE patients with the Gln/Gln versus Gln/Arg or Arg/Arg genotypes was 1.553 (95% CI=0.9573–2.520; $p=0.0729$) (Table 2). OR for the Gln/Gln or Gln/Arg versus Arg/Arg genotype was 1.551 (95% CI=1.122–2.144, $p=0.0077$). We also found a significantly higher frequency of the XRCC1 399 Gln allele in patients than in controls, amounting to 0.39 and 0.31, respectively (Table 2). The OR for the 399 Gln allele in patients with SLE was 1.406 (95% CI=1.111–1.779, $p=0.0045$). The p -value of the χ^2 test for the trend observed for the XRCC1 Gln399Arg polymorphism was also statistically significant ($p_{\text{trend}}=0.0048$). The statistical power of this study was 76% for Gln/Gln Gln/Arg genotypes.

Association of XRCC1 Arg399Gln genotypes with clinical symptoms of SLE

The most significant differences in the distribution of XRCC1 Gln/Gln or Arg/Gln versus Arg/Arg genotype was found in SLE patients with malar rash and phototosensitivity manifestations. These values amounted to OR=1.693 (95% CI=1.024–2.801, $p=0.0395$) and OR=1.700 (95% CI=1.029–2.810, $p=0.0376$) (Table 1), respectively. However, neither p -value was statistically significant after Bonferroni correction: $p_{\text{corr}}=0.711$ and $p_{\text{corr}}=0.677$, respectively. However, there was a significant contribution of the Gln/Gln or Arg/Gln

TABLE 2. ASSOCIATION BETWEEN XRCC1 ARG399GLN POLYMORPHIC VARIANTS AND THE RISK OF SYSTEMIC LUPUS ERYTHEMATOSUS

Genotype	SLE (frequency)	Controls (frequency)	OR (95% CI)	p^a	p_{trend}^b
Arg/Arg	99 (0.37)	173 (0.48)			0.0048
Arg/Gln	127 (0.48)	151 (0.42)			
Gln/Gln	39 (0.15)	36 (0.10)	1.553 (0.957–2.520) ^c	0.0729 ^c	
Arg/Gln + Gln/Gln	166 (0.63)	187 (0.52)	1.551 (1.122–2.144) ^d	0.0077 ^d	
Minor allele frequency	0.39	0.31	1.406 (1.111–1.779) ^e	0.0045	

^a χ^2 analysis.

^b χ^2 test for trend.

^c(Gln/Gln vs. Arg/Gln and Arg/Arg).

^d(Gln/Gln and Arg/Gln vs. Arg/Arg).

^e(Gln vs. Arg).

versus Arg/Arg genotype to the presence of either a malar rash or phototosensitivity manifestations OR=2.241 (1.328–3.78, $p=0.0023$, $p_{\text{corr}}=0.0414$) (Table 1). We did not find a significant association between the XRCC1 Arg399Gln polymorphism with other SLE clinical manifestations (Table 1). There was also no contribution of the XRCC1 Arg399Gln polymorphism to the presence of anti-dsDNA, anti-Smith, anti-snRNP, anti-Ro, anti-Scl-70, or anti-phospholipid Abs. We did not find significant differences in SLE disease activity index (Bombardier *et al.*, 1992) at diagnosis between XRCC1 Arg399Gln genotype groups.

Meta-analysis of the XRCC1 Arg399Gln polymorphism

The meta-analysis was performed using data pooled from three studies conducted in Taiwanese Han Chinese (Lin *et al.*, 2009), Brazilian (Bassi *et al.*, 2008), and Polish populations. There was no heterogeneity between these studies in the analysis of XRCC1 Arg399Gln genotypes and the Gln allele. The p -value for the heterogeneity tests was >0.10 . The OR for SLE patients with the Gln/Gln versus Gln/Arg or Arg/Arg genotypes was 1.17 (95% CI=0.84–1.64; $p=0.39$), (Table 3). OR for the Gln/Gln or Gln/Arg versus Arg/Arg genotype was 1.44 (95% CI=1.15–1.80, $p=0.0019$) (Table 3). The OR for the 399 Gln allele in patients with SLE was 1.27 (95% CI=1.08–1.51, $p=0.0051$).

Discussion

It has been reported that DNA repair is diminished in patients with SLE (Benke and Belmar, 1991; Bashir *et al.*, 1993; McCurdy *et al.*, 1997). Leucocytes from these patients exhibited increased levels of spontaneous single strand breaks and accumulation of oxidative DNA lesions as compared to those of healthy individuals (Benke and Belmar, 1991; Bashir *et al.*, 1993). Moreover, SLE lymphocytes exposed to γ -radiation or SLE neutrophils with oxidative DNA damages may display reduced DNA repair ability (McCurdy *et al.*, 1997; McConnell *et al.*, 2002).

We found that the XRCC1 399Gln gene variant can be a risk factor for SLE incidence in a sample of the Polish population. Moreover, meta-analysis of Taiwanese Han Chinese (Lin *et al.*, 2009), Brazilian (Bassi *et al.*, 2008), and Polish populations showed that this gene variant can be associated with SLE incidence.

Recent studies conducted by Lin *et al.* (2009) in the Taiwanese Han Chinese population demonstrated a statistically

significant higher frequency of the XRCC1 399 Arg/Gln heterozygote in patients with SLE than in controls. In contrast, Bassi *et al.* (2008) did not confirm the contribution of the XRCC1 Arg399Gln polymorphism to SLE development in Brazilian populations. However they observed the association of XRCC1 Gln/Gln or Arg/Gln genotypes with presence of anti-dsDNA Ab (Bassi *et al.*, 2008).

In our study, patients with the XRCC1 Gln/Gln or Arg/Gln genotypes exhibited a significantly increased risk of developing either malar rash or phototosensitivity. An association between the XRCC1 Arg/Gln heterozygotes and phototosensitivity or malar rash was observed in SLE patients from the Taiwanese Han Chinese population (Lin *et al.*, 2009). Furthermore, in this population, the XRCC1 Arg/Gln heterozygote has also been associated with hematologic and arthritis manifestations and presence of antinuclear Abs (Lin *et al.*, 2009).

These differences in the effect of the XRCC1 Arg399Gln genotypes on the incidence of SLE and clinical manifestations in various ethnicities may be due to the racial heterogeneity or size of the studied groups. This distinction may also result from different populations' exposure to various environmental chemicals interacting with the XRCC1 Arg399Gln genotypes. This eventually may lead to different effects on the risk of SLE incidence in the studied ethnicities (Sarzi-Putini *et al.*, 2005; Jönsen *et al.*, 2007).

To date, the XRCC1 399 Gln polymorphic variant has also been recognized as a genetic modifier for increasing the formation of DNA adducts and DNA damage in individuals exposed to cigarette smoke, aflatoxin B1, 1,3-butadiene, vinyl chloride metabolites, or styrene (Lunn *et al.*, 1999; Abdel-Rahman and El-Zein 2000); Godderis *et al.*, 2004; Li *et al.*, 2009; Weng *et al.*, 2009; Wang *et al.*, 2010). Moreover, the XRCC1 399 Gln gene variant has been associated with lymphoblastic leukemia and carcinomas of head and neck, stomach, lung, prostate, colon, and breast (Sturgis *et al.*, 1999; Abdel-Rahman *et al.*, 2000; Divine *et al.*, 2001; Duarte *et al.*, 2005; Chen *et al.*, 2006; Silva *et al.*, 2007; Tumer *et al.*, 2010). The XRCC1 399 Gln gene variant may also contribute to pterygium, schizophrenia, atherosclerotic coronary artery disease, and asthma incidence (Saadat *et al.*, 2008; Chiang *et al.*, 2010; Bazo *et al.*, 2011).

XRCC1 protein is a crucial component of the base excision repair (BER) pathway for DNA damage. Although XRCC1 does not display enzymatic activity, it functions as a scaffold

TABLE 3. META-ANALYSIS OF THE XRCC1 ARG399GLN POLYMORPHISM AND ASSOCIATION WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Tested model	No. of studies	Sample size		Test of association ^a			Test of heterogeneity ^b	
		SLE	Controls	OR	95% CI	p-Value	χ^2	p-Value
Recessive model	3	571	689	1.17	0.84–1.64	0.39	4.03	0.13
Gln/Gln versus Arg/Gln + Arg/Arg								
Dominant model	3	571	689	1.44	1.15–1.80	0.0019	2.12	0.35
Gln/Gln + Arg/Gln versus Arg/Arg								
Allelic effect	3	1142	1378	1.27	1.08–1.51	0.0051	1.55	0.46
Gln versus Arg								

Significant results are highlighted in bold font.

^aMantel-Haenszel fixed-effect model.

^bBreslow and Day method.

to coordinate the activity of the other proteins in the BER machinery, including glycosylases, an endonuclease (APE1), DNA polymerase β , a ligase, and Poly (ADP-ribose) Polymerases (PARP1 and PARP2) (Lindahl and Wood, 1999; Batar *et al.*, 2010). The Arg399Gln polymorphism is situated in the central part of the XRCC1 BRCT1 domain, associated with the functioning of PARP1, PARP2, and APE1 (Vidal *et al.*, 2001; Schreiber *et al.*, 2002). Monaco *et al.* (2007) showed that the XRCC1 Arg399Gln substitution produces significant conformational alterations at several other sites in the BRCT1 domain. These alterations can be crucial in protein-protein interactions and may subsequently reduce the capability of the BER machinery formation. The decreased ability of the XRCC1 399 Gln protein in DNA repair has recently been demonstrated. Li *et al.* (2009) showed that immortalized lymphoblasts from vinyl chloride workers bearing the XRCC1 399 Arg/Arg genotype and exposed to etheno-adenosine adduct exhibited an average repair efficiency of 82%. In contrast, immortalized lymphoblasts from workers having the XRCC1 399 Gln/Gln genotype and exposed to the same adduct displayed an average repair efficiency of 32% (Li *et al.*, 2009).

DNA damage can be produced by endogenous factors, including reactive oxygen species, or indirectly during BER, or exogenous factors such as chemicals and ionizing radiation (Thompson and West, 2000; Rastogi *et al.*, 2010; Sutandyo, 2010). UV irradiation may damage DNA and is a powerful inducer of SLE in susceptible individuals (Pirner *et al.*, 1992; Sarzi-Puttini *et al.*, 2005). Impaired DNA repair may induce an autoimmune response in susceptible individuals with the XRCC1 399 Gln protein variant that has been exposed to DNA damage factors. This DNA damage may produce nucleoprotein complexes containing new composites or conformation epitopes or their cleavage products, which may present immunocryptic peptides that stimulate autoreactive T lymphocytes (Takeda and Dynan, 2001; Beyer *et al.*, 2002; Lee *et al.*, 2002; Mihara *et al.*, 2002; van Bavel *et al.*, 2010).

Our genetic investigation suggests the possible contribution of the XRCC1 399 Gln variant to SLE development and to either a malar rash or phototosensitivity manifestations. However, our genetic studies did not reach a power of 80%, due to a small sample size. Therefore, to reinforce the role of the XRCC1 399 Gln gene variant as a risk factor in SLE development and clinical manifestations of SLE, further studies of this polymorphism's distribution in other sample populations would be valuable.

Acknowledgments

This study was supported by grant no. 502-01-01124182-07474, Poznań University of Medical Sciences.

Disclosure Statement

No competing financial interests exist.

References

- Abdel-Rahman, S., Soliman, A.S., Bondy, M.L., Omar, S., El-Badawy, S.A., Khaled, H.M., Seifeldin, I.A., and Levin, B. (2000). Inheritance of the 194Trp and the 399Gln variant alleles of the DNA repair gene XRCC1 are associated with increased risk of early-onset colorectal carcinoma in Egypt. *Cancer Lett* **159**, 79–86.
- Abdel-Rahman, S.Z., and El-Zein, R.A. (2000). 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* **159**, 63–71.
- Bashir, S., Harris, G., Denman, M.A., Blake, D.R., and Winyard, P.G. (1993). Oxidative DNA damage and cellular sensitivity to oxidative stress in human autoimmune diseases. *Ann Rheum Dis* **52**, 659–666.
- Bassi, C., Xavier, D.J., Palomino, G., Nicolucci, P., Soares, C., Sakamoto-Hojo, E., and Donadi, E. (2008). Efficiency of the DNA repair and polymorphisms of the XRCC1, XRCC3 and XRCC4 DNA repair genes in systemic lupus erythematosus. *Lupus* **17**, 988–995.
- Batar, B., Guven, M., Onaran, I., Tutluoglu, B., and Kanigur-Sultuybek, G. (2010). DNA repair gene XRCC1 polymorphisms and the risk of asthma in a Turkish population. *Allergy Asthma Proc* **31**, 349–354.
- Bazo, A.P., Salvadori, D., Jr., Salvadori, R.A., Sodré, L.P., da Silva, G.N., de Camargo, E.A., Ribeiro, L.R., and Salvadori, D.M. (2011). DNA repair gene polymorphism is associated with the genetic basis of atherosclerotic coronary artery disease. *Cardiovasc Pathol* **20**, e9–e15.
- Benke, P.J., and Belmar, P. (1991). Phytohemagglutinin-stimulated lymphocytes from patients with systemic lupus erythematosus demonstrate DNA damage. *Metabolism* **40**, 1037–1042.
- Beyer, T.D., Kolowos, W., Dumitriu, I.E., Voll, R.E., Heyder, P., Gaip, U.S., Kalden, J.R., and Herrmann, M. (2002). Apoptosis of the teratocarcinoma cell line Tera-1 leads to the cleavage of HERV-K10gag proteins by caspases and/or granzyme B. *Scand J Immunol* **56**, 303–309.
- Bombardier, C., Gladman, D.D., Urowitz, M.B., Caron, D., and Chang, C.H. (1992). Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* **35**, 630–640.
- Chen, L., Ambrosone, C.B., Lee, J., Sellers, T.A., Pow-Sang, J., and Park, J.Y. (2006). Association between polymorphisms in the DNA repair genes XRCC1 and APE1, and the risk of prostate cancer in white and black Americans. *J Urol* **175**, 108–112; discussion 112.
- Chiang, C.C., Tsai, Y.Y., Bau, D.T., Cheng, Y.W., Tseng, S.H., Wang, R.F., and Tsai, F.J. (2010). Pterygium and genetic polymorphisms of the DNA repair enzymes XRCC1, XPA, and XPD. *Mol Vis* **16**, 698–704.
- Crispin, J.C., Kyttaris, V.C., Terhorst, C., and Tsokos, G.C. (2010). T cells as therapeutic targets in SLE. *Nat Rev Rheumatol* **6**, 317–325.
- Cucherat, M., Boissel, J.P., Leizorovicz, A., and Haugh, M.C. (1997). EasyMA: a program for the meta-analysis of clinical trials. *Comput Methods Programs Biomed* **53**, 187–190.
- Divine K.K., Gilliland F.D., Crowell R.E., Stidley C.A., Bocklage, T.J., Cook D.L. and Belinsky, S.A. (2001). The XRCC1 399 glutamine allele is a risk factor for adenocarcinoma of the lung. *Mutat Res* **461**, 273–278.
- Duarte, M.C., Colombo, J., Rossit, A.R., Caetano, A., Borim, A.A., Wornath, D., and Silva, A.E., (2005). Polymorphisms of DNA repair genes XRCC1 and XRCC3, interaction with environmental exposure and risk of chronic gastritis and gastric cancer. *World J Gastroenterol* **11**, 6593–6600.
- Flesher, D.L., Sun, X., Behrens, T.W., Graham, R.R., and Criswell, L.A. (2010). Recent advances in the genetics of systemic lupus erythematosus. *Expert Rev Clin Immunol* **6**, 461–479.

- Godderis, L., De Boeck, M., Haufrond, V., Emmery, M., Mateuca, R., Gardinal, S., Kirsch-Volders, M., Veulemans, H., and Lison, D. (2004). Influence of genetic polymorphisms on biomarkers of exposure and genotoxic effects in styrene-exposed workers. *Environ Mol Mutagen* **44**, 293–303.
- Gröndal, G., Gunnarsson, I., Rönnelid, J., Rogberg, S., Klareskog, L., and Lundberg, I. (2000). Cytokine production, serum levels and disease activity in systemic lupus erythematosus. *Clin Exp Rheumatol* **18**, 565–570.
- Herrick, A.L., Rafferty, J.A., and Margison, G.P. (1995). DNA repair deficiency in systemic lupus erythematosus; cause or consequence of disease and implications for management. *Lupus* **4**, 423–424.
- Hochberg, M.C. (1997). Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* **40**, 1725.
- Hom, G., Graham, R.R., Modrek, B., Taylor, K.E., Ortmann, W., Garnier, S., Lee, A.T., Chung, S.A., Ferreira, R.C., Pant, P.V., Ballinger, D.G., Kosoy, R., Demirci, F.Y., Kamboh, M.I., Kao, A.H., Tian, C., Gunnarsson, I., Bengtsson, A.A., Rantapää-Dahlqvist, S., Petri, M., Manzi, S., Seldin, M.F., Rönnblom, L., Syvänen, A.C., Criswell, L.A., Gregersen, P.K., and Behrens, T.W. (2008). Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. *N Engl J Med* **358**, 900–909.
- Hong, Y.C., Lee, K.H., Kim, W.C., Choi, S.K., Woo, Z.H., Shin, S.K., and Kim, H. (2005). Polymorphisms of XRCC1 gene, alcohol consumption and colorectal cancer. *Int J Cancer* **116**, 428–432.
- Jönsen, A., Bengtsson, A.A., Nived, O., Truedsson, L., and Sturfelt, G. (2007). Gene-environment interactions in the aetiology of systemic lupus erythematosus. *Autoimmunity* **40**, 613–617.
- Lee, K.J., Dong, X., Wang, J., Takeda, Y., and Dynan, W.S. (2002). Identification of human autoantibodies to the DNA ligase IV/XRCC4 complex and mapping of an autoimmune epitope to a potential regulatory region. *J Immunol* **169**, 3413–3421.
- Li, Y., Long, C., Lin, G., Marion, M.J., Freyer, G., Santella, R.M., and Brandt-Rauf, P.W. (2009). Effect of the XRCC1 codon 399 polymorphism on the repair of vinyl chloride metabolite-induced DNA damage. *J Carcinog* **8**, 14.
- Lin, Y.J., Wan, L., Huang, C.M., Chen, S.Y., Huang, Y.C., Lai, C.H., Lin, W.Y., Liu, H.P., Wu, Y.S., Chen, C.M., Tsai, Y.H., Tsai, C.H., Sheu, J.J., and Tsai, F.J. (2009). Polymorphisms in the DNA repair gene XRCC1 and associations with systemic lupus erythematosus risk in the Taiwanese Han Chinese population. *Lupus* **18**, 1246–1251.
- Lindahl, T., and Wood, R.D. (1999). Quality control by DNA repair. *Science* **286**, 1897–1905.
- Lunn, R.M., Langlois, R.G., Hsieh, L.L., Thompson, C.L., and Bell, D.A. (1999). XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. *Cancer Res* **59**, 2557–2561.
- McConnell, J.R., Crockard, A.D., Cairns, A.P., and Bell, A.L. (2002). Neutrophils from systemic lupus erythematosus patients demonstrate increased nuclear DNA damage. *Clin Exp Rheumatol* **20**, 653–660.
- McCurdy, D., Tai, L.Q., Frias, S., and Wang, Z. (1997). Delayed repair of DNA damage by ionizing radiation in cells from patients with juvenile systemic lupus erythematosus and rheumatoid arthritis. *Radiat Res* **147**, 48–54.
- Mihara, S., Suzuki, N., Takeba, Y., Soejima, K., and Yamamoto, S. (2002). Combination of molecular mimicry and aberrant autoantigen expression is important for development of anti-Fas ligand autoantibodies in patients with systemic lupus erythematosus. *Clin Exp Immunol* **129**, 359–369.
- Mok, C.C., and Lau, C.S. (2003). Pathogenesis of systemic lupus erythematosus. *J Clin Pathol* **56**, 481–490.
- Monaco, R., Rosal, R., Dolan, M.A., Pincus, M.R., Brandt-Rauf, P.W. (2007). Conformational effects of a common codon 399 polymorphism on the BRCT1 domain of the XRCC1 protein. *Protein J* **26**, 541–546.
- Pirner, K., Rubbert, A., Salinger, R., Kalden, J.R., and Manger, B. (1992). Significance of ultraviolet light in the pathogenesis of systemic lupus erythematosus: case report and discussion of the literature. *Z. Rheumatol* **51**, 20–24.
- Rastogi, R.P., Richa, Kumar, A., Tyagi, M.B., and Sinha, R.P. (2010). Molecular mechanisms of ultraviolet radiation-induced DNA damage and repair. *J Nucleic Acids* **2010**, 592980.
- Saadat, M., Pakyari, N., and Farrashbandi, H. (2008). Genetic polymorphism in the DNA repair gene XRCC1 and susceptibility to schizophrenia. *Psychiatry Res* **157**, 241–245.
- Sarzi-Puttini, P., Atzeni, F., Iaccarino, L., and Doria, A. (2005). Environment and systemic lupus erythematosus: an overview. *Autoimmunity* **38**, 465–472.
- Schreiber, V., Amé, J.C., Dollé, P., Schultz, I., Rinaldi, B., Fraulob, V., Ménissier-de Murcia, J., and de Murcia, G. (2002). Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1. *J Biol Chem* **277**, 23028–23036.
- Sekigawa, I., Naito, T., Hira, K., Mitsuishi, K., Ogasawara, H., Hashimoto, H., and Ogawa, H. (2004). Possible mechanisms of gender bias in SLE: a new hypothesis involving a comparison of SLE with atopy. *Lupus* **13**, 217–222.
- Silva, S.N., Moita, R., Azevedo, A.P., Gouveia, R., Manita, I., Pina, J.E., Rueff, J., and Gaspar, J. (2007). Menopausal age and XRCC1 gene polymorphisms: role in breast cancer risk. *Cancer Detect Prev* **31**, 303–309.
- Stohl, W., Metyas, S., Tan, S.M., Cheema, G.S., Oamar, B., Xu, D., Roschke, V., Wu, Y., Baker, K.P., and Hilbert, D.M. (2003). B lymphocyte stimulator overexpression in patients with systemic lupus erythematosus: longitudinal observations. *Arthritis Rheum* **48**, 3475–3486.
- Sturgis, E.M., Castilli, E.J., Li, L., Zheng, R., Eicher, S.A., Clayman, G.L., Strom, S.S., Spitz, M.R., and Wei, Q. (1999). Polymorphisms of DNA repair gene XRCC1 in squamous cell carcinoma of the head and the neck. *Carcinogenesis* **20**, 2125–2129.
- Sutandyo, N. (2010). Nutritional carcinogenesis. *Acta Med Indones* **42**, 36–42.
- Tajouri, L., Mellick, A.S., Ashton, K.J., Tannenber, A.E., Nagra, R.M., Tourtellotte, W.W., and Griffiths, L.R. (2003). Quantitative and qualitative changes in gene expression patterns characterize the activity of plaques in multiple sclerosis. *Brain Res Mol Brain Res* **119**, 170–183.
- Takeda, Y., and Dynan, W.S. (2001). Autoantibodies against DNA double-strand break repair proteins. *Front Biosci* **6**, D1412–D1422.
- Tan, E.M., Cohen, A.S., Fries, J.F., Masi, A.T., McShane, D.J., Rothfield, N.F., Schaller, J.G., Talal, N., and Winchester, R.J. (1982). The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* **25**, 1271–1277.
- Thacker, J., and Zdzienicka, M.Z. (2004). The XRCC genes: expanding roles in DNA double-strand break repair. *DNA Repair (Amst)* **3**, 1081–1090.
- Thompson, L.H., and West, M.G. (2000). XRCC1 keeps DNA from getting stranded. *Mutat Res* **459**, 1–18.
- Tudek, B. (2007). Base excision repair modulation as a risk factor for human cancers. *Mol Aspects Med* **28**, 258–275.

- Tumer, T.B., Yilmaz, D., Tanrikut, C., Sahin, G., Ulusoy, G., and Arinç, E. (2010). DNA repair XRCC1 Arg399Gln polymorphism alone, and in combination with CYP2E1 polymorphisms significantly contribute to the risk of development of childhood acute lymphoblastic leukemia. *Leuk Res* **34**, 1275–1281.
- van Bavel, C.C., Dieker, J.W., Tamboer, W.P., van der Vlag, J., and Berden, J.H. (2010). Lupus-derived monoclonal auto-antibodies against apoptotic chromatin recognize acetylated conformational epitopes. *Mol Immunol* **48**, 248–256.
- Vidal, A.E., Boiteux, S., Hickson, I.D., and Radicella, J.P. (2001). XRCC1 coordinates the initial and late stages of DNA abasic site repair through protein-protein interactions. *EMBO J* **20**, 6530–6539.
- Wang, Q., Wang, A.H., Tan, H.S., Feng, N.N., Ye, Y.J., Feng, X.Q., Liu, G., Zheng, Y.X., and Xia, Z.L. (2010). Genetic polymorphisms of DNA repair genes and chromosomal damage in workers exposed to 1,3-butadiene. *Carcinogenesis* **31**, 858–863.
- Weng, H., Weng, Z., Lu, Y., Nakayama, K., and Morimoto, K. (2009). Effects of cigarette smoking, XRCC1 genetic polymorphisms, and age on basal DNA damage in human blood mononuclear cells. *Mutat Res* **679**, 59–64.
- Wong, M., and Tsao, B.P. (2006). Current topics in human SLE genetics. *Springer Semin Immunopathol* **28**, 97–107.

Address correspondence to:

Paweł P. Jagodziński, Ph.D.

Department of Biochemistry and Molecular Biology

Poznań University of Medical Sciences

6 Święcickiego St.

60-781 Poznań

Poland

E-mail: pjagodzi@am.poznan.pl

Received for publication February 7, 2011; received in revised form May 12, 2011; accepted May 12, 2011.