

Article

## Polymorphisms in DNA Repair Genes (*APEX1*, *XPB*, *XRCC1* and *XRCC3*) and Risk of Preeclampsia in a Mexican Mestizo Population

Ada Sandoval-Carrillo <sup>1</sup>, Edna M. Méndez-Hernández <sup>2</sup>, Fernando Vazquez-Alaniz <sup>3</sup>,  
Marisela Aguilar-Durán <sup>1</sup>, Alfredo Téllez-Valencia <sup>2</sup>, Marcelo Barraza-Salas <sup>2</sup>,  
Francisco X. Castellanos-Juárez <sup>1</sup>, Osmel La Llave-León <sup>1</sup> and José M. Salas-Pacheco <sup>1,\*</sup>

<sup>1</sup> Institute for Scientific Research, Juarez University of Durango State, 34000 Durango, México;  
E-Mails: adda-sandoval@hotmail.com (A.S.-C.); aguilar\_duran\_marisela@hotmail.com (M.A.-D.);  
xavier\_castellanos@hotmail.com (F.X.C.-J.); ollave56@yahoo.es (O.L.L.-L.)

<sup>2</sup> Faculty of Medicine and Nutrition, Juarez University of Durango State, 34000 Durango, México;  
E-Mails: edna\_madai@hotmail.com (E.M.M.-H.); tellezalfredo@gmail.com (A.T.-V.);  
sbmaj30@hotmail.com (M.B.-S.)

<sup>3</sup> General Hospital of Durango, Secretary of Health, Durango, 34000 Durango, México;  
E-Mail: feralaniz1@hotmail.com

\* Author to whom correspondence should be addressed; E-Mail: jsalas\_pacheco@hotmail.com;  
Tel.: +52-618-8122921; Fax: +52-618-8116226.

Received: 21 January 2014; in revised form: 17 February 2014 / Accepted: 4 March 2014 /  
Published: 11 March 2014

---

**Abstract:** Variations in genes involved in DNA repair systems have been proposed as risk factors for the development of preeclampsia (PE). We conducted a case-control study to investigate the association of Human apurinic/apyrimidinic (AP) endonuclease (*APEX1*) Asp148Glu (rs1130409), Xeroderma Pigmentosum group D (*XPB*) Lys751Gln (rs13181), X-ray repair cross-complementing group 1 (*XRCC1*) Arg399Gln (rs25487) and X-ray repair cross-complementing group 3 (*XRCC3*) Thr241Met (rs861539) polymorphisms with PE in a Mexican population. Samples of 202 cases and 350 controls were genotyped using RTPCR. Association analyses based on a  $\chi^2$  test and binary logistic regression were performed to determine the odds ratio (OR) and a 95% confidence interval (95% CI) for each polymorphism. The allelic frequencies of *APEX1* Asp148Glu polymorphism showed statistical significant differences between preeclamptic and normal women ( $p = 0.036$ ). Although neither of the polymorphisms proved to be a risk factor for the disease, the *APEX1* Asp148Glu polymorphism showed a tendency of association (OR: 1.74,

95% CI = 0.96–3.14) and a significant trend ( $p$  for trend = 0.048). A subgroup analyses revealed differences in the allelic frequencies of *APEX1* Asp148Glu polymorphism between women with mild preeclampsia and severe preeclampsia ( $p$  = 0.035). In conclusion, our results reveal no association between *XPB* Lys751Gln, *XRCC1* Arg399Gln and *XRCC3* Thr241Met polymorphisms and the risk of PE in a Mexican mestizo population; however, the results in the *APEX1* Asp148Glu polymorphism suggest the need for future studies using a larger sample size.

**Keywords:** preeclampsia; polymorphisms; *APEX1*; *XPB*; *XRCC1*; *XRCC3*

---

## 1. Introduction

Preeclampsia (PE) is a hypertensive multisystemic disorder unique to humans, affecting approximately 10% of all pregnancies with a slightly higher incidence in developing countries. It is a major cause of maternal death and is responsible for high rates of fetal morbidity and mortality [1]. PE is characterized by *de novo* hypertension (two blood pressure measurements  $\geq 140/90$  mm Hg) and proteinuria ( $>300$  mg/24 h) that develops after 20 weeks of gestation in a formerly normotensive woman [2]. The pathophysiology is characterized by abnormal vascular response to placentation that is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system, and endothelial cell dysfunction [3].

Increasing evidence suggests that oxidative stress plays an important role in the pathogenesis of PE [4,5]. In healthy pregnancies, a balance is maintained between lipid peroxides and anti-oxidative processes. In contrast, PE pregnancies are characterized by an imbalance in these processes leading to an increase in oxidative stress [6–8]. Oxygen concentrations at the fetal-maternal interface fluctuate during pregnancy as a consequence of the vascular remodeling within the tissues of the uterus [9]. Infection/inflammation, intense tissue remodeling, and changes in vascular perfusion generate reactive oxygen species (ROS)—including  $O_2^-$ , hydroxyl radical, and hydrogen peroxide ( $H_2O_2$ )—all of which are capable of damaging nucleic acids, proteins, and lipids if levels of these ROS overwhelm the intracellular anti-oxidative defenses [10].

Most damaged DNA can be removed and recovered through pathways carried by DNA repairing enzymes. The normal function of these enzymes is, therefore, important for the maintenance of genomic integrity [11]. A variety of DNA repair processes such as base excision repair (BER), nucleotide excision repair (NER) and mismatch and double-strand break repairs have evolved to perform critical repair functions. DNA repair deficiency has been linked to mutations in some genes that result in a complete loss of DNA repair protein function, whereas more subtle differences in repair capacity occur through the inheritance of polymorphisms within genes [12]. Various DNA repair genes carry genetic polymorphisms with potential to modulate gene function and alter DNA repair capacity [13].

Human apurinic/aprimidinic (AP) endonuclease (*APEX1*) gene is located at chromosome 14q11.2 and codifies one of the main enzymes in BER pathway, which accounts for nearly all of the abasic site cleavage activity observed in cellular extracts [14]. *APEX1* cleaves the phosphodiester backbone

immediately at the 5' of abasic site, via hydrolytic mechanism, in order to generate a single strand DNA break leaving a 3'-hydroxyl and 5'-deoxyribose phosphate terminus [15]. The *APEX1* Asp148Glu (rs1130409) polymorphism have been reported to have higher sensitivity to ionizing radiation [16], and some authors describe the association of the allele G with prostate cancer [17,18].

The excision repair cross-complementing rodent repair deficiency, group 2 (*ERCC2*) gene, also called the xeroderma pigmentosum group D (*XPD*) gene, is located at chromosome 19q13.3. The *XPD* protein is essential in the NER pathway. This enzyme has a dual role: (i) uncoiling the double helix at the site of DNA lesions and (ii) transcription [19]. Recently, several studies have shown that variant alleles of polymorphism for *XPD* Lys751Gln (rs13181) has been associated with increased DNA adduct levels [20–22] and with reduced capacity to DNA repair [23] and with cancer risk [24–26].

The X-ray repair cross-complementing group 1 (*XRCC1*) gene is located at 19q13.2 and produce multidomain protein that acts as a scaffolding intermediate by interacting with Ligase III, DNA polymerase- $\beta$  and poly-ADP-ribose polymerase (PARP) [27,28]. *XRCC1* protein plays a crucial role in the coordination of two overlapping repair pathways, BER and single strand break repair (SSBR) [29]. Substitutions of Arg194Trp and Arg399Gln (rs25487) may alter the function of the *XRCC1* protein [30,31].

The X-ray repair cross-complementing group 3 (*XRCC3*) gene is located at chromosome 19q13.3 and is a member of the RecA/Rad51-related protein complex responsible for the homologous recombinational repair (HRR) of double-strand DNA and is necessary for the stability of the genome [32–34]. The C > T transition is the most often occurring polymorphism in the *XRCC3* gene at codon 241, causing an amino acid change (Thr to Met, rs861539) [35]. Carriers of the Met allele showed a relatively high DNA adduct level in lymphocytes, which could be associated with reduced DNA repair capacity [21,36].

At date, very few studies analyze the possible association between this polymorphisms and risk of preeclampsia [37,38]. In the present study we aimed to investigate the association between *APEX1* Asp148Glu, *XPD* Lys751Gln, *XRCC1* Arg399Gln and *XRCC3* Thr241Met polymorphisms and the risk of preeclampsia in a Mexican population.

## 2. Results and Discussion

### 2.1. Results

A total of 202 cases and 350 controls were included in this study. Of 202 cases, 32 (15.84%), 142 (70.29%) and 28 (13.86%) presented mild PE, severe PE and eclampsia, respectively. Table 1 shows the clinical characteristics. As expected, a difference in pathognomonic variables was observed. Furthermore, we found differences between groups at weeks of pregnancy ( $p < 0.001$ , Table 1).

**Table 1.** Clinical characteristics of preeclamptic (cases) and healthy pregnant women (controls).

Clinical features	Cases, <i>n</i> = 202	Controls, <i>n</i> = 350	<i>p</i> -value
Age (years) <sup>a</sup>	24.53 (7.70)	23.57 (6.57)	0.108 <sup>b</sup>
Weeks of pregnancy <sup>a</sup>	35.92 (4.75)	37.97 (3.82)	<0.001 <sup>b</sup>
Number of pregnancies <sup>a</sup>	2.38 (2.20)	2.24 (1.44)	0.353 <sup>b</sup>
Systolic blood pressure (mm Hg) <sup>a</sup>	157.96 (18.71)	109.26 (10.27)	<0.001 <sup>b</sup>
Diastolic blood pressure (mm Hg) <sup>a</sup>	102.75 (13.19)	68.82 (8.98)	<0.001 <sup>b</sup>
Mean arterial pressure (mm Hg) <sup>a</sup>	121.17 (13.34)	82.18 (8.50)	<0.001 <sup>b</sup>

<sup>a</sup> Media ( $\pm$  Standard deviation); <sup>b</sup> Independent sample *T* test.

**Table 2.** Allele and genotype frequencies of *APEXI* Asp148Glu, *XPB* Lys751Gln, *XRCC1* Arg399Gln and *XRCC3* Thr241Met polymorphisms in preeclamptic (cases), healthy pregnant women (controls) and mild and severe preeclamptic women subgroups.

Polymorphisms	Cases, <i>n</i> = 202	Controls, <i>n</i> = 350	<i>p</i> -value	Mild PE, <i>n</i> (%)	Severe PE, <i>n</i> (%)	<i>p</i> -value
<i>APEX1</i> Asp148Glu *						
Asp	0.61	0.68	0.036 <sup>a</sup>	44 (70.96)	158 (56.42)	0.035 <sup>a,b</sup>
Glu	0.39	0.32		18 (29.03)	122 (43.57)	
Asp/Asp	0.40	0.49	0.143 <sup>a</sup>	16 (51.61)	49 (35)	0.140 <sup>a,b</sup>
Asp/Glu	0.41	0.38		12 (38.7)	60 (42.85)	
Glu/Glu	0.19	0.13		3 (9.67)	31 (22.14)	
<i>XPB</i> Lys751Gln						
Lys	0.79	0.80	0.662 <sup>a</sup>	51 (82.25)	222 (78.16)	0.475 <sup>a,b</sup>
Gln	0.21	0.20		11 (17.74)	62 (21.83)	
Lys/Lys	0.61	0.63	0.900 <sup>a</sup>	22 (70.96)	85 (59.85)	0.284 <sup>a,b</sup>
Lys/Gln	0.35	0.34		7 (22.58)	52 (36.61)	
Gln/Gln	0.04	0.03		2 (6.45)	5 (3.52)	
<i>XRCC1</i> Arg399Gln						
Arg	0.75	0.74	0.514 <sup>a</sup>	48 (75)	212(75.17)	0.976 <sup>a,b</sup>
Gln	0.25	0.26		16 (25)	70 (24.82)	
Arg/Arg	0.58	0.56	0.816 <sup>a</sup>	17 (53.12)	83 (58.86)	0.352 <sup>a,b</sup>
Arg/Gln	0.34	0.36		14 (43.75)	46 (32.62)	
Gln/Gln	0.07	0.08		1 (3.12)	12 (8.51)	
<i>XRCC3</i> Thr241Met						
Thr	0.86	0.83	0.211 <sup>a</sup>	57 (89.06)	231 (84.92)	0.395 <sup>a,b</sup>
Met	0.14	0.17		7 (10.93)	41 (15.07)	
Thr/Thr	0.73	0.67	0.276 <sup>a</sup>	26 (81.25)	97 (71.32)	0.344 <sup>a,b</sup>
Thr/Met	0.24	0.31		5 (15.62)	37 (27.2)	
Met/Met	0.02	0.02		1 (3.12)	2 (1.47)	

<sup>a</sup> Pearson's *Chi-squared* is significant at  $p \leq 0.05$ ; <sup>b</sup> The test was performed between mild PE and severe PE groups;

\* The control group for this polymorphism was integrated by 204 women.

Allelic and genotypic frequencies of *APEXI* Asp148Glu, *XPB* Lys751Gln, *XRCC1* Arg399Gln and *XRCC3* Thr241Met polymorphisms are shown in Table 2. All polymorphisms were in HWE. The variant allele frequencies of *APEXI* Asp148Glu, *XPB* Lys751Gln and *XRCC3* polymorphisms in our

control group were consistent with our previous studies [39]. The allelic frequencies of *APEXI* Asp148Glu showed statistical significant differences between groups ( $p = 0.036$ ). However, these differences were not observed in the genotypic frequencies ( $p = 0.143$ ). No differences in allelic or genotypic frequencies between cases and controls were observed in any of the others polymorphisms tested (Table 2,  $p > 0.05$ ).

A subgroup analyses (mild and severe preeclampsia) revealed no differences in genotypic frequencies of *APEXI* Asp148Glu, *XPB* Lys751Gln, *XRCC1* Arg399Gln and *XRCC3* Thr241Met polymorphisms between women with severe preeclampsia and mild preeclampsia (Table 2). Regarding allelic frequencies, only statistical significant differences between mild PE and severe PE in the *APEXI* Asp148Glu polymorphism were found ( $p = 0.035$ , Table 2). Additionally, the mild and severe PE groups were tested against their respective control groups, however, statistically significant differences were not found (data no shown).

The risk of preeclampsia by the presence of these polymorphisms was determined. A logistic regression model adjusted for age was used and the results of Table 3 showed that any of the polymorphisms are a risk factor for the disease; however, the *APEXI* Asp148Glu polymorphism showed a tendency of association (OR: 1.74, 95% CI = 0.96–3.14). Furthermore, a significant trend was observed ( $p$  for trend = 0.048).

**Table 3.** Polymorphisms association with preeclampsia.

Polymorphisms	Cases, <i>n</i>	Controls, <i>n</i>	OR	95% CI	<i>p</i> -value
<i>APEXI</i> Asp148Glu					
Asp/Asp	80	98	1.00	(referent)	
Asp/Glu	82	77	1.26	0.84–1.97	0.166
Glu/Glu	37	26	1.74	0.96–3.14	
<i>p</i> value for trend					0.048
<i>XPB</i> Lys751Gln					
Lys/Lys	123	220	1.00	(referent)	
Lys/Gln	70	118	1.11	0.72–1.707	0.868
Gln/Gln	8	12	1.15	0.413–3.227	
<i>p</i> value for trend					0.655
<i>XRCC1</i> Arg399Gln					
Arg/Arg	118	195	1.00	(referent)	
Arg/Gln	69	126	0.939	0.608–1.45	0.854
Gln/Gln	15	29	0.818	0.393–1.70	
<i>p</i> value for trend					0.528
<i>XRCC3</i> Thr241Met					
Thr/Thr	144	235	1.00	(referent)	
Thr/Met	48	108	0.76	0.487–1.195	0.211
Met/Met	4	6	4.047	0.443–36.972	
<i>p</i> value for trend					0.197

Abbreviations: CI, confidence interval; OR, odds ratio.

## 2.2. Discussion

One of the main features of preeclampsia is an inadequate trophoblast cell invasion that leads to an incomplete remodeling of the spiral artery, reduction in utero-placental perfusion, and a state of placental ischemia. A factor known to be increased in response to placental ischemia is the production of ROS. When ROS production exceeds the capacity of detoxification, they can cause oxidative damage to DNA [29]. The biological importance of oxidative DNA damage remains to be determined, but it is reasonable to suggest that such DNA damage could affect the transcriptional regulation of placental genes involved in implantation and placentation and/or cell fate decisions (apoptosis), thereby contributing to the pathogenesis of PE. Recently, Tadesse *et al.* [40] demonstrated that oxidative stress-induced DNA damage and repair is present in higher amounts in the placentas of women with PE vs. gestational age matched normotensive controls.

DNA repair mechanisms are in place to protect against such damage and imply a role for DNA repair genes in the response of the placenta to ischemia. Oxidative DNA damage is repaired by both BER and NER mechanisms [41]. Therefore, genetic polymorphism in BER and NER genes may influence individual variations in DNA repair capacity, which may be associated with risk of developing PE.

The majority of work has focused on evaluate genes involved in antioxidant defense systems rather than DNA repair systems. While some studies suggest the association between polymorphisms of genes involved in antioxidant systems and preeclampsia [42], others have found no association [43]. Specifically, in a Mexican population, data from our laboratory suggest that a *GSTT1* null polymorphism might be associated with preeclampsia and that this risk increases with the combination of both *GSTT1* and *GSTM1* null polymorphisms [44].

On the other hand, to date, very few studies evaluate the relationship between polymorphisms in DNA repair genes and the risk of PE. Vural *et al.* [38] evaluate polymorphisms in *APEX1*, *XRCC1* and *XPB* in a Turkish population. Although they report that none of the studied polymorphisms has been associated with the risk of PE, they suggest that their results need to be taken as preliminaries due to relatively small sample size. Furthermore, Saadat *et al.* [37] investigate the association between the genetic polymorphisms of *XRCC1* and *XRCC7* and risk of PE in an Iranian population. They analyze 151 patients with preeclampsia and their results suggest that the 399Gln allele of the *XRCC1* is a significant risk factor for PE development.

In this study, we analyze the relation between *APEX1* Asp148Glu, *XPB* Lys751Gln, *XRCC1* Arg399Gln and *XRCC3* Thr241Met polymorphisms and the risk of PE in a Mexican population. Although our results showed no association between *APEX1* Asp148Glu and PE like previously reported by Vural *et al.* [38], our data showed a tendency of association (OR: 1.74, 95% CI = 0.96–3.14) and a significant trend ( $p$  for trend = 0.048). These results, together with the statistical significant difference observed in the allelic frequency of this polymorphism between women with mild preeclampsia and severe preeclampsia ( $p$  = 0.035), suggest a need for future studies with a larger sample to elucidate the role of this polymorphism in the PE in our population.

Our results in the other polymorphisms suggest no association with the risk of the PE. These results are in disagreement with Saadat *et al.* [37], but are in agreement with the reported by Vural *et al.* [38], in the *XRCC1* Arg399Gln polymorphism. With respect to the *XPB* Lys751Gln polymorphism our

results are in agreement with Vural *et al.* [38]. Finally, to our understanding any studies has analyzed the association between the *XRCC3* Thr241Met polymorphism and the risk to PE; the results of this study are the first to suggest no association.

The limitations of our study include the lack of oxidative damage measurements in blood samples or placenta that might suggest a possible association between the levels of DNA damage, the genotypes analyzed and PE. Furthermore, our study had limited statistical power because of the low frequency of some of the variants genotypes.

### 3. Experimental Section

#### 3.1. Subjects and Study Design

This case-control study was conducted between March 2011 and September 2013. The study was approved by the Ethics Investigation Committee in the Hospital General of the Health Secretary of Durango, Mexico, in accordance with the Code of Ethics of the Declaration of Helsinki. Signed informed consent was obtained from all patients and controls before participation in the study. We recruited 202 women diagnosed with preeclampsia (cases) and 350 normoevolutive pregnant women (controls). The inclusion criteria were all those women diagnosed with mild PE (blood pressure (BP)  $\geq 140/90$  mm Hg and proteinuria  $\geq 30$  mg/dL), severe PE (BP  $\geq 160/110$  mm Hg and proteinuria  $\geq 2000$  mg/dL) and eclampsia (defined as occurrence, in a woman with preeclampsia, of seizures that cannot be attributed to other causes). Control group was conformed by healthy pregnant women attending at the same hospital; without hypertensive, pathological or metabolic disorders during pregnancy. The control group was followed to corroborate the normality of the blood pressure values.

#### 3.2. DNA Extraction and Genotyping of Samples

Genomic DNA from each individual was obtained from blood samples obtained by venous puncture using the QIAamp DNA Blood extraction kit (Qiagen, Hilden, Germany). The concentration and quality were analyzed in a NanoDrop 2000 (Thermo Scientific, Wilmington, DE, USA). The single nucleotide polymorphisms were analyzed using a 48-well plate StepOne Real Time PCR system (Applied Biosystems, Carlsbad, CA, USA). A typical RT-PCR reaction contained 10 ng of genomic DNA, 0.625  $\mu$ L of 40X Taqman SNP genotyping assay and 5.0  $\mu$ L of Taqman genotyping Master Mix (Applied Biosystems, Foster City, CA, USA). The predesigned assays were C\_\_\_8921503\_10, C\_\_\_3145033\_10, C\_\_\_622564\_10 and C\_\_\_8901525\_10 (rs1130409, rs13181, rs25487 and rs861539, respectively; Applied Biosystems, Foster City, CA, USA). The amplification conditions were initial denaturation at 95 °C for 10 min, 92 °C during 15 s, and 60 °C for 90 s (42 cycles) with one additional cycle at 60 °C during 30 s. Samples were processed by duplicate.

#### 3.3. Statistical Analysis

The clinical characteristics were expressed as mean and were compared by using the Student's *t*-test. The allele and genotype frequencies were calculated by direct counting. Deviation from the Hardy-Weinberg equilibrium (HWE) constant was tested using a  $\chi^2$  test with 1 degree of freedom. The differences of distributions of the polymorphisms were performed by  $\chi^2$  analysis using SPSS software

(version 15.0; SPSS Inc., Chicago, IL, USA);  $p < 0.05$  was considered statistically significant. Odds ratio was calculated from allelic and genotype frequencies with 95% confidence intervals (95% CI) using the SNPstats software program (2006, Catalan Institute of Oncology, Barcelona, Spain).

#### 4. Conclusions

Although our results suggest that there is no an association between *XPD* Lys751Gln, *XRCC* Arg399Gln and *XRCC3* Thr241Met polymorphisms and the risk of PE, the results in the *APEX1* Asp148Glu polymorphism suggest the needed of future studies using a larger sample size. Furthermore, studies in other regions from Mexico also are needed to confirm our findings. Silva-Zolezzi *et al.* [45] described genetic differences among Mexican Mestizos from different regions of Mexico, mainly due to differences in Amerindian and European contributions; samples from central regions were closer to Amerindian Zapotecos, while samples from northern regions were located closer to Europeans.

#### Acknowledgments

This work was supported by Grant 2011-01-161553 from CONACYT/México to Salas-Pacheco J.M. Sandoval-Carrillo A. was supported by doctoral fellowship from CONACYT. We thank Antuna-Salcido I., Chávez-Villa V., Drumond-López J. and López-Araujo L. for excellent technical assistance.

#### Conflicts of Interest

The authors declare no conflict of interest.

#### References

1. Aguilar-Duran, M.; Salvador-Moysén, J.; Galaviz-Hernandez, C.; Vázquez-Alaniz, F.; Sandoval-Carrillo, A.A.; Velázquez-Hernández, N.; Salas-Pacheco, J.M. Haplotype analysis of *TGF-β1* gene in a preeclamptic population of northern Mexico. *Pregnancy Hypertens.: Int. J. Women's Cardiovasc. Health* **2014**, *4*, 14–18.
2. *Technical Guidelines for Prevention, Diagnosis and Management of Preeclampsia/Eclampsia*; Secretary of Health, México Government: México DF, México, 2007.
3. Sibai, B.; Dekker, G.; Kupferminc, M. Pre-eclampsia. *Lancet* **2005**, *365*, 785–799.
4. Patil, S.B.; Kodliwadmth, M.V.; Kodliwadmth, M. Lipid peroxidation and antioxidant activity in complicated pregnancies. *Clin. Exp. Obstet. Gynecol.* **2009**, *36*, 110–112.
5. Siddiqui, I.A.; Jaleel, A.; Tamimi, W.; Al Kadri, H.M. Role of oxidative stress in the pathogenesis of preeclampsia. *Arch. Gynecol. Obstet.* **2010**, *282*, 469–474.
6. Wang, Y.; Walsh, S.W. Placental mitochondria as a source of oxidative stress in pre-eclampsia. *Placenta* **1998**, *19*, 581–586.
7. Kaur, G.; Mishra, S.; Sehgal, A.; Prasad, R. Alterations in lipid peroxidation and antioxidant status in pregnancy with preeclampsia. *Mol. Cell. Biochem.* **2008**, *313*, 37–44.
8. Poranen, A.K.; Ekblad, U.; Uotila, P.; Ahotupa, M. Lipid peroxidation and antioxidants in normal and pre-eclamptic pregnancies. *Placenta* **1996**, *17*, 401–405.



9. Brosens, J.J.; Parker, M.G.; McIndoe, A.; Pijnenborg, R.; Brosens, I.A. A role for menstruation in preconditioning the uterus for successful pregnancy. *Am. J. Obstet. Gynecol.* **2009**, *200*, 615 e1–615 e6.
10. Valko, M.; Leibfriz, D.; Moncol, J.; Cronin, M.T.; Mazur, M.; Telser, J. Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol.* **2007**, *39*, 44–84.
11. Hazra, T.K.; Das, A.; Das, S.; Choudhury, S.; Kow, Y.W.; Roy, R. Oxidative DNA damage repair in mammalian cells: A new perspective. *DNA Repair* **2007**, *6*, 470–480.
12. Shen, M.R.; Jones, I.M.; Mohrenweiser, H. Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. *Cancer Res.* **1998**, *58*, 604–608.
13. Xi, T.; Jones, I.M.; Mohrenweiser, H.W. Many amino acid substitution variants identified in DNA repair genes during human population screenings are predicted to impact protein function. *Genomics* **2004**, *83*, 970–979.
14. Chen, D.S.; Herman, T.; Demple, B. Two distinct human DNA diesterases that hydrolyze 3'-blocking deoxyribose fragments from oxidized DNA. *Nucleic Acids Res.* **1991**, *19*, 5907–5914.
15. Demple, B.; Harrison, L. Repair of oxidative damage to DNA: Enzymology and biology. *Annu. Rev. Biochem.* **1994**, *63*, 915–948.
16. Hu, J.J.; Smith, T.R.; Miller, M.S.; Mohrenweiser, H.W.; Golden, A.; Case, L.D. Amino acid substitution variants of APE1 and XRCC1 genes associated with ionizing radiation sensitivity. *Carcinogenesis* **2001**, *22*, 917–922.
17. Chen, L.; Ambrosone, C.B.; Lee, J.; Sellers, T.A.; Pow-Sang, J.; Park, J.Y. Association between polymorphisms in the DNA repair genes *XRCC1* and *APE1*, and the risk of prostate cancer in white and black Americans. *J. Urol.* **2006**, *175*, 108–112; discussion 112.
18. Kelley, M.R.; Cheng, L.; Foster, R.; Tritt, R.; Jiang, J.; Broshears, J.; Koch, M. Elevated and altered expression of the multifunctional DNA base excision repair and redox enzyme Ape1/ref-1 in prostate cancer. *Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res.* **2001**, *7*, 824–830.
19. Lehmann, A.R. The xeroderma pigmentosum group D (*XPD*) gene: One gene, two functions, three diseases. *Genes Dev.* **2001**, *15*, 15–23.
20. Hou, S.M.; Falt, S.; Angelini, S.; Yang, K.; Nyberg, F.; Lambert, B.; Hemminki, K. The XPD variant alleles are associated with increased aromatic DNA adduct level and lung cancer risk. *Carcinogenesis* **2002**, *23*, 599–603.
21. Matullo, G.; Palli, D.; Peluso, M.; Guarrera, S.; Carturan, S.; Celentano, E.; Krogh, V.; Munnia, A.; Tumino, R.; Polidoro, S.; *et al.* *XRCC1*, *XRCC3*, *XPD* gene polymorphisms, smoking and (32)P-DNA adducts in a sample of healthy subjects. *Carcinogenesis* **2001**, *22*, 1437–1445.
22. Palli, D.; Russo, A.; Masala, G.; Saieva, C.; Guarrera, S.; Carturan, S.; Munnia, A.; Matullo, G.; Peluso, M. DNA adduct levels and DNA repair polymorphisms in traffic-exposed workers and a general population sample. *Int. J. Cancer* **2001**, *94*, 121–127.
23. Spitz, M.R.; Wu, X.; Wang, Y.; Wang, L.E.; Shete, S.; Amos, C.I.; Guo, Z.; Lei, L.; Mohrenweiser, H.; Wei, Q. Modulation of nucleotide excision repair capacity by XPD polymorphisms in lung cancer patients. *Cancer Res.* **2001**, *61*, 1354–1357.
24. Wiencke, J.K. DNA adduct burden and tobacco carcinogenesis. *Oncogene* **2002**, *21*, 7376–7391.

25. Tang, D.; Cho, S.; Rundle, A.; Chen, S.; Phillips, D.; Zhou, J.; Hsu, Y.; Schnabel, F.; Estabrook, A.; Perera, F.P. Polymorphisms in the DNA repair enzyme XPD are associated with increased levels of PAH-DNA adducts in a case-control study of breast cancer. *Breast Cancer Res. Treat.* **2002**, *75*, 159–166.
26. Pastorelli, R.; Cerri, A.; Mezzetti, M.; Consonni, E.; Airoldi, L. Effect of DNA repair gene polymorphisms on BPDE-DNA adducts in human lymphocytes. *Int. J. Cancer* **2002**, *100*, 9–13.
27. Kubota, Y.; Nash, R.A.; Klungland, A.; Schar, P.; Barnes, D.E.; Lindahl, T. Reconstitution of DNA base excision-repair with purified human proteins: Interaction between DNA polymerase beta and the XRCC1 protein. *EMBO J.* **1996**, *15*, 6662–6670.
28. Thompson, L.H.; West, M.G. *XRCC1* keeps DNA from getting stranded. *Mutat. Res.* **2000**, *459*, 1–18.
29. Caldecott, K.W. *XRCC1* and DNA strand break repair. *DNA Repair* **2003**, *2*, 955–969.
30. Duell, E.J.; Wiencke, J.K.; Cheng, T.J.; Varkonyi, A.; Zuo, Z.F.; Ashok, T.D.; Mark, E.J.; Wain, J.C.; Christiani, D.C.; Kelsey, K.T. Polymorphisms in the DNA repair genes *XRCC1* and *ERCC2* and biomarkers of DNA damage in human blood mononuclear cells. *Carcinogenesis* **2000**, *21*, 965–971.
31. Relton, C.L.; Daniel, C.P.; Fisher, A.; Chase, D.S.; Burn, J.; Tawn, E.J. Polymorphisms of the DNA repair gene *XRCC1* and the frequency of somatic mutations at the glycophorin A locus in newborns. *Mutat. Res.* **2002**, *502*, 61–68.
32. Cui, X.; Brenneman, M.; Meyne, J.; Oshimura, M.; Goodwin, E.H.; Chen, D.J. The *XRCC2* and *XRCC3* repair genes are required for chromosome stability in mammalian cells. *Mutat. Res.* **1999**, *434*, 75–88.
33. Griffin, C.S.; Simpson, P.J.; Wilson, C.R.; Thacker, J. Mammalian recombination-repair genes *XRCC2* and *XRCC3* promote correct chromosome segregation. *Nat. Cell Biol.* **2000**, *2*, 757–761.
34. Brenneman, M.A.; Weiss, A.E.; Nickoloff, J.A.; Chen, D.J. *XRCC3* is required for efficient repair of chromosome breaks by homologous recombination. *Mutat. Res.* **2000**, *459*, 89–97.
35. Pramanik, S.; Devi, S.; Chowdhary, S.; Surendran, S.T.; Krishnamurthi, K.; Chakrabarti, T. DNA repair gene polymorphisms at *XRCC1*, *XRCC3*, *XPD*, and *OGG1* loci in Maharashtrian population of central India. *Chemosphere* **2011**, *82*, 941–946.
36. Matullo, G.; Guarrera, S.; Carturan, S.; Peluso, M.; Malaveille, C.; Davico, L.; Piazza, A.; Vineis, P. DNA repair gene polymorphisms, bulky DNA adducts in white blood cells and bladder cancer in a case-control study. *Int. J. Cancer* **2001**, *92*, 562–567.
37. Saadat, I.; Beyzaei, Z.; Aghaei, F.; Kamrani, S.; Saadat, M. Association between polymorphisms in DNA repair genes (*XRCC1* and *XRCC7*) and risk of preeclampsia. *Arch. Gynecol. Obstet.* **2012**, *286*, 1459–1462.
38. Vural, P.; Degirmencioglu, S.; Dogru-Abbasoglu, S.; Saral, N.Y.; Akgul, C.; Uysal, M. Genetic polymorphisms in DNA repair gene *APE1*, *XRCC1* and *XPD* and the risk of pre-eclampsia. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2009**, *146*, 160–164.
39. Vazquez-Alaniz, F.; Pedraza-Reyes, M.; Barraza-Salas, M.; Castellanos-Juarez, F.X.; Tellez-Valencia, A.; Sandoval-Carrillo, A.A.; Maravilla-Dominguez, M.A.; la Llave-Leon, O.; Salas-Pacheco, J.M. Genetic variation in oxidative stress and DNA repair genes in a Mexican population. *Ann. Hum. Biol.* **2013**, *40*, 355–359.

40. Tadesse, S.; Kidane, D.; Guller, S.; Luo, T.; Norwitz, N.G.; Arcuri, F.; Toti, P.; Norwitz, E.R. *In vivo* and *in vitro* evidence for placental DNA damage in preeclampsia. *PLoS One* **2014**, *9*, e86791.
41. Frosina, G. Overexpression of enzymes that repair endogenous damage to DNA. *Eur. J. Biochem.* **2000**, *267*, 2135–2149.
42. Sharma, D.; Trivedi, S.S.; Bhattacharjee, J. Oxidative stress and eNOS (Glu298Asp) gene polymorphism in preeclampsia in Indian population. *Mol. Cell. Biochem.* **2011**, *353*, 189–193.
43. Rosta, K.; Molvarec, A.; Enzsoly, A.; Nagy, B.; Ronai, Z.; Fekete, A.; Sasvari-Szekely, M.; Rigo, J., Jr.; Ver, A. Association of extracellular superoxide dismutase (SOD3) Ala40Thr gene polymorphism with pre-eclampsia complicated by severe fetal growth restriction. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2009**, *142*, 134–138.
44. Sandoval-Carrillo, A.; Aguilar-Duran, M.; Vázquez-Alaniz, F.; Castellanos-Juárez, F.X.; Barraza-Salas, M.; Sierra-Campos, E.; Téllez-Valencia, A.; la Llave-León, O.; Salas-Pacheco, J.M. Polymorphisms in *GSTT1* and *GSTM1* genes are associated to increased risk of preeclampsia in Mexican mestizo population. *Genet. Mol. Res.* **2014**, *13* (AOP), doi:10.4238/2014.January.17.3.
45. Silva-Zolezzi, I.; Hidalgo-Miranda, A.; Estrada-Gil, J.; Fernandez-Lopez, J.C.; Uribe-Figueroa, L.; Contreras, A.; Balam-Ortiz, E.; del Bosque-Plata, L.; Velazquez-Fernandez, D.; Lara, C.; *et al.* Analysis of genomic diversity in Mexican Mestizo populations to develop genomic medicine in Mexico. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 8611–8616.

© 2014 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).