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Polymorphisms in genes implicated in base excision repair (BER) pathway are associated with susceptibility to Paget's disease of bone

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ABSTRACT

Paget's disease of bone (PDB) is a chronic bone metabolic disorder. Currently, PDB is the second most frequent bone disorder. PDB is a focal disorder affecting the skeleton segmentally but the cause of which is unknown. It has been hypothesised that somatic mutations could be responsible for the mosaicism described in PDB patients. Therefore, our hypothesis is that defective response to DNA damage may lead to somatic mutations favouring an increased risk of PDB. So that we have analysed polymorphisms in DNA repair genes involved in the BER, NER and DSBR pathways in order to evaluate the role of these variants in modulating PDB risk. We found statistically significant differences in genotypic and allelic distribution for polymorphisms in genes implicated in the BER pathway. Our results showed that carrying the allele T of XRCC1 rs1799782 polymorphism and the allele G of APEX rs1130409 polymorphism increased the risk of developing PDB. These polymorphisms could cause a lower DNA repair efficiency and this might lead to local somatic mutations favouring bone metabolic alterations characteristic of PDB. This is the first report showing an association between polymorphism in genes implicated in the BER pathway with PDB.

1. Introduction

Paget's disease of bone (PDB) (OMIM: 167250) is a chronic bone metabolic disorder affecting the skeleton segmentally. The pagetic bone is characterized by an increase in bone resorption followed by a compensatory bone formation that results in a variegated and anarchic bone structure. The principal alteration resides in osteoclasts that increase in size, proliferation and activity [1,2]. Some patients are asymptomatic, whereas others develop pain, osteoarthritis, fracture, bone deformity, deafness, and nerve compression syndromes secondary to bone growth or tumour transformation generally into osteosarcoma [3–6]. Currently, PDB is the second most frequent bone disorder and affects up to 3% of Caucasians over 55 years old [7]. In Spain the prevalence is 1,3% with an irregular geographic distribution leading to areas of high prevalence like the Vitigudino region (Salamanca) with a prevalence of 5,7% [8].

The most accepted etiopathogenic hypothesis to explain the origin of the PDB considers that PDB is the consequence of the synergic action of environmental and genetic factors. The genetic determination would explain the individual susceptibility to developing the disease. There is evidence that genetic alterations play an important role in the development of PDB. There is a strong tendency to familial aggregation, with a seven-fold increase in risk of suffering PDB in families of patients [1,2]. To date, the most important known genetic factor predisposing to PDB is mutation in Sequestosome1 (SQSTM1) gene but it has been reported that only between 20 and 40% of patients with a family history of the disease and 5–10% of sporadic patients are carriers of a mutation in SQSTM1 gene [9,10]. PDB is a focal disorder affecting the skeleton segmentally but the cause of which is unknown, it has been hypothesised that somatic mutations could be responsible for the mosaicism described in PDB patients [11,12].

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A defective response to DNA damage caused by exogenous or endogenous agents may lead to mutations favouring an increased risk of disease [13]. The main pathways for DNA repair are base excision repair (BER), nucleotide excision repair (NER), double strand break repair (DSBR) and mismatch repair (MMR). The BER pathway repairs small lesions produced by oxidative damage and alkylating agents [14], the NER pathway removes bulky helix distorting DNA lesions caused by UV radiation and exposure to chemical carcinogens [15], the DSBR repairs double strand breaks induced by ionizing radiation and exposure to toxic cell products [16] and the MMR corrects mismatches and insertions or deletions caused during DNA replication [17].

Thus, the aim of our study was to characterize whether polymorphisms in genes implicated in the DNA repair mechanisms could modify the risk of developing PDB. Therefore, in this study we have analysed common polymorphisms in DNA repair genes involved in the BER (XRCC1 rs1799782, APEX rs1130409), NER (ERCC2 rs13181, ERCC1 rs11615, XPC rs2228000) and DSBR (XRCC3 rs1799794 and KU70 rs2267437) pathways in order to evaluate the role of these variants in modulating PDB risk.

2. Materials and methods

2.1. Subjects

We have studied 214 PDB patients recruited in the Service of Rheumatology at the University Hospital of Salamanca (Spain) between January 1990 and February 2016 that were not carriers of SQSTM1 gene mutation. According to the prevalence of PDB [7] we calculated that a series of 152 patients would be representative of our PDB population. As a control group, 333 sex-matched healthy subjects over 40 years old without previous history of PDB or cancer were recruited from the same hospital during the same period of time. To confirm that the healthy subjects did not have a silent PDB, we tested alkaline phosphatase (ALP) levels and performed bone radiography to exclude bone affection.

Clinical and analytical variables such as gender, age at diagnosis, family history of PDB, number of affected bones, Renier's index, presence of complications (fractures, coxopathy and cranial nerve involvement) and ALP levels were collected from each patient. ALP was adjusted according to the upper limit of ALP standard range following the function: ALP/upper ALP (adjusted ALP). PDB patients with elevated plasma ALP and normal levels of liver derived enzymes, were classified as having active PDB. In the familial cases we have included only one affected patient of each family.

The experimental protocol was in accordance with the Declaration of Helsinki (2008) of the World Medical Association, approved by the University Hospital of Salamanca Ethics Committee and in compliance with the Spanish data protection law (LO 15/1999) and specifications (RD 1720/2007). All who accepted to participate in the study signed a written consent.

2.2. DNA insolation and polymorphism genotyping

Genomic DNA was extracted from peripheral blood leukocytes by standard phenol/chloroform procedure [18].

Genotyping of polymorphisms included in the study (Table 1) was performed using TaqMan 5′-exonuclease allelic discrimination assays that contain sequence-specific forward and reverse primers to amplify the polymorphic sequences and two probes labelled with VIC and FAM dyes to detect both alleles of each polymorphism [19]. PCR reactions were carried out using TaqMan universal PCR Master Mix following instructions in a Step-One Plus Real-time PCR system. To assess reproducibility, a random selection of 5% of the samples were re-genotyped, all of these genotypes matched with the genotypes initially designated.

Table 1
DNA repair genes polymorphisms included in the study.

Function	Gene	SNP ID	Assay ID[a]	Change	HWE[b]
Base excision repair	XRCC1	rs1799782	C_11463404_10	Arg194Trp	> 0.05
(BER)	APEX	rs1130409	C_8921503_10	Asp148Glu	> 0.05
Nucleotide excision	ERCC2 (XPD)	rs13181	C_3145033_10	Lys751Gln	> 0.05
repair	ERCC1	rs11615	C_2532959_10	Asn118Asn	> 0.05
(NER)	XPC	rs2228000	C_16018061_10	Ala499Val	> 0.05
Double-strand break	XRCC3	rs1799794	C_2983904_10	c.-316A > G	> 0.05
(DSBR)	KU70	rs2267437	C_15872242_20	c.-731C > G	> 0.05

[a] All the assays were commercially.
[b] HWE: Hardy-Weinberg equilibrium in control group.

2.3. Statistical analysis

The Healthy subjects group was tested for conformity to the Hardy-Weinberg equilibrium using chi-squared test for each polymorphism. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated for each polymorphic variant using unconditional logistic regression models to evaluate the association with PDB risk. These statistical analyses were performed using SPSS software. For the analysis, differences with a p-value < 0.05 were considered as statistically significant.

3. Results

A total of 214 PDB patients and 333 healthy subjects were analysed. The clinical variables of the series are summarized in Table 2. The distribution of genotypes of XRCC1 rs1799782, APEX rs1130409, ERCC2 rs13181, ERCC1 rs11615, XPC rs2228000, XRCC3 rs1799794 and KU70 rs2267437 polymorphisms in control samples were in Hardy-Weinberg equilibrium (Table 1).

The genotypic frequencies of the polymorphisms included in the study and the results of the association analysis between PDB and healthy subjects are summarized in Table 3. No significant differences were found in genotypic distribution for ERCC2 rs13181, ERCC1 rs11615, XPC rs2228000, XRCC3 rs1799794 and KU70 rs2267437 polymorphisms between PDB patients and healthy subjects. However, we found statistically significant differences in genotypic distribution for polymorphisms in genes implicated in the BER pathway. Homozygous TT genotype of the XRCC1 rs1799782 polymorphism was associated with increased risk of developing PDB. In the case of APEX rs1130409 polymorphism, being a carrier of the variant allele G increased the risk of suffering PDB (Table 3).

No significant differences were found in the allelic distribution for polymorphisms in genes implicated in the NER and DSBR pathways between PDB patients and controls (Table 4). However, we found

Table 2
Clinical characteristics of PDB patients included in the study.

Clinical characteristics	Results
Male sex, n (%)	119 (55,6%)
Age at diagnosis, mean ± SD	68,69 ± 10,66
Polyostotic involvement, n (%)	137 (64,0%)
Number of affected bones, mean ± SD	2,73 ± 1,99
Renier's index, mean ± SD	16,56 ± 11,95
Adjusted ALP, mean ± SD	3,75 ± 4,87
Patients with active PDB, n (%)	171 (79,9%)
Familial history of PDB, n (%)	18 (8,4%)
Fracture or fissures, n (%)	14 (6,5%)
Coxopathy, n (%)	21 (9,8%)
Cranial nerve involvement, n (%)	26 (12,1%)

Table 3
Genotypic frequencies of DNA repair genes polymorphisms included in our study among patients and healthy subjects. (p-values were adjusted by sex and age.)

SNP	Genotype	Controls	PDB patients	p-Value	OR (95%CI)
XRCC1	CC	318 (95,5%)	196 (91,6%)		1,00
rs1799782	CT	12 (3,6%)	8 (3,7%)	0,866	1,08 (0,43–2,69)
	TT	3 (0,9%)	10 (4,7%)	0,011	5,40 (1,47–19,89)
	CC	318 (95,5%)	196 (91,6%)		1,00
	CT + TT	15 (4,5%)	18 (8,4%)	0,040	1,87 (1,18–3,39)
	CC + CT	330 (99,1%)	204 (95,3%)		1,00
	TT	3 (0,9%)	10 (4,7%)	0,011	5,39 (1,46–19,82)
APEX	TT	108 (32,4%)	45 (21,0%)		1,00
rs1130409	TG	155 (46,5%)	112 (52,3%)	0,011	1,73 (1,13–2,65)
	GG	70 (21,0%)	57 (26,6%)	0,008	1,95 (1,19–3,20)
	TT	108 (32,4%)	45 (21,0%)		1,00
	TG + GG	225 (67,6%)	169 (79,0%)	0,004	1,80 (1,20–2,69)
	TT + TG	263 (79,0%)	157 (73,4%)		
	GG	70 (21,0%)	57 (26,6%)	0,129	
ERCC2	AA	154 (46,2%)	87 (40,7%)		
rs13181	AC	132 (39,6%)	92 (43,0%)	0,424	
	CC	47 (14,1%)	35 (16,4%)		
	AA	154 (46,2%)	87 (40,7%)		
	AC + CC	179 (53,8%)	127 (59,3%)	0,199	
	AA + AC	286 (85,9%)	179 (83,6%)		
	CC	47 (14,1%)	35 (16,4%)	0,474	
ERCC1	CC	117 (35,1%)	86 (40,2%)		
rs11615	CT	171 (51,4%)	99 (46,3%)	0,454	
	TT	45 (13,5%)	29 (13,6%)		
	CC	117 (35,1%)	86 (40,2%)		
	CT + TT	216 (64,9%)	128 (59,8%)	0,233	
	CC + CT	288 (86,5%)	185 (86,4%)		
	TT	45 (13,5%)	29 (13,6%)	0,990	
XPC	CC	186 (55,9%)	108 (50,5%)		
rs2228000	CT	124 (37,2%)	86 (40,2%)	0,371	
	TT	23 (6,9%)	20 (9,3%)		
	CC	186 (55,9%)	108 (50,5%)		
	CT + TT	147 (44,1%)	106 (49,5%)	0,217	
	CC + CT	310 (93,1%)	194 (90,7%)		
	TT	23 (6,9%)	20 (9,3%)	0,301	
XRCC3	AA	168 (50,5%)	121 (56,5%)		
rs1799794	AG	136 (40,8%)	73 (34,1%)	0,284	
	GG	29 (8,7%)	20 (9,3%)		
	AA	168 (50,5%)	121 (56,5%)		
	AG + GG	165 (49,5%)	93 (43,5%)	0,164	
	AA + AG	304 (91,3%)	194 (90,7%)		
	GG	29 (8,7%)	20 (9,3%)	0,799	
KU70	CC	122 (36,6%)	68 (31,8%)		
rs2267437	CG	158 (47,4%)	104 (48,6%)	0,376	
	GG	53 (15,9%)	42 (19,6%)		
	CC	122 (36,6%)	68 (31,8%)		
	CG + GG	211 (63,4%)	146 (68,2%)	0,244	
	CC + CG	280 (84,1%)	172 (80,4%)		
	GG	53 (15,9%)	42 (19,6%)	0,264	

Table 4
Allelic frequencies of DNA repair genes polymorphisms included in our study among patients and healthy subjects. (p-values were adjusted by sex and age.)

SNP	Allele	Controls	PDB patients	p-Value	OR (95%CI)
XRCC1	C	648 (97,3%)	400 (93,5%)		1,00
rs1799782	T	18 (2,7%)	28 (6,50%)	0,003	2,52 (1,37–4,61)
APEX	T	371(55,7%)	202 (47,2%)		1,00
rs1130409	G	295 (44,3%)	226 (52,8%)	0,006	1,40 (1,10–1,79)
ERCC2	A	440 (66,1%)	266 (62,1%)		
rs13181	C	226 (33,9%)	162 (37,9%)	0,186	
ERCC1	C	405 (60,8%)	271 (63,3%)		
rs11615	T	261 (39,2%)	157 (36,7%)	0,405	
XPC	C	496 (74,5%)	302 (70,6%)		
rs2228000	T	170 (25,5%)	126 (29,4%)	0,155	
XRCC3	A	472 (70,9%)	315 (73,6%)		
rs1799794	G	194 (29,1%)	113 (26,4%)	0,327	
KU70	C	402 (60,4%)	240 (56,1%)		
rs2267437	G	264 (39,6%)	188 (43,9%)	0,160	

Table 5
Distribution of XRCC1 rs1799782 and APEX rs1130409 polymorphisms among PDB patients and healthy subjects. (p-values were adjusted by sex and age.)

SNPs	Alleles	Controls	PDB patients	p-Value	OR (95%CI)
XRCC1/ APEX	C/T	324 (97,3%)	193 (90,2%)		1,00
XRCC1/ APEX	T/G	9 (2,7%)	21 (9,8%)	0,001	3,91 (1,75–8,72)

statistically significant differences in allelic distribution for XRCC1 rs1799782 and APEX rs1130409 polymorphisms between patients and healthy subjects. Allele T of XRCC1 rs1799782 confers an increased risk of developing the disease. In the case of APEX rs1130409, being a carrier of allele G was associated with increased risk of developing PDB (Table 4). Moreover, carrying the allele T of XRCC1 rs1799782 and allele G of APEX rs1130409 increased the risk of developing PDB (Table 5).

No significant differences were found in the analysis of the different

clinical forms and the genotypic distributions of XRCC rs1799782, APEX rs1130409, ERCC2 rs13181, ERCC1 rs11615, XPC rs2228000, XRCC3 rs1799794 and KU70 rs2267437 polymorphisms.

4. Discussion

The etiology of PDB is unknown; nevertheless, there are several observations that suggest that genetic alterations may be crucial in the development of the disease. To date, the most important known genetic factor predisposing to PDB is mutation in SQSTM1 gene, but it has been reported that only between 20 and 40% of patients with a family history of the disease, and 5–10% of sporadic patients carry a mutation in SQSTM1 gene [9,10]. It is known that PDB is a focal bone disorder with asymmetric distribution. It has been hypothesised that somatic mutations could be responsible for the mosaicism described in PDB patients, several studies described p.P392L variant as a somatic mutation in SQSTM1 gene in the affected bone, but not in peripheral blood [11,12]. Our hypothesis is that a defective response to DNA damage could lead to somatic genetic alterations favouring an increased risk of PDB, therefore we have analysed polymorphisms in DNA repair genes involved in the BER (XRCC1 rs1799782, APEX rs1130409), NER (ERCC2 rs13181, ERCC1 rs11615, XPC rs2228000) and DSBR (XRCC3 rs1799794 and KU70 rs2267437) pathways in order to evaluate the role of these variants in modulating PDB risk. Five polymorphisms are missense and produce amino acid changes (XRCC1 rs1799782, APEX rs1130409, ERCC2 rs13181, ERCC1 rs11615, XPC rs2228000) and two are intronic polymorphisms (XRCC3 rs1799794 and KU70 rs2267437).

No significant differences were found in genotypic and allelic distribution in DNA repair genes polymorphisms involved in NER and DSBR pathways included in our work; nevertheless, these results do not exclude an involvement for any of these genes in PDB pathogenesis due to we have only studied a selected polymorphism for each gene. However, we found statistically significant differences in genotypic and allelic distribution for polymorphisms in genes implicated in the BER pathway. The BER pathway repairs small lesions produced by oxidative damage and alkylating agents. The first step in the BER pathway is the recognition and removal from the DNA of the damage base by a specific DNA glycosylase. As a result, an intact AP site (location of DNA in which it does not have a purine or pyrimidine base) is created. This AP site is processed by the APEX protein and DNA polymerase β, which remove the sugar fragment and process the nick to generate the OH and 5′-phosphate sites necessary for the new synthesis. A new nucleotide is inserted by the DNA polymerase β with the assistance of XRCC1, a scaffolding protein that interacts with repair enzymes, and finally, the ligase III seals the nick and generates a repaired product [14,20]. Our results showed that carrying the allele T of XRCC1 rs1799782 polymorphism and allele G of APEX rs1130409 polymorphism increased the risk of developing PDB. This is the first report in which variants in genes implicated in the BER pathway were associated with the risk of developing PDB, since, historically, they have been associated with risk of cancer.

The XRCC1 rs1799782 polymorphism is located in exon 6 of XRCC1 and is a C > T substitution in the codon 194 that leads to a Arg194Trp variant. However, despite that XRCC1 rs1799782 polymorphism has been extensively studied, contradictory results have been reported on its functional significance. Some studies have not found any association between XRCC1 rs1799782 polymorphism and defective DNA repair [21,22], others have described a lower DNA repair efficiency associated with the 194Trp variant of the XRCC1 protein [23,24] and others have reported that DNA repair was reduced in patients carrying the 194Arg variant [25–27]. Our results suggested that being a carrier of 194Trp variant of XRCC1 protein increases the risk of suffering PDB and this could be due to a lower DNA repair efficiency. The APEX rs1130409 polymorphism has been associated with an increased risk of suffer diseases such as cerebral infarction, hypertension or cancer [28–31]. The APEX rs1130409 polymorphism implies an Asp148Glu variation in the endonuclease domain of the APEX protein and it has been suggested that it does not reduce endonuclease activity [32,33]. Nevertheless, it could be possible that the 148Glu variant of the APEX protein could reduce the ability to communicate with the other BER proteins [28] and cause a deficient DNA repair.

DNA damage could play a crucial role in skeletal diseases. It has been reported in animal models that mutations in proteins involved in DNA repair are linked to aging related bone diseases such as osteoporosis [34]. Reactive oxygen species (ROS) are emerging as an intracellular DNA damage factor that is important in the deregulation of bone metabolism, including RANKL-dependent osteoclast differentiation and consequently in PDB [35]. One of the mechanisms implicated in the repair of DNA damage caused by ROS is the BER pathway [14]. Our hypothesis is that 194Trp and 148Glu variants of XRCC1 and APEX proteins could cause a lower DNA repair efficiency by the BER pathway and this might favour somatic mutations in localized bone stem cells favouring bone metabolic alterations characteristic of PDB.

Previous studies conducted by our group (manuscript submitted) and others [36,37] have found carriers of SQSTM1 gene mutation that do not develop the disease within a PDB family, as well as cases of PDB that do not show SQSTM1 gene mutation. Thus, we can speculate that abnormalities in BER system could favour somatic mutations in isolated bone stem cells and when these mutations involve genes implicated in bone metabolism such as SQSTM1 they could lead to PDB. Thus, we can speculate that SQSTM1 gene mutation could be a germline or somatic “passenger” mutation that would only be involved in PDB when a second somatic yet unknown “driver” mutation occurs.

In summary, this is the first report showing an association between polymorphism in genes implicated in the BER pathway with PDB and reinforce the hypothesis that somatic mutation could be implicated in PDB. Whole exome analysis of pagetic and healthy bone is necessary to further confirm this hypothesis.

Declarations of interest

None.

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