RESEARCH ARTICLE

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Genetic Polymorphisms in *ERCC1* Gene and Their Association with Response to Radiotherapy in Moroccan Patients with Nasopharyngeal Carcinoma

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Abstract

Objective: Nasopharyngeal carcinoma (NPC) is a severe malignant disease. Despite its low frequency, NPC is very common in North African population. Radiotherapy is the standard therapeutic treatment of NPC. However, radioresistance hampers the success of treatment. At the molecular scale, radioresistance is due to genetic variations involved in DNA repair pathways in NPC patients. Several studies reported that single nucleotide polymorphisms (SNPs) in excision repair cross complementing group 1 (*ERCC1*) could be associated with radioresistance. In this optic, the present study aimed to evaluate the association between DNA repair gene polymorphisms *ERCC1* C8092A and *ERCC1* C118T and radiotherapy response of patients with NPC. **Methods:** A total of 95 patients with confirmed NPC were recruited at the Mohammed VI Center for Cancer Treatment, Casablanca - Morocco between 2016 and 2018. Two single nucleotide polymorphisms in *ERCC1* gene were genotyped. Multiple analysis software was used to assess the correlation between these SNPs and radio-therapeutic response. **Results:** Sequencing of *ERCC1* C8092A polymorphism revealed that CC and CA genotypes were found in 51.6% and 45.3% of cases, respectively, whereas the homozygote AA genotype was reported in only 3.1% of cases. For *ERCC1* C118T polymorphism, the heterozygote CT genotype was identified in 49.5% of cases. Homozygotes genotypes CC and TT were detected in 17.9% and 32.6% respectively of NPC cases. Of note, no significant association was found between the *ERCC1* C8092A polymorphism and response to radiation therapy (p=0.81). Similarly, there was no significant association between the response to radiotherapy and allelic distribution (p=0.56). Likewise, no correlation was observed neither with genotypes (p=0.07) nor with alleles (p=0.09) of *ERCC1* C118T polymorphism and response to radiation therapy. **Conclusion:** Our results clearly showed that *ERCC1* C8092A and *ERCC1* C118T polymorphisms were not associated with response to radiotherapy in Moroccan NPC patients. Large studies are warranted to confirm the role of these SNPs in therapeutic response of NPC patients.

Keywords: Nasopharyngeal carcinoma- *ERCC1* C8092A- *ERCC1* C118T- radioresistance- Morocco

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Introduction

Nasopharyngeal carcinoma (NPC) is a unique squamous-cell tumor arising from the epithelial cell lining of the nasopharynx (Guo et al., 2019). This malignancy is a common type of cancer in Southeast Asia and a leading cause of death (Lee et al., 2019). Morocco, as other North African countries, has an intermediate incidence of NPC (3–8 per 100,000 inhabitants) and the majority of NPC patients are diagnosed at an advanced stage due to its deep anatomy (Renaud et al., 2020). Given its exquisitely sensitivity to radiation, NPC is mainly treated with radiotherapy, which is largely reported as the gold standard treatment approach (Chua et al., 2019). Moreover, concordant reports suggest that patients diagnosed at an early stage of the disease had a complete remission (Luftig., 2013).

Actually, the main problems faced by clinicians after radiotherapy treatment are the radiation-induced fibrosis, toxicity and the emergence of radio-resistant tumor cells.

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Indeed, and despite the excellent control with modern radiotherapy techniques, some NPC patients have partial remission and develop local recurrence and distant metastasis, which hampers the treatment success (Yuan et al., 2016).

Currently, many studies are underway to investigate the biological mechanisms involved in carcinogenesis and how they affect radiation response. Of note, these genetic alterations can impact tumor sensitivity to radiotherapy (Riou et al., 2019). Scientific evidences have shown that radiotherapy induce DNA damage in tumor by breaking single-strand (SSBs) and double-strand (DSBs) DNA and also carries damage on nucleotides before their incorporation in DNA strands (He et al., 2018). Hence, many DNA-repair pathways are used to repair DNA damages and to maintain cell and tissue homeostasis, including base excision repair (BER) and nucleotide excision repair (NER) (Klinakis et al., 2020). In contrast, these DNA-repair pathways represent a potential mechanism of cancer resistance to radiation induced DNA damages and radiotherapy (Ferreira and Dutreix., 2019). Extensive studies have shown that radio-resistance is the consequence of some single nucleotide polymorphisms (SNPs) affecting genes involved in DNA reparation (Hirakawa et al., 2020), paving the way for new investigations highlighting novel genetic biomarkers that could be used as efficient prognostic tools or as therapeutic targets.

NER is the predominant DNA damage repair pathway and the excision repair cross complementing group 1 (*ERCC1*) gene plays a key role in NER pathway to recognize DNA damage in the initial repair stage and to ensure an efficient DNA repair (Obiedat et al., 2018). Many investigations have highlighted the association between SNPS of *ERCC1* gene and platinum-based therapy efficacy in ovarian, colorectal and gastric cancers and have shown the interest to use this biomarker to predict clinical outcomes of platinum-based chemotherapy (Abyarghamsari et al., 2019).

Among the different *ERCC1* polymorphisms, many studies indicated that C8092A (rs3212986) and C118T (rs11615) SNPs may be useful as effective biomarkers for clinical outcomes prediction and for targeted therapy approach for better management of various cancers (Chen et al., 2017).

ERCC1 C8092A (rs3212986) SNP is a substitution of cytosine by adenine, located on the 3′ untranslated region of the *ERCC1* gene (Shen et al., 1998) involved in the translational repression of *ERCC1* mRNA (Jin et al., 2014) and affecting *ERCC1* mRNA stability (Zhou et al., 2004). *ERCC1* rs3212986 polymorphism was reported to predict fair survival outcome in Japanese patients with pharyngo-laryngeal squamous cell carcinoma (Hirakawa et al., 2020), it was also suggested as a potential biomarker to predict smoking related lung cancer (Yu et al., 2018).

C118T (rs11615) SNP in the *ERCC1* gene, located at exon 4 and lead to AAC/AAT change at postion118 (Ding et al., 2015). Interestingly, C118T SNP is associated with differential mRNA levels (Park et al., 2003) and higher levels of the enzyme′s expression could decrease the response to the chemotherapy regimens containing platinum drugs (Warnecke-Eberz et al., 2009). In this field, many studies have been conducted on the evaluation of the effect of polymorphism of *ERCC1* in carcinogenesis and response to chemotherapy regimens and have reported that this polymorphism is a useful marker to predict response to chemotherapy and survival in subjects living with osteosarcoma (Biason et al., 2012), colorectal (Yin et al., 2011) and gastric (Abyarghamsar et al., 2019) cancers.

In this context, growing interest is given to evaluate the association between *ERCC1* SNPs and radio-resistance and how they can influence individual variations to radiotherapy response. Thus, the present study was planned to assess the presence of C8092A (rs3212986) and C118T (rs11615) SNPs in Moroccan patients with NPC and to determine their association with resistance to radiotherapy treatment.

Materiel and Methods

Study population

Ninety-five NPC patients were diagnosed and recruited between 2016 and 2018 at Mohammed VI Center for Cancer Treatment, Casablanca, Morocco. Patients were mainly from Casablanca and neighboring regions. The study protocol was approved by the Ethics Committee of Ibn Rochd University Hospital, Casablanca - Morocco and written informed consent was obtained from each recruited patient.

Genotyping Conditions

Genomic DNA was prepared from peripheral blood leucocytes using phenol chloroform method and quantified utilizing NanoDrop 2000 UV-Vis Spectrophotometer (Thermo Fisher Scientific). *ERCC1* C8092A and C118T SNPs screening was carried out by PCR amplification and DNA sequencing. For PCR amplification, primers flanking the regions containing *ERCC1* C8092A and C118T SNPs are reported in Table 1.

PCR amplification was performed in a total volume of 25µl, containing 1X PCR buffer, 0.2µM of each dNTP, 0.2mM of each primer, 0.5U Platinum Taq DNA polymerase (Invitrogen) and 100ng of genomic DNA. Amplification mixtures were first denatured at 94°C for

Table 1. Primers for PCR Amplification

Gene/ SNP	Primer sense	Primer sequence	Tm °C	Fragment length (Bp)
ERCC1 C118T	For	5’-AGGAGGGCCCTGTGGTTATC-3’	48	265
	Rev	5’-AGGCTTCTCATAGAAC-3’		
ERCC1 C8092A	For	5’-AGTCTCTGGGGAGGGATTCT-3’	56	204
	Rev	5’-ACAGTGCCCCAAGAGGAGAT-3’		

7 min. Then, 40 cycles of PCR were performed with denaturation at 94°C for 30 s, primer annealing at the corresponding Tm for 30 s and primer extension at 72°C for 30 s. At the end of the last cycle, the mixtures were incubated at 72°C for 7 min. For every reaction, a negative control, in which DNA template was omitted from the amplification mixture, was included. After amplification, PCR products were analyzed by electrophoresis on 2% agarose gels followed by staining with ethidium bromide (10 mg/ml).

PCR products were purified using ExoSAP-IT® clean up system (USB, USA) to eliminate unincorporated primers and dNTPs. Direct sequencing was performed on an ABI 3130XL DNA analyzer (Applied Biosystems, Foster city, CA, USA), using the same primers that served for PCR and BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster city, CA, USA), according to manufacturer's protocol. Briefly, sequencing reactions were performed in a final volume of 10µl, containing 200ng of purified PCR product, 1µl of 2.5X Big Dye ready reaction mix and 10 pmol of the specific primer. The sequencing mixtures were incubated at 95°C for 1min and 25 cycles were performed as: denaturation at 95°C for 10s, primer annealing at 50°C for 5s and extension at 60°C for 4 min. Sequencing products were finally purified using sephadex G-50 gel-exclusion chromatography (GE Healthcare Life Sciences) to eliminate the excess of unincorporated labeled ddNTPs. Obtained sequences were analyzed using BioEdit Sequence Alignment Editor and Basic Local Alignment Search Tool (BLAST).

Data and statistical analyzes

Radioresistant/ radiosensitive status was attributed based on the clinical evolution of patients treated with radiotherapy. Indeed, cured cases after the follow up period of six months were considered radiosensitive. In contrast, radio-resistance status was attributed to NPC cases that relapsed, developed local or distant disease within the first six months following the radiotherapy treatment.

All statistical analyses were carried out using SPSS for Windows, version 22 (SPSS Inc, Chicago) to detect the association between the genotyping results and the response to radiotherapy. p values <0.05 were considered statistically significant.

Results

Characteristics of the study Population

Characteristics and clinico-pathological parameters of the 95 studied NPC patients are summarized in Table 2. The mean age of patients was 44.1 with extreme ages of 12 and 82 years old. Among patients, 60% (57/95) were males and 40% (38/95) were females, with a sex ratio of 1.57. Most of them have not a consanguineous marriage (90.6%) or familial antecedents of any type of cancer (78.9%). Overall, 46.3% of cases had a rural childhood habitat; most of them were not smokers (70.5%) and not alcohol consumers (93.8%).

Histologically, the majority of NPC patients showed non-keratinizing undifferentiated tumors (93.7%). Clinical stages of NPC were classified according to the Union for International Cancer Control /American Joint Committee on Cancer (UICC/AJCC) TNM (tumor-node-metastasis) staging system, version 7. Accordingly, 81.1% (77/95) of patients with NPC were diagnosed at advanced stages (III and IV) and 18.9% (18/95) at an earlier disease stage (I and II).

ERCC1 polymorphisms in population study

Successful amplification and sequencing targeting *ERCC1* polymorphisms (C8092A and C118T) was obtained for all 95 NPC patients and results of genotypic and allelic frequencies distribution are reported in Table 3. For C8092A SNP, genotypes CC and CA prevail and were found in 51.6% (49/95) and 45.3% (43/95) of cases, respectively, whereas the homozygote AA genotype was found in only 3.1% of cases (3/95). Accordingly, analysis of allelic frequency showed that C8092 allele found in 74.2% of cases was predominant whereas allele A8092 was found in only 25.8% of cases.

For C118T SNP, the heterozygote CT genotype prevails and was reported in 49.5% (47/95) of NPC cases.

Table 2. Socio-Economic and Clinical Characteristics of Recruited NPC Patients

Variables	N	%
Gender		
Male	57	60
Female	38	40
Age		
≤ 30 years	23	24.2
> 30 years	72	75.8
Consanguinity		
No	86	90.6
Yes	9	9.4
Familial antecedent		
No	75	78.9
Yes	20	21.1
Childhood habitat		
Rural	44	46.353.7
Urban	51	
Smoking status		
Smokers	28	29.4
Non Smokers	67	70.6
Alcohol consumption		
Drinkers	6	6.2
Non drinkers	89	93.8
Clinical stages		
Stage I and II	18	18.9
Stage III and IV	77	81.1
Histological type		
Keratinizing tumors	1	1.1
Non-keratinizing tumors	5	5.2
Non-keratinizing undifferentiated tumors	89	93.7

Table 3. Distribution of C8092A and C118T Genotypes in NPC Cases

SNPs		C8092A			C118T	
N (%)		N	%		N	%
Genotypes	C/C	49	51.6	C/C	17	17.9
	C/A	43	45.3	C/T	47	49.5
	A/A	3	3.1	T/T	31	32.6
Alleles	C	141	74.2	C	81	42.4
	A	49	25.8	T	109	57.6

Homozygotes genotypes CC and TT were reported in 17.9% (17/95) and 32.6% (31/95) of cases, respectively. Analysis of allelic frequency showed that C allele was present in 42.4% of cases and T allele in 57.6% of cases.

Correlation between ERCC1 polymorphisms distribution and clinico-pathological parameters of NPC patients

The distribution of *ERCC1* SNPs C8092A and C118T genotypes in the 95 NPC cases according to clinical stages of NPC is reported in Table 4. For C8092A SNP, C/C genotype prevails in early carcinoma stages (stages I and II) and was detected in 66.7% of patients, C/A genotype was detected in only 33.3% of NPC patients, with an absence of A/A genotype. In advanced stages of NPC (stages III and IV), C/C, C/A and A/A genotypes were detected in 48.1%, 48% and 3.9% of patients, respectively. Statistical analysis did not show any significant association between *ERCC1* C8092A SNP and NPC clinical stages (p=0.202). Similarly, in terms of alleles distribution, no significant association was obtained between C/A alleles and NPC clinical stages (p=0.161).

Regarding *ERCC1* C118T SNP, no significant difference was found between clinical stage and genotype distribution (p=0.994) and allele frequencies (p=0.740). CC, CT and TT genotypes as well as C and T alleles were found with same frequencies in early and advanced stages.

Correlation between *ERCC1* Polymorphisms distribution and clinical evolution of NPC patients

Among the 95 studied patients, 63 were treated with radiotherapy and clinical evolution was available for only 61 of them; 2 patients were treated in the private sector and their outcomes were not available.

Table 5 sets out the association between *ERCC1* SNPs C8092A and C118Tgenotypes and response to radiotherapy. For *ERCC1* C8092A polymorphism, homozygous CC and heterozygous CA genotypes prevail in both radio-resistant and radiosensitive cases. In the same way, C and A alleles were reported globally with the same frequencies in radio-resistant and radio-sensitive cases. Statistical analyses showed no significant association between the radio-resistance status and, C8092A genotypes (p=0.81) and allelic frequencies (p=0.56).

For C118T SNP, CT genotype prevails in radio-resistant cases (60.4%, 32/53) and TT in radiosensitive cases (62.5%, 5/8). A borderline significance was obtained

Table 4. Association between *ERCC1* SNPs and Clinical Stages

Clinical stages	N	C8092A						
		Genotypes				Alleles		
		CC (%)	CA (%)	AA (%)	p	C(%)	A(%)	p
Stage I and II	18	12 (66.7)	6 (33.3)	0 (0)		30 (83.3)	6 (16.7)	
Stage III and IV	77	37 (48.1)	37(48)	3 (3.9)	0.202	111 (72.1)	43 (27.9)	0.161
		C118T						
		CC (%)	CT(%)	TT(%)	p	C(%)	T(%)	p
Stage I and II	18	3 (16.7)	9 (50)	6 (33.3)		15 (41.7)	21(58.3)	
Stage III and IV	77	14 (18.2)	38 (49.3)	25 (32.5)	0.994	66 (42.9)	88 (57.1)	0.74

Table 5. Association between *ERCC1* Polymorphisms and Radiotherapy Response

Clinical outcome	N	Genotypes				Alleles		
		C8092A						
		CC (%)	CA (%)	AA (%)	p	C (%)	A (%)	p
Radiosensitive	53	25 (47.1)	27 (51)	1(1.9)	0.81	77 (72.6)	29 (27.4)	0.56
Radioresistant	8	4 (50)	4 (50)	0		12 (75)	4 (25)	
		C118T						
		CC (%)	CT (%)	TT (%)	p	C (%)	T (%)	p
Radiosensitive	53	9 (17)	32 (60.4)	12 (22.6)	0.07	50 (47,2)	56 (52.8)	0.091
Radio-resistant	8	1(12.5)	2 (25)	5 (62.5)		4 (25)	12 (75)	

between *ERCC1* C118T polymorphism genotypes and radio-resistance status (p=0.07). Similarly, a borderline association was found between radio-resistance status and allelic frequency (p=0.091), as T allele prevails in radiosensitive cases.

Discussion

Worldwide, due to a significant difference between patients, the efficacy of radiotherapy is the main challenge that physicians encounter when treating NPC patients (Yeh et al., 2021). Within this frame, the identification of biomarkers that can predict radiation sensitivity and/or clinical outcomes will enable NPC patients to benefit from a personalized therapy. Many studies in the last few decades have reported that SNPs in DNA repair genes could be correlated with radiotherapy response in a variety of cancers, including non-small cell lung cancer (NSCLC) (Jiang et al., 2021), rectal cancer (Qin et al., 2015), breast cancer (Lee et al., 2020), head and neck squamous cell carcinoma (HNSCC) (Jin et al., 2014) and NPC (Borchiellini et al., 2017).

In the present study, the interest was particularly given to *ERCC1* C8092A (rs321986) and *ERCC1* C118T (rs11615), which have been shown to be contributing factors in the development of NPC (Yang et al., 2009). Our findings revealed that both *ERCC1* SNPs are not significantly associated with NPC clinical stages as they were found in both early and advanced stages. Our results are consistent with previous research conducted on 267 NPC patients and 304 cancer-free controls in the Southwest Chinese population, indicating that the single nucleotide polymorphism *ERCC1* C8092A is not associated with clinical stage. Moreover, Yang et al. have reported that *ERCC1* C8092A genotypic frequencies in early stages of NPC were not significantly different from those in advanced stages (P > 0.05) (Yang et al., 2009). Furthermore, Yang et al. reported that *ERCC1* C8092A genotypic frequencies in early stages of NPC were not significantly different from those in advanced stages (P > 0.05) (Yang et al., 2009).

The role of *ERCC1*, as a key element of the NER pathway, in DNA damage recognition and repair has been largely explored along with response to chemotherapy but, to the best of our knowledge, its association with radio-resistance in NPC is poorly studied. Molecular exploration showed that *ERCC1* C8092A SNP was found in both radio-resistant and radiosensitive cases. Statistical analysis showed no significant association between the radio-resistance status and, *ERCC1* C8092A genotypes (p=0.81) and allelic frequencies (p=0.56). These results are in agreement with a previously study conducted by Du et al., 2018 highlighting that *ERCC1* C8092A SNP was not correlated with the radio-therapeutic response in Chinese lung cancer patients treated with intensity modulated radiation therapy.

Similarly, no significant association was observed between *ERCC1* C8092A SNP and response to chemotherapy treatment. In a meta-analysis, including 2097 patients with NSCLC who received platinum-based chemotherapy, the correlation between *ERCC1* C8092A polymorphism and response to treatment did not show any significant association (Yin et al., 2011) Consistent with these findings, another meta-analysis including 44 published studies reporting no significant association between *ERCC1* C8092A polymorphism and response to platinum-based chemotherapies in 5944 NSCLC patients, further supports our results, (Huang et al., 2014). Chen et al identified *ERCC1* C8092A genotype as an independent predictor of poor progression free survival (PFS) (HR, 1.63; 95%; CI, 1.08- 2.61; P, 5.047) in 101 NPC patients treated with cisplatin-based chemotherapy (Chen et al., 2013). In addition, Jin et al. found that *ERCC1* C8092A polymorphism was correlated with PFS in 75 nasopharyngeal carcinoma patients who received either radiotherapy alone or chemo-radiotherapy (Jin et al., 2014).

Interestingly, a recent study showed that patients with HNSCC exhibiting the *ERCC1* 8092 (C/A+A/A) genotype, treated with chemo-radiotherapy (CRT), had significantly poorer survival rate than those with *ERCC1* 8092 C/C genotype, highlighting the opportunity of using this SNP as an independent predictor of CRT response and patients survival outcomes (Hirakawa et al., 2020)

Of particular interest, a borderline association was found between *ERCC1* C118T SNP and radio-resistance status among Moroccan NPC patients. Worldwide, the association between *ERCC1* C118T SNP and chemo- and/or radio-therapy outcome is well documented and discussed in different cancers. In this field, Jiang et al. have shown that this SNP can play an important role in the prediction of radiotherapy sensitivity and prognosis of NSCLC (Jiang et al., 2021). Indeed, NSCLC patients carrying the C allele (CC or CT genotypes) had a significantly better survival compared to those bearing the T allele (TT genotype) (30.9 vs. 16.2 months; P=0.003). These results were confronted by finding of Du et al. reporting a significant association between *ERCC1* C118T genotypes and radiotherapy outcomes in lung (Du et al., 2018) and esophageal cancer patients (Warnecke-Eberz et al., 2009). Of particular interest, Carles et al., have highlighted the role of *ERCC1* C118T SNP as a marker for response to radiotherapy in Spanish patients with Stage I to II head-and-neck cancer, widening the range of application of this SNP to predict clinical stage as well as radio-therapeutic status. Conversely, Wang et al., by following 176 patients of NSCLC treated with radio-chemotherapy, didn't observe any significant relation between *ERCC1* C118T SNP and treatment outcomes.

In the same way, several studies have shown that the *ERCC1* C118T SNP is a valuable biomarker for responses to chemotherapeutic drugs, particularly cisplatin, with a high predictive value for platinum-based chemotherapy in patients with late-stage bladder cancer (Xu et al., 2016), ovarian malignancies (Vella et al., 2011), and patients at advanced NSCLC (Dong et al., 2012; Wei et al., 2011). In the present study, the borderline significance observed between radio-resistance status and, SNP genotypes and allelic frequencies may be mainly due to the low sample size and the restricted number of studied SNPs in *ERCC1* gene.

To the best of our knowledge, this is the first study

investigating the role of DNA excision repair gene *ERCC1* polymorphisms in patients with NPC and results are very informative: (1) *ERCC1* C8092A and *ERCC1* C118Tgenotypes were found in both early and advanced disease stages, with no significant difference; (2) *ERCC1* C8092A SNP was not found to be significantly associated with radio-resistance status; (3) Borderline significances were obtained between radio-resistance status and, *ERCC1* C118T genotypes (p=0.07) and allelic frequencies, which need to be confirmed on a larger sample size to get conclusive results.

The main limitations of the study are the relatively small sample size and lack of additional patient's information that could be of interest for more explorations. Moreover, the follow-up period of most patients did not exceed three years, which is not enough to estimate appropriately clinical evolutions, patients' outcomes and PFS.

Author Contribution Statement

Concept: M.A., M.E.M., M.K.; Design: M.A., M.E.M., N.T., N.B.; Supervision: I.C., M.K.; Material: R.B., A.Gi., I.C.; Data collection &/or processing: A.Gi., A.Gu., A.B., K.B., N.E.B.; Analysis and/or interpretation: R.B., M.A.; Literature search: R.B.; M.A.; Writing: R.B., I.C., M.E.M., Critical review: A.F.M., M.A.; M.K

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Scientific Body approval

The present study is part of a student thesis and was approved by the doctoral committee of Mohammed V University.

Ethical approval

The study protocol was approved by the Ethics Committee of Ibn Rochd Hospital of Casablanca, Morocco on November, 2017.

Availability of data (if apply to your research)

Data supporting the conclusions of this article are included within the article. The datasets used and/or analyzed during the current study will be made available from the corresponding author on request.

Conflict of interest

None declared.

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