Polymorphisms in the *ATG16L1* Gene are Associated with Psoriasis Vulgaris

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Psoriasis is an immune-mediated inflammatory disorder of the skin with a complex pathogenesis and a strong genetic component (1). Several regions in the genome, including the psoriasis susceptibility locus 1 (PSOR1), have been identified as conferring susceptibility to psoriasis (2–4). However, the complete genetic background of psoriasis remains to be established. Autophagy is a fundamental biological process that is involved in cell growth and plays a role in innate and adaptive immunity. In particular, autophagy-selective responses contribute to inflammatory bowel disease (IBD) (5, 6), neurodegeneration (7), and cancer (8). The ATG16L1 protein, which is encoded by the *ATG16L1* gene (2q37), is a key component of a large protein complex essential for autophagy (9), and polymorphisms within this gene have been reported to be associated with Crohn's disease (5). Taking into consideration that genes in the autophagy pathway play an important role in inflammation and immunity, and as a part of our ongoing research on the impact of genetic variants to the risk of psoriasis vulgaris, the aim of the present study was to assess whether polymorphisms in *ATG16L1* gene might also contribute to the risk of psoriasis.

MATERIALS AND METHODS

A cohort of 241 unaffected controls (mean age 35.01 ± 13.60 years, 131 females) with no personal or family history of psoriasis and 299 patients with plaque-type (non-pustular) psoriasis vulgaris (mean age 41.11 ± 13.87 years, age of onset 20.90 ± 8.16 years, 132 females) of Estonian origin were enrolled into a case control study. Clinical examination was performed at the outpatient clinic in the Department of Dermatology and Venereology, University of Tartu. The ethics committee of the University of Tartu approved the study and informed consent was obtained from all participants. Six single nucleotide polymorphisms (SNPs) (rs10210302, rs12994971, rs2241880, rs2241879, rs7587633 and rs13005285) spanning a region of 36 Kb within the *ATG16L1* gene were selected in our analysis, based on the criteria that SNPs had a minor allele frequency (MAF) > 5% in the Utah population of European descent (CEU) and had been validated. The polymorphic sites in the study except the rs2241880 SNP were genotyped using the SNPlex Genotyping System (Applied Biosystems, Foster City, CA, USA) according to manufactures' instructions (10). The rs2241880 SNP was genotyped using the Taqman SNP 5′ allelic discrimination assay (Applied Biosystems) as reported previously (11). Logistic regression was used to obtain odds ratio (OR) values and Walds' confidence intervals (CI) for alleles and genotypes using the R program (www.r-project.org). Linkage disequilibrium (LD) and haplotype analysis was performed using Shesis software (http://analysis.bio-x.cn/myAnalysis.php). A p-value of < 0.05 was considered statistically significant for all analyses.

RESULTS

No significant deviation from the Hardy–Weinberg equilibrium in psoriasis or in the control group was observed (data not shown). The frequencies of alleles and genotypes are presented in Table I. The data analysis showed that the frequencies of the rs10210302 CC (35.5% vs. 27.8%), rs12994971 CC (35.8% vs. 27.8%), rs2241880 AA (36.5% vs. 27.8%), rs2241879 GG (35.5% vs. 27.4%) and rs13005285 TT (19.4% vs. 13.3%) were higher in psoriasis group compared with controls, respectively. Moreover, the frequency distribution (45.0% vs. 38.2%) of the rs13005285 T allele was significantly different (OR = 1.32, 95% CI = 1.03–1.69, $p = 0.024$). LD analysis of the ATG16L1 SNPs showed a highly significant association for each locus pair D′ > 0.95 (data not shown). Haplotype analysis of the ATG16L1 loci (rs10210302–rs12994971–rs2241880–rs2241879–rs7587633–rs13005285) revealed 5 haplotypes (frequency > 0.004) in both the affected and unaffected subjects (Table II). In particular, the frequency distribution of the CCAGTT haplotype was higher (37.3 vs. 32.7%) in the psoriasis group compared with the controls; but it did not reach the level of statistical significance (Table II). On the other hand, the frequency distribution of the CCAGTG was significantly lower (OR = 0.20, 95% CI = 0.04–0.90, $p = 0.021$).

DISCUSSION

We should take into account that, since the frequency distribution of the CCAGTG haplotype is low in our studied population, this might reflect that a larger cohort is required in order to be able to control our findings. Taking into consideration that the autophagy genes play an important role in the immune regulation including thymic selection, lymphocyte development and survival, antigen presentation and tissue homeostasis (12), the autophagy pathway consequently has an impact in several immunological stimuli. Thus, we could speculate that, since the ATG16L1 molecule is a member of this pathway, it probably also plays an important role in immune response, which needs further investigation. Noticeably, it has been reported that defects in the ATG16L1 protein might result in reduced production of antimicrobial peptides by small-intestinal Paneth cells and increased production of secreted pro-inflammatory cytokines, including the IL-1β and IL18, by macro-

Table I. *Genotype and allele frequency (%) distribution of ATG16L1 SNPs in psoriasis patients and controls*

ATG16L1 SNPs	Controls, *n* (%) (*n* = 241)	Psoriasis, *n* (%) (*n* = 299)	OR (95% CI)	*p*
rs10210302				
CC	67 (27.8)	106 (35.5)	1[a]	
CT	132 (54.8)	142 (47.4)	0.67 (0.46–1.00)	0.050
TT	42 (17.4)	51 (17.1)	0.76 (0.46–1.27)	0.30
C	266 (55.2)	354 (59.2)	1[a]	
T	216 (44.8)	244 (40.8)	0.84 (0.66–1.08)	0.18
rs12994971				
CC	67 (27.8)	107 (35.8)	1[a]	
CT	132 (54.8)	142 (47.5)	0.67 (0.45–0.99)	0.045
TT	42 (17.4)	50 (16.7)	0.74 (0.44–1.24)	0.26
C	266 (55.2)	356 (59.5)	1[a]	
T	216 (44.8)	242 (40.5)	0.83 (0.65–1.06)	0.15
rs2241880				
AA	67 (27.8)	109 (36.5)	1[a]	
AG	132 (54.8)	140 (46.8)	0.65 (0.44–0.95)	0.029
GG	42 (17.4)	50 (16.7)	0.73 (0.43–1.21)	0.23
A	266 (55.2)	358 (59.9)	1[a]	
G	216 (44.8)	240 (40.1)	0.82 (0.64–1.05)	0.12
rs2241879				
AA	42 (17.4)	50 (16.7)	0.74 (0.44–1.23)	0.25
AG	133 (55.2)	143 (47.8)	0.66 (0.45–0.98)	0.042
GG	66 (27.4)	106 (35.5)	1[a]	
A	217 (45.0)	243 (40.6)	0.83 (0.65–1.06)	0.14
G	265 (55.0)	355 (59.4)	1[a]	
rs7587633				
CC	96 (39.8)	112 (37.5)	1[a]	
CT	123 (51.1)	149 (49.8)	1.03 (0.72–1.49)	0.83
TT	22 (9.1)	38 (12.7)	1.48 (0.81–2.67)	0.19
C	315 (65.4)	373 (62.4)	1[a]	
T	167 (34.6)	225 (37.6)	1.13 (0.88–1.46)	0.31
rs13005285				
GG	89 (36.9)	88 (29.4)	1[a]	
GT	120 (49.8)	153 (51.2)	1.28 (0.88–1.88)	0.18
TT	32 (13.3)	58 (19.4)	1.83 (1.08–3.09)	0.023
G	298 (61.8)	329 (55.0)	1[a]	
T	184 (38.2)	269 (45.0)	1.32 (1.03–1.69)	0.024

[a]Referent estimate.

phages, which might lead to intestinal inflammation (13, 14). Most recent, it has also been documented that dendritic cells from individuals with Crohn's disease carrying a mutation in *ATG16L1* gene are defective in autophagy, bacterial handling and antigen presentation (15). Hence, the latter evidence supports the notion of an important role of the ATG16L1 molecule in immune signalling and cell activation, and a putative role of *ATG16L1* in susceptibility of psoriasis might also be considered. In particular, a possible defect in the ATG16L1 molecule might affect the autophagy machinery on signalling pathways that regulate cytokine production and result in accumulation of damaged proteins and organelles that are toxic, leading to cell death, tissue damage and chronic inflammation. The precise mechanisms by which the disease-associated autophagy genes affect autophagy pathways are not yet known. However, elucidation of the function of the autophagy genes in the future may lead to potentially novel therapies for treating the diseases in which they are involved.

Table II. *Haplotype frequency distribution of ATG16L1 polymorphisms in psoriasis patients and controls*

ATG16L1 haplotypes[a]	Controls (%) (*n* = 482)	Psoriasis (%) (*n* = 598)	OR (95% CI)	*p*
CCAGCG	15.2	13.9	0.89 (0.63–1.25)	0.52
CCAGCT	5.3	7.7	1.50 (0.91–2.47)	0.10
CCAGTG	1.8	0.4	0.20 (0.04–0.90)	0.021
CCAGTT	32.7	37.3	1.22 (0.95–1.57)	0.11
TTGACG	44.8	40.0	0.82 (0.64–1.04)	0.11

[a]rs10210302–rs12994971–rs2241880–rs2241879–rs7587633–rs13005285.

In conclusion, to our knowledge the present study is the first report addressing a possible impact of the *ATG16L1* gene on the risk of psoriasis. Meanwhile, additional molecular and functional studies in different ethnic groups will be required to ascertain the contribution of the *ATG16L1* gene in psoriasis susceptibility.

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