

Polymorphism of the *TAP1* gene in Polish patients with psoriasis vulgaris

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Abstract. Psoriasis vulgaris is a HLA-associated common and persistent inflammatory skin disease of unknown aetiology. The transporters associated with antigen processing (*TAP*) genes are polymorphic genes located in the HLA class II region and due to their essential involvement in class I antigen presentation might be additional susceptibility genes to psoriasis. To investigate the possible involvement of the *TAP1* gene in the pathogenesis of psoriasis, we analysed its polymorphism in 169 Polish patients with psoriasis vulgaris and compared them with 66 healthy controls. The frequency of *TAP1***D* was significantly increased in the patients, compared to the control group. The *TAP* alleles were also analysed with respect to the age of onset of psoriasis in the patients but no significant differences were recorded. In conclusion, our data suggest that the *TAP1***D* allele could lead to genetic susceptibility to psoriasis vulgaris in Poles.

Key words: gene polymorphism, psoriasis, *TAP* genes.

Psoriasis vulgaris is an inflammatory, hyperproliferative disease of the skin, affecting 1–3% of Caucasians (Ikaheimo et al. 1996). Although the aetiology of the disease is still unknown, the genetic basis for psoriasis is beyond doubt. So far the strongest genetic association has been found for early onset psoriasis and major histocompatibility complex (*MHC*) genes, especially *HLA-Cw6*. There is also some evidence that psoriasis is a T-cell mediated autoimmune process. Activated lymphocytes, other immune accessory cells and lymphokines have been detected in psoriatic plaques (Elder et al. 1994; Henseler et al. 1998). T-cells accumulate early in psoriatic plaques and their cytokines induce abnormal keratinocyte proliferation. In addition to *HLA* genes, immune responses are dependent on several genes encoding molecules that generate and translocate antigenic peptides. The genes in-

involved in class I and II antigen processing pathways include *TAP*, *LMP*, and *HLA-DM*, and may be considered as candidate genes for research on susceptibility to psoriasis. The *TAP* genes are located in the HLA class II region, between the *DQB1* and *DPA1* loci, and exhibit genetic polymorphisms. The *TAP* genes consist of *TAP1* and *TAP2* genes, which encode a heterodimer molecule that forms a heterodimeric complex for delivering antigenic peptides to the endoplasmic reticulum prior to the assembly of class I heavy chain α_2 -microglobulin dimers (Pyo et al. 2003). Two polymorphic sites have been found in the *TAP1* gene and four in the *TAP2* gene. There are four allele combinations of polymorphism in *TAP1* and eight combinations in *TAP2* (Powis et al. 1993). *TAP* polymorphism has been investigated in several HLA-associated diseases in Caucasian patients (e.g. ankylosing spondylitis,

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multiple sclerosis and insulin-dependent diabetes mellitus). The functional consequences of *TAP* polymorphism are still unknown. It has been suggested that psoriasis may be triggered by the direct activation of CD8 and/or NK T-cells bearing receptors for MHC class I molecules (Bos

Frequencies of the *TAP1* alleles for the psoriasis patients and the control group are shown in the Table 1. below. We found that *TAP1***A* was the most frequent allele in both groups. Its frequency in the patients was much lower than in healthy donors (66% vs. 82.6%).

Table 1. *TAP1* alleles frequencies in Polish psoriasis patients in general, type I and type II psoriasis patients, and the healthy control group

<i>TAP1</i> allele	Psoriasis (2n=338)	Type I (2n=274)	Type II (2n=64)	Control (2n=132)
<i>TAP1</i> * <i>A</i>	223 (66.0%)*	181 (66.1%)	42 (65.6%)	109 (82.6%)
<i>TAP1</i> * <i>B</i>	51 (15.1%)	39 (14.2%)	39 (14.2%)	15 (11.3%)
<i>TAP1</i> * <i>C</i>	12 (3.5%)	9 (3.3%)	3 (4.7%)	5 (3.8%)
<i>TAP1</i> * <i>D</i>	52 (15.4%)*	45 (16.4%)	7 (11.0%)	3 (2.3%)

* $p < 0.05$

and De Rie 1999). Therefore the interaction of specific TAP molecules and peptides might cause altered activity of specific *HLA-C*, such as low expression on the cell surface, resulting in the activation of NK cell cytotoxicity to own cells in psoriasis patients, and the associated *TAP* alleles might play a role in the development of psoriasis (Pyo et al. 2003).

For this study we recruited 169 unrelated Caucasian psoriasis patients ($n = 169$; 63 females and 106 males) from the Department of Dermatology, Venereology and Allergology, Medical University of Gdańsk, Poland. Patients were divided according to positive family history and age of onset of psoriasis into two subgroups: type I psoriasis (onset before the age of 40 and positive family history, $n = 138$; 54 females and 84 males) and type II psoriasis (onset later than at the age of 40 and negative family history, $n = 31$; 9 females and 22 males). Healthy Polish volunteer blood donors formed the control group ($n = 66$; 21 females and 45 males). Genomic DNA was extracted from mononuclear cells of peripheral blood according to the enzymatic method of Blood DNA Prep Plus (A&A Biotechnology, Gdańsk, Poland). In our study we used the amplification refractory mutation system (ARMS) PCR method for analysing the *TAP1* gene polymorphism, according to the procedure described by Powis et al. (1993). In each person the two dimorphic sites of the *TAP1* gene encoding different amino acids in positions 333 and 637 were analysed. Each allele of the *TAP1* gene was defined by the combination of polymorphisms at different positions, as follows: *TAP1***A* (Ile-333 and Asp-637), *TAP1***B* (Val-333 and Gly-637), *TAP1***C* (Val-333 and Asp-637) and *TAP1***D* (Ile-333 and Gly-637).

There were no significant differences in frequencies of *TAP1***B* and *TAP1***C* alleles between the groups. The analysis also showed that the frequency of allele *TAP1***D* in psoriasis patients was significantly increased, as compared to the control (15.4% to 2.3%). There were no significant differences in the frequencies of *TAP1* alleles for type I and type II psoriasis.

There have been several reports so far on the analysis of *TAP* alleles in patients with psoriasis. In Germany, Fakler et al. (1994) analysed the *TAP2* gene polymorphism in psoriasis, and showed no significant difference in allele frequencies between the control group and psoriasis type I and/or type II. Two years later, Hohler et al. (1996) reported an increase in the *TAP1***A* allele in Caucasian patients with juvenile onset psoriasis and decrease in the frequency of the other *TAP1* alleles. Ikaheimo et al. (1997) compared five dimorphic amino acid positions of *TAP* genes between the psoriasis and control group but there were no significant differences. A study of Japanese patients with psoriasis, performed by Saeki et al. (1998), showed a decrease in *TAP2***E* allele frequency, but the difference was not significant. They also compared the frequencies of *TAP* alleles between patients with early onset psoriasis (before the age of 30) and late onset psoriasis (after the age of 30), but did not find any differences. The most recent study of Pyo et al. (2003), on association of *TAP* genes with psoriasis in Koreans, showed that the frequency of *TAP2***B* was significantly increased, while *TAP1***B* and *TAP2***A* frequencies were decreased in psoriasis patients, compared with the control group. Our results indicate that psoriasis patients have more frequently the *TAP1***D* allele, which could lead to genetic

susceptibility toward psoriasis vulgaris in Poles. However, further investigations and a much deeper and refined statistical analysis of a larger data set are needed for a definitive conclusion.

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