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SHORT COMMUNICATION

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CARD15 mutations in patients with plaque-type psoriasis and psoriatic arthritis: lack of association

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Abstract Psoriasis has a strong genetic component in the development of the disease as indicated by familial occurrence and a high concordance rate among monozygotic twins. In genome-wide scans for psoriasis several susceptibility loci have been detected, but the disease-causing genes have not yet been identified. A recent scan, performed on psoriatic arthritis (PsA), which occurs in about 15% of the psoriasis patients showed a significant locus on chromosome 16 in a region that was already described by genome scan for psoriasis. *CARD15*, a major susceptibility gene for Crohn's disease (CD) on chromosome 16q, is an interesting candidate gene for psoriasis, because there is a documented clinical association of CD with psoriasis, and recently the association of *CARD15* mutations with PsA was reported in Newfoundland population. We investigated the association of this variant with PsA and the overall psoriasis genotype in 59 independent patients with PsA in comparison with 361 age and sex-matched controls. In addition, a second cohort of 89 independent North American PsA patients was included. The diagnosis of psoriasis was made by a dermatologist based on standard clinical criteria. In these patients, PsA was defined as an inflammatory joint disease, negative rheumatoid factor, and lack of another causative condition for arthritis. Using case-control analysis, the G908R mutation was weakly associated with psoriasis and PsA, but due to the low frequency of this mutation statistical significance was not reached. All other variants including leu1007fsinsC and R702W did not show any association with psoriasis or PsA. In conclusion, a disease-causing role for *CARD15* mutations could not be confirmed in German or American subjects with PsA.

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Psoriasis is a chronic inflammatory skin disorder of unknown etiology affecting around 2% of the general population in the US and Europe. There is a strong genetic component in the development of the disease as indicated by familial occurrence and a high concordance rate among monozygotic twins [4]. In a genome-wide scan for psoriasis susceptibility loci, a putative susceptibility region was detected on chromosome 16q [12]. A recent scan, performed on psoriatic arthritis, which occurs in about 15% of the patients with plaque-type psoriasis, confirmed a significant locus in that region [8].

CARD15, a major susceptibility gene for Crohn's disease (CD) on chromosome 16q, is an interesting candidate gene for psoriasis, because there is a documented clinical association of CD with psoriasis [10]. Previous investigations of one or more of the major CD-associated *CARD15* variants in patients with psoriasis did not reveal any significant association [2, 13]. Recently, Rahman et al. reported on the association of CARD15 mutations with PsA [14]. As the principal finding, association of R702W was highly significant with an odds ratio of 3.50.

We investigated association of this variant with PsA in patients from our collaborative cohort of more than

Table 1 Genotypes of *CARD15* variants in patients with psoriatic arthritis

	German			US		
	Controls	PsA	OR (95% CI)	Controls	PsA	OR (95% CI)
R702W						
wt/wt	316	53	0.85 (0.36–2.01)[a]	303	80	1.15 (0.51–2.60)[a]
wt/mut	34	5		23	7	
mut/mut	1	0		0	0	
G908R						
wt/wt	349	58	1.50 (0.26–8.82)[a]	311	83	1.02 (0.29–3.58)[a]
wt/mut	4	1		11	3	
mut/mut	0	0		0	0	
leu1007fsinsC						
wt/wt	323	54	0.97 (0.41–2.26)[a]	312	82	1.27 (0.42–3.83)[a]
wt/mut	31	5		12	4	
mut/mut	0	0		0	0	

PsA psoriatic arthritis subset ($n = 146$) of psoriasis patients compared with healthy controls ($n = 686$) in a German and an American cohort; missing values are due to technical errors. *OR* odds ratios are based on the presence of at least one mutated allele versus none, *95% CI*: 95% confidence intervals, *wt* wild type, *mut* mutated allele

[a] $P > 0.05$ after adjustment for multiple testing

800 independent cases with plaque-type psoriasis in comparison with age and sex-matched controls. From the German cohort, 59 unequivocal PsA cases could be identified, 89 independent PsA patients were included from the North American cohort. The diagnosis of psoriasis was made by a dermatologist based on standard clinical criteria. In these patients, PsA was defined as an inflammatory joint disease, negative rheumatoid factor, and lack of another causative condition for arthritis. Appropriate control populations from Germany and North America, respectively, were sampled from local blood donor services. All probands were found to be free of relevant diseases by history, physical examination, and standard laboratory testing.

CARD15 variants were genotyped as described [7] and data were curated in an integrated database [6].

For the whole study population, no significant association of psoriasis with *CARD15* mutations was found (data not shown). As indicated in Table 1, in the two subset of patients with PsA none of the three mutations tested showed a significant association with the disease. Combined odds ratios for the whole PsA study population were also lacking any significant association (Table 2). While the number of PsA patients in our cohort is substantially lower than in the study done by Rahman et al., our subset of patients with PsA still has a power of 80% to detect an odds ratio of at least 2.1 with an observed frequency of the R702W mutation in controls of 10% and a significance level of 0.05 [3]. The G908R mutation was weakly associated with psoriasis and PsA, but due to the low frequency of this mutation statistical significance was not reached. Interestingly, the leu1007fsinsC mutation was less frequent in our psoriasis cohort than in the control population, although not statistically significant after correction for multiple comparisons. In summary, the reported effect of R702W on PsA could not be reproduced in this sample of German and American psoriasis patients.

Table 2 Common odds ratio for *CARD15* variants

Variant	OR	95% CI
R702W	1.00	0.52–1.92
G908R	1.12	0.37–3.43
leu1007fsinsC	1.08	0.51–2.28

OR common odds ratios (Mantel-Haenszel) calculated for the combined subset of German and American PsA patients are based on the presence of at least one mutated allele versus none; *95% CI*: 95% confidence intervals

As the allele frequency of the R702W variant in the control populations of both studies is very similar, the reported effect of Rahman et al. may either be population-specific or may be the result of LD to some as yet unidentified variant in the *CARD15* gene or its genomic neighborhood. Moreover, the Newfoundland population is a relatively isolated one, in which several founder effects have been identified [15, 16]. While the R702W allele seems too common to be the source of a founder effect, it is possible that such an effect is present in a gene with which *CARD15* interacts. Alternatively, selection bias may partly explain the divergent results. Clinical assessment of PsA is a critical issue, as a specific diagnostic test is not available. There are several clinical phenotypes in PsA [11] and the published prevalence of PsA in psoriasis patients varies between 7 and 30% [17]. PsA patients attending a rheumatologic department can be expected to be more severely affected than patients recruited from a psoriasis population. Accordingly, Rahman et al. (2003) noted that patients carrying the R702W mutation had a tendency towards an increased rate of corticosteroid medication and joint surgery, reflecting pronounced disease severity.

In conclusion, our results fail to confirm an effect of *CARD15* variants in PsA. This is in accordance with very recent reports from both an Italian and from a Germany

cohort also lacking any significant association of *CARD15* variants in PsA [5, 9]. However, the confirmation of chromosome 16q as a putative susceptibility locus for psoriasis [1] supports further analysis of this region.

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