Deletion of late cornified envelope genes, LCE3C_LCE3B-del, *is not associated with psoriatic arthritis in Tunisian patients*

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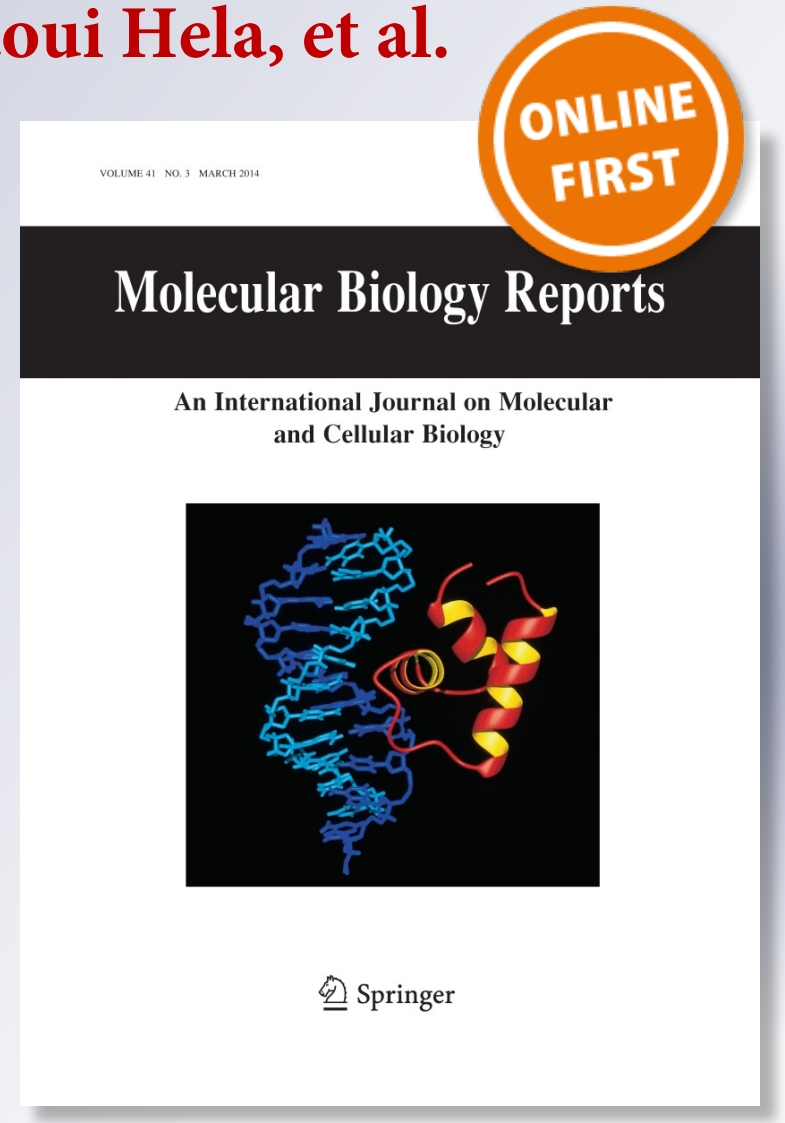

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Deletion of late cornified envelope genes, *LCE3C_LCE3B-del*, is not associated with psoriatic arthritis in Tunisian patients

Bouchlaka Souissi Chiraz · Ammar Myriam · Zarra Ines · Jordan Catherine · Bouazizi Fatma · Cheour Ilhem · Tekaya Raoudha · Zeglaoui Hela · Fourati Hela · Bouajina Elyes · Doss Nejib · Helms Cindy · Elgaaied Amel · Sellami Slaheddine

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Abstract A deletion of two genes from the late cornified envelope (LCE), *LCE3B* and *LCE3C* within epidermal differentiation complex on chromosome 1 was shown to be associated with both psoriasis and psoriatic arthritis (PsA) in several populations. To assess whether this deletion may contribute to the genetic predisposition to PsA in Tunisia, a total of 73 patients with PsA and 120 healthy matched controls were screened for the deletion, *LCE3C_LCE3B-del*, and its tag SNP, rs4112788. We also evaluated a possible relationship between PSORS1 and LCE3C_LCE3B-del through genotyping two proxy markers to HLA-C (rs12191877 and rs2073048). Our results did not provide evidence for association between the *LCE3C_LCE3B-del* nor the rs4112788 and the PsA. Similarly, no significant epistatic effect was observed. Our data suggest that The LCE deletion, previously identified in patients with psoriasis, is not of a major importance in the development of PsA in Tunisian patients supporting the current perception that different genetic risk factors contribute to skin and joint disease. However, these results need to be confirmed by additional large-scale studies of Tunisian PsA patients and controls.

Keywords Late cornified envelope · Psoriatic arthritis · Genetic association · Single nucleotide polymorphism

Introduction

Psoriatic arthritis (PsA) is a chronic, inflammatory arthropathy that is accompanied in most cases by psoriatic skin and nail lesions. The clinical and radiographic features of PsA are highly variable and can involve joints (synovitis), the spine (spondylitis) and juxta-articular tendons

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B. S. Chiraz (✉) · A. Myriam · B. Fatma · E. Amel
Laboratory of Genetics, Immunology and Human Pathologies, Faculty of Sciences, University of Tunis El Manar, 2092 Tunis, Tunisia
e-mail: souissichiraz@topnet.tn

Z. Ines
Dermatology Department, La Rabta Hospital, 1007 Tunis, Tunisia

J. Catherine · H. Cindy
Division of Human Genetics, Department of Genetics, Washington University School of Medicine, St. Louis, MO 63110, USA

C. Ilhem · S. Slaheddine
Osteoarthritis-osteoporosis Research Laboratory, Rheumatology Department, LaRabta Hospital, 1007 Tunis, Tunisia

T. Raoudha
Rheumatology Department, Charles Nicolle Hospital, 1006 Tunis, Tunisia

Z. Hela · B. Elyes
Rheumatology Department, Farhat Hached Hospital, 4000 Sousse, Tunisia

F. Hela
Rheumatology Department, Hedi Chaker Hospital, 3029 Sfax, Tunisia

D. Nejib
Dermatology Department, Military Hospital, 1008 Tunis, Tunisia

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and ligaments (dactylitis, enthesitis) [1, 2]. PsA is equally likely to occur in males and females during the third to fifth decade of life (30–50 years). The exact prevalence of PsA is unknown, but it has been reported that is more common in Caucasians and it develops in approximately 6–48 % of patients with psoriasis depending on the population studied [3–7]. In Tunisia, the estimated prevalence of psoriasis is 2 % giving the disease an overall prevalence of 0.06 % [8].

PsA is a genetically complex disease that results from interplay between multiple genetic and environmental factors. The genetic basis of PsA is supported by evidence from family and twin studies. Different studies suggest that the genetic contribution to PsA may be higher (sibling recurrence risk $\lambda_s > 30$) than that for psoriasis ($\lambda_s = 8–12$) [9–14]. Several candidate gene studies and genome-wide association studies have revealed a number of common genes or loci shared between the two conditions. Examples of alleles and gene loci found to harbor variants associated with both psoriasis and PsA include the *HLA-Cw*06* allele, *IL12B, IL23A, IL23R, NAT9*, *SLC9A3R1, RAPTOR*, *TNFAIP3* and *TNIP1* [15–23]. Other studies identified differences in the genetic basis of the two diseases. A 32.2 kb deletion of two genes in the late cornified envelope (LCE) gene cluster, *LCE3C_LCE3B-del*, was originally reported as a psoriasis risk factor in psoriasis [24]. The LCE is part of the epidermal differentiation complex (EDC) localised in PSORS4 (psoriasis-susceptibility locus 4), on chromosome 1q21.3, and the *LCE3C* and *LCE3B* genes have a putative role in skin barrier function. Also the *LCE3C_LCE3B-del* variant was correlated with different levels of replication [24–30]. Despite this, in a previous study, we found no association of this locus with susceptibility to psoriasis in the Tunisian population [31]. The *LCE3C_LCE3B-del* has also been tested in PsA patients with conflicting results. Some studies noted a significant association [32, 33] while others failed to detect any such association [27, 34]. Hence replication is required to establish if the *LCE3C_LCE3B-del* confers susceptibility to either or both diseases. To our knowledge, no molecular studies of PsA have been done in Northern African populations. These observations prompted us to investigate a possible genetic association between the *LCE3C_LCE3B-del* allele and PsA in the Tunisian population. It is not known whether the genetic risk factor is the deletion or a variant in strong linkage disequilibrium (LD), so we also genotyped the SNP, rs4112788 (T/C), which is in the same LD block Linkage studies have suggested potential epistasis of PSORS1 (the major psoriasis-susceptibility locus 1) in MHC locus with PSORS4. To test for any interaction between the LCE3C_LCE3B-*del* locus and the PSORS1, we genotyped two SNP within the HLA-C region (rs12191877(T/C) and rs2073048 (G/A)) that have been associated with psoriasis in other populations [21, 35].

Patients

All subjects were recruited between 2007 and 2011 and gave their written informed consent for participation in this study. This study was approved by the local Research Ethics Committee. A total of 73 unrelated PsA patients (M/F 44/29; mean age (±SD) 44.93 ± 13.79 years) were recruited from the Departments of Rheumatology at four Tunisian Hospitals (La Rabta Hospital of Tunis, Charles Nicolle Hospital of, Tunis; Farhat Hached Hospital of Sousse and Hedi Chaker Hospital of Sfax).

Each patient underwent a detailed examination by a rheumatologist using a standardized questionnaire covering clinical manifestations, disease duration in joints and skin, age at onset of psoriasis and/or PsA, disease course, and family history of PsA, psoriasis or other skin diseases. The majority of samples satisfied the Classification criteria for PsA (CASPAR) classification system but some were collected prior to the introduction of this classification system [36].

Among the PsA patients, 23 subjects had peripheral arthritis (31 %), 12 of whom had fewer than 5 joints affected (mono- and oligo-arthritis) and 11 with more than five joints affected (polyarthritis); 22 subjects presented with axial involvement (spondylitis) (31 %); 26 subjects had both peripheral and axial manifestations. Among all patients, 26 had enthesis. Joint disease was confirmed by scintigraphy, radiography, or magnetic resonance imaging, where appropriate. All PsA patients had clinical manifestations of psoriasis at the time of study enrollment; plaque-form predominated, and 28 % had pitting nail involvement. Patients did not have any other relevant disease. Table 1 summarizes the main characteristics of the patients.

The control group consisted of 120 unrelated, healthy subjects (M/F 83/37, mean age (±SD) 44 ± 14.56 years) recruited by dermatologists from the Hospital of La Rabta of Tunis and The Military Hospital of Tunis in Tunisia. The controls matched the patient groups for sex, age and regions. None of the control subjects had a rheumatic condition, psoriasis or any other inflammatory disease.

Methods

Blood samples were collected from all subjects in EDTA anticoagulant, and DNA was isolated from whole blood using phenol/chloroform extraction.

LCE3C_LCE3B-*del* genotyping

40 ng of DNA from each sample were genotyped for the EDC deletion by the allele-specific polymerase chain reaction with a modified protocol used by de Cid et al. [24]. Two pairs of primers were combined and were as follows: LCE3-1F:5′-

Table 1 Characteristics of patients with PsA

Number of PsA patients *n* (male/female)	73 (44/29)
Mean age, years ± SD	44.93 ± 13.79
Mean disease duration in joints, years ± SD	12.75 ± 6.64
Mean disease duration in skin, years ± SD	19.16 ± 6.40
Arthritis pattern	
Oligoarthritis, *n* (%)	12 (16 %)
Polyarthritis, *n* (%)	11 (15 %)
Axial arthritis, *n* (%)	22 (30 %)
Peripheral+axial arthritis, n [oligo+axial/poly+axial] (%)	26 [12/14] (36 %)
Isolated enthesis, *n* (%)	2 (3 %)
Enthetis+peripherall and/or axial arthritis, *n* (%)	26 (36 %)
Psoriasis skin lesion	
Plaque, *n* (%)	64 (88 %)
Guttate, *n* (%)	4 (5 %)
Pustular, *n* (%)	2 (3 %)
Palmoplantar pustular, *n* (%)	3 (4 %)
Age at onset of psoriasis	
Type 1 (<40 years)	56 (78 %)
Type 2 (>40 years)	17 (22 %)
Nail involvement, *n* (%)	28 (38 %)
With family PsA or psoriasis history *n* (%)	15 (21 %)

GGATACTAAGAAGTTCTCAC-3′, LCE3-1R:5′GTGGTG AGAGAGGGCATCTC-3′ amplifying a product of 351 pb, spanning the deletion breakpoint, and corresponding to a deleted allele and LCE3-2F: 5′-CATTAGCCTGGAGCTT TTGC-3′, LCE3-2R: 5′-ACAAGTGATAACATTGTCAG GAGG-3′ located within the LCE3C_LCE3B gene cluster and amplifying a product of 561 pb for a wild type allele. Ten microliters of each reaction were electrophoresed on 2 % agarose gels (supplementary Fig. 1).

SNP genotyping

We selected three SNPs for genotyping the rs4112788 which is in LD with *LCE3C_LCE3B-del* and two others the rs12191877 and rs2073048 to test the epistatic effect between PSORS1 and PSORS4.

For that, we used the Sequenom's MassARRAY system (San Diego, CA, USA) according to the manufacturers' specifications for the iPLEX chemistry using 10 ng of genomic DNA. All 73 individuals in the patient group and the 120 individuals in the control group were successfully typed for *LCE3C_LCE3B-del* and for the three SNP.

Statistical analysis

The expected population genotype frequencies (according to the Hardy–Weinberg equilibrium) were compared to our observed genotype frequency findings using the software package Arlequin (version 3.01). Statistical differences between cases and controls in genotype and allele frequency were assessed using the χ^2 test. the odds ratios (OR) values with 95 % confidence intervals (CI) were calculated using the Epi info 6.0 software and P values ≤ 0.05 were considered statistically significant. The minimum detectable effect size with a statistical power of 80 % was assessed [37] using Epi info 6.0 software. To assess the interaction between deletion of LCE genes and PRORS1 markers (rs12191877 and rs2073048), we used the PLINK epitasis test integrated in the PLINK software.

Results

We have carried out a case–control association study of the common deletion, *LCE3C_LCE3B-del*, in a group of 73 Tunisian PsA patients versus 120 ethnically matched controls. Genotyping was performed using the direct allele-specific PCR amplification for *LCE3C_LCE3B-del* and through the Sequenom MassARRAY system for the rs4112788 (T/C), which is in the same LD block with the deletion [24]. All individuals are successfully genotyped. The observed genotype frequencies of the *LCE3C_LCE3B-del* as well as rs4112788 did not differ from those expected under Hardy–Weinberg equilibrium in patients or controls (Table 2). It is worthwhile to point out that all the genotypes of *LCE3C_LCE3B-del* and the rs4112788 were concordant. Thus, all patients and controls who were homozygous for the deletion were also homozygous CC for the rs4112788, all non-deletion homozygotes were homozygous TT at the SNP, and all individuals who were heretozygous for the *LCE3C-LCE3B* deletion were heterozygous CT for rs4112788.

As noted in Table 3, the genotype frequencies of the *LCE3C_LCE3B-del* in PsA patients were not different from those in normal controls under the three genetic models (codominant, dominant, recessive). A similar result was found for the allele frequencies in cases versus those in controls. The deleted allele frequency was found to be 0.69 in cases and 0.7 in controls. For the non-deleted allele, the allele frequencies were 0.31 in a patient group and 0.3 in the control group ($P = 0.843$).

Stratification analysis was performed according to type of arthritis (axial/peripheral disease, oligoarticular/polyarticular distribution, with/without enthesis), age of onset of psoriasis (type 1 and type 2), presence or absence of nail dystrophy, and presence or absence of family history. There was no evidence for association of the deletion with any of these parameters ($P > 0.05$, data not shown).

In addition, we investigated the association between the LCE3C_LCE3B-del and the HLA-C through its proxy

Table 2 Hardy–Weinberg equilibrium test for *LCE3C_LCE3B-del* and the rs4112788 in PsA cases and controls from Tunisia

Group	Controls			Cases		
	Obs. het	Exp. het	*P* value	Obs. het	Exp. het	*P* value
Variant						
LCE3C_LCE3B-del	0.400	0.421	0.662	0.410	0434	0.786
rs4112788	0.400	0.421	0.662	0.410	0434	0.786

Obs. het observed heterozygous genotype, *Exp. het* expected heterozygous genotype

Table 3 Genotypes and alleles distribution for the *LCE3C_LCE3B-del* in arthritis psoriasis and controls from Tunisia

Gene	Genotypes and alleles	Controls ($N = 120$) (%)	Cases ($N = 73$) (%)	*P* value (yates correction)	OR (95 % CI)
	Co-dominant model				
	1 1	12 (10 %)	8 (11 %)	–	1*
	1 2	48 (40 %)	30 (41 %)	0.895	–
	2 2	60 (50 %)	35 (48 %)	0.991	–
	Dominant model				
	1 1	12	8	–	1*
	1 2+2 2	108	65	0.974	–
	Recessive model				
	2 2	60	35	–	1*
	1 2+1 1	60	38	0.897	–
	Alleles				
	1 (wild)	72 (30 %)	46 (31 %)	–	1*
	2 (mutated)	168 (70 %)	100 (69 %)	0.843	–

95 % *CI* confidence interval, *1** reference group

markers (rs12191877 and rs2073048) and evaluated the potential interaction between PSORS1 and LCE3C_LCE3B-del using the two typed SNPs within the HLA-C region. We did not observe evidence for SNP association with PsA [rs12191877, $P = 0.1555$, OR 0.8276, CI (0.6373–1.075) and rs2073048, $P = 0.3396$, OR 0.7349, CI (0.3897–1.386)] in our samples even in subgroup analysis by type of arthritis or the aforementioned parameters. Similarly, no significant epistasic effect was detected, using the epistasis PLINK test between EDC del/rs12191877, neither EDCdel/rs2073048.

Discussion

The deletion of two genes in the LCE gene cluster, *LCE3C* and *LCE3B* (*LCE3C_LCE3B-del*), was previously found to be a susceptibility factor for psoriasis in several populations. As the skin manifestations represent a common feature of both psoriasis and PsA, the implication of the LCE gene cluster in the pathogenesis of PsA has been tested. All the reported studies have been in European or Asian populations, but no data has been published regarding *LCE3C_LCE3B-del*, in the Tunisian population. We therefore used a case–control study to investigate whether the LCE deletion contributes to susceptibility to PsA in the Tunisian population. We also investigated the distribution of rs4112788, a SNP that is in strong LD with the deletion.

In the present study, no association has been found between the *LCE3C_LCE3B* deletion and PsA. Our results are in agreement with a previous study which reported a negative association between *LCE3C_LCE3B-del* and PsA in individuals of German origin [34]. Genotypes of the rs4112788 were always correlated with the genotype of the deletion. This result confirms that the rs4112788 can be used as a proxy for the deletion, confirms that the *LCE3C_LCE3B-del* was genotyped accurately, and excludes the possibility of association between PsA and rs4117288. Given the exactly concordant genotypes between the *LCE3C_LCE3B-del* and the rs4112788, it is highly unlikely that genotyping error determined can account for the lack of association.

Since Tunisia is a Mediterranean country, patients are presumed to share some alleles or mutations with some others neighbouring country such as Italy or Spain [38]. Nevertheless, contrarily to Docampo et alwhich observed a significant association between PsA and the LCE3C_LCE3B-del tag SNP in the Italian and Spanish cohorts [33], our results showed no evidence of association despite the common ethnical origin of the Italian, Spanish and Tunisian populations. Our findings are also in contrast to studies of PsA in the British and Irish samples [32].

The inconsistencies in these results could exist for a number of reasons. First, they could be due to the high prevalence of the *LCE3C_LCE3B-del* allele or its tag SNP (rs4117288, T allele) in the control group. The frequencies of the *LCE3C_LCE3B*-del allele observed in our control group (70 %) and in the German (65.5 %) were significantly higher compared with the prevalence of the *LCE3C_LCE3B-del* allele in Italian controls (57.1 %) or the rs4117288 T allele in the Spanish (55.9 %). This result

was also supported by the metaanalysis of Riveira-Munoz et al. [30] suggesting that an increase frequency of the risk allele in controls decreases its apparent effect on PsA risk. Second, genetic association studies usually require large cohorts of participants. One limitation of our findings is that the number of patients/controls investigated was insufficient to reach a power of 80. Although our patient group was limited in size, it offered a major advantage in that we had very detailed information on clinical course and disease symptoms. This is a premise for conducting reliable analysis of sub-phenotypes including type of articulation, age of onset of psoriasis (type 1 and type 2), presence or absence of nail dystrophy, presence or absence of family history. However, we did not observe evidence for association in any of the subsets tested in contrast to Docampo et al. [33] who identified a nominally stronger association in patients with oligoarticular versus polyarticular disease in the Italian population.

Several studies have shown that HLA-C is an important genetic determinant of both PsA and psoriasis, and focused on the epistasis between LCE3C_LCE3B-del and the PSOS1 locus [30, 39]. In the current study, no association between the HLA-C and PsA and nor epistatic effect were observed in the Tunisian PsA arthritis patients. This is consistent with a previous study that we reported no association of the EDC del with susceptibility to psoriasis in the Tunisian population. Hence differences in the genetic background of the populations, population specific effects, variations in environmental exposure as well as the variability of the disease itself can explain the discrepancy.

In conclusion, the EDC deletion, primarily identified in patients with skin type psoriasis, does not seem to be of a major importance in our Tunisian PsA patients. This supports the current perception that, while there are some common genetic factors for psoriasis and PsA, there are also clearly distinct variants that contribute to the genetic predisposition to PsA. These results need to be confirmed by additional large-scale studies of Tunisian PsA patients and controls. Furthermore, analysis of additional genes within and outside the EDC could lead to the identification of additional risk variants and elucidate distinct aetiological pathways of PsA.

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Conflict of interest We state that we have no commercial affiliations, consultancies, stock or equity interests and patent-licensing arrangements that could be considered to pose a conflict of interest regarding the submitted article. We state that this work has been approved by the local Research Ethics Committee of la Rabta Hospital of Tunis. The authors declare that they have no conflict of interest.

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