

The Role of TAP1 and TAP2 Gene Polymorphism in Idiopathic Bronchiectasis in Children

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Summary. Bronchiectasis is characterized by permanent changes in the structure and function of the airways. Its cause cannot be identified in some cases. A genetic disease can predispose to bronchiectasis in our country, where consanguinity of parents is common. Transporter associated with antigen presentation (TAP) deficiency syndrome is characterized by recurrent bacterial lower respiratory tract infections, which cause bronchiectasis. Our aim was to document the relationship between idiopathic bronchiectasis and TAP gene polymorphisms. Forty-four patients with idiopathic bronchiectasis and 100 healthy individuals as the control group were included. DNA was extracted and gene polymorphisms for TAP1 and TAP2 were studied. When compared to healthy controls, in the patient group, Ile/Ile genotype was decreased and Ile/Val genotype was increased in TAP1-333 polymorphism analysis; Asp/Asp and Gly/Gly genotypes were decreased and Asp/Gly frequency was increased in TAP1-637 polymorphism analysis; Ile/Val genotype was increased and Ile/Ile genotype was decreased in TAP2-379 polymorphism analysis; and Thr/Thr genotype frequency was decreased and Thr/Ala and Ala/Ala genotypes were increased in TAP2-665 polymorphism analysis. No statistically significant difference between patient and control groups was noted only in TAP2-565 polymorphism analysis. These results indicate that TAP gene polymorphisms may have had a role in the development of bronchiectasis in our patient group. Therefore, TAP deficiency syndrome should be considered in children with idiopathic diagnosis, since early diagnosis of the disease will improve life quality and survival. *Pediatr Pulmonol.* 2007; 42:237–241. © 2007 Wiley-Liss, Inc.

Key words: bronchiectasis; TAP1; TAP2 gene polymorphism.

INTRODUCTION

Bronchiectasis is characterized by irreversible dilation of the airways associated with frequent bacterial infections and inflammatory destruction of the bronchial and peribronchial tissue. Cystic fibrosis, infections, tuberculosis, primary ciliary dyskinesia, and immune deficiencies are some of the causes of bronchiectasis in children.¹ However, there is a group of children whose etiology remains unknown in spite of extensive investigations.

The TAP1 (transporter associated with antigen presentation) and TAP2 genes are two major histocompatibility complex (MHC) genes located in the class II region of the human leukocyte antigen (HLA) locus on chromosome 6. These genes encode a heterodimer, termed as TAP, which is located on the membrane of the endoplasmic reticulum (ER). It is a member of the ATP-binding cassette family of transport proteins that play important roles in antigen processing and presentation. TAP transports peptides from the cytoplasm into the ER, where they are assembled with HLA class I molecules and are subsequently presented to CD8+ T cells.^{2–5} Therefore, the function of TAP molecules is believed to be important in the initiation and regulation of immune response.⁵ TAP1

and TAP2 genes are polymorphic both in mice and humans and their polymorphisms have been shown to influence the selection of peptide epitopes in rats.⁵ However, data about

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polymorphisms of TAP genes in different human populations point to little functional significance.³

Deletion or mutation of either or both TAP1 and TAP2 genes causes TAP deficiency syndrome, where translocation of peptides into the ER is severely affected. Little is known about human genetic TAP defects. In reported cases, recurrent bacterial infections of the upper respiratory tract usually occur within the first 6 years of life and are characterized by chronic purulent rhinitis complicated by nasal septum perforation, nasal polyps, sinusitis, and otitis media. Patients frequently have involvement of the lower respiratory tract with recurrent bacterial pneumonia and eventually bronchiectasis.² Necrotizing granulomatous skin lesions, typically located on the extremities and in the midface, polyarthritis, and involvement of nervous and gastrointestinal systems have been reported in some patients as well.²

Because bronchiectasis has been reported in patients with TAP deficiency and we had a group of patients with unexplained bronchiectasis, we postulated that a defect in TAP genes may be contributory in these patients. The exact diagnosis of this syndrome is by the identification of the mutation. However, because we were unable to perform mutation studies in our hospital, we preferred to investigate TAP polymorphisms in our patients, because TAP gene polymorphisms have been shown to be associated with some autoimmune or infectious diseases in previous studies.^{3,5-9}

MATERIALS AND METHODS

Control Subjects

Blood samples of unrelated, healthy individuals (n: 100) from different geographical regions of Anatolia were obtained and a repository was constituted at TÜBİTAK DNA/Cell Bank & Gene Research Laboratory. The subjects were between 25 and 45 years of age and the male/female ratio of the group was 1:1.2.

Patient Group

Forty-four children (20 males, 24 females) with idiopathic bronchiectasis aged between 3 and 20 years (median 13 years) were included in the study. Cystic fibrosis, congenital (primary antibody and cellular immunodeficiencies, disorders of phagocyte function and complement system) or acquired (HIV infection, malignancies, bone marrow or solid organ transplantation, immunosuppressive drug use) immunodeficiency disorders, primary ciliary dyskinesia, tuberculosis, and foreign body aspiration were ruled out in every patient. All patients had complaints like chronic cough, recurrent pneumonia, sputum expectoration and crackles and/or rhonchi, and clubbing on the physical examination suggestive of bronchiectasis. Consanguinity between

parents was present in 19 (43.2%) and similar complaints in siblings in 7 (15.9%) patients. Bronchiectasis was diagnosed with high resolution computed tomography of thorax in all patients and was confirmed in the pathologic examination of lobectomy materials in 10 patients. Bronchiectasis was located in right lower lobe in 20, right middle lobe in 16, right upper lobe in 10, left lower lobe in 33, and left upper lobe in 11 patients; involvement of more than one lobe was seen in 27 patients. Every patient was treated with oral or parenteral antibiotics, chest physiotherapy, and expectorants. Informed consent was obtained from all control donors and all patients (or parents in the case of young patients).

Genomic DNA Isolation

Peripheral blood samples (10 cc) were taken into EDTA tubes. Genomic DNA was isolated from these samples according to standard procedure.¹⁰ DNA was stored in TE buffer (pH: 7.5) at 80°C until use.

Analysis of TAP Gene Polymorphisms

PCR (polymerase chain reaction)–RFLP (restriction fragment length polymorphism) was used to determine TAP1 and TAP2 polymorphisms. Two polymorphisms in the TAP1 gene (positions 333 and 637) and three polymorphisms in the TAP2 gene (positions 379, 565, and 665) were analyzed in this study. Genomic DNA samples (0.25 µg) were amplified in 25 µl reaction mixtures containing 0.25 µg of each oligonucleotide primer, 200 µM dNTP's, 1Xtaq DNA polymerase buffer, and 0.5 units of Taq DNA polymerase (Promega, Madison, WI) overlaid with mineral oil. Reaction conditions using a thermal cycler (MJ Research PTC 200, MJ Research Inc., Watertown, MA) were 95°C for 5 min, 35 cycles of 94°C for 1 min, the appropriate annealing temperature for 2 min, 72°C for 2 min and 72°C for 10 min. The amplified fragments were digested with the discriminating restriction enzymes. Digestion products were separated by electrophoresis in 4% agarose gel (3% Nusieve, 1% Seakem. LE, Rockland, ME), stained with ethidium bromide and visualized under UV light (Figs. 1 and 2). The PCR primers and restriction enzymes used in this study are shown in Table 1.

Statistical Analysis

Because TAP genes can be found as heterozygous at more than one position, genotype and amino acid frequencies rather than allele or haplotype frequencies were preferred. Both genotype and amino acid frequencies were calculated for patients and control subjects. Amino acid frequencies were compared by using 2×2 chi square test with df of 1, and genotype frequencies were compared by using 3×2 chi square test with df of 2 utilizing the

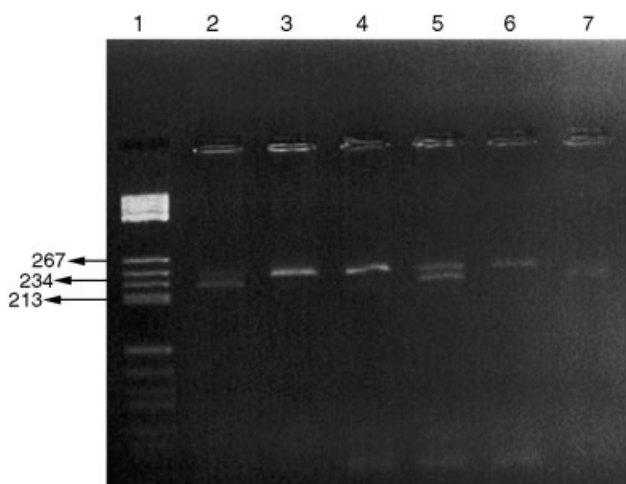


Fig. 1. Analysis of TAP2-665 polymorphism by restriction with *MspI*.

- 1 : DNA marker (pBR322 *HaeIII* digest)
 2, 5 : Ala/Thr (227 bp/207 bp + 20 bp)
 3, 4, 6 : Ala/Ala (227 bp/227bp)
 7 : Thr/Thr (207 bp + 20 bp/207 bp + 20 bp)

statistical program, Stats version 1.1 (Decision Analyst, Inc., Arlington, VA).

RESULTS

When TAP1-333 polymorphism was evaluated, it was found that the Ile/Ile genotype was statistically significantly decreased in the patient group and the Ile/Val genotype was increased ($\chi^2 = 7.97$, df: 2, $P \leq 0.025$).

TAP1-637 polymorphism analysis showed that genotype frequency distribution was different between patient and control groups ($\chi^2 = 27$, df: 2, $P < 0.001$), with a

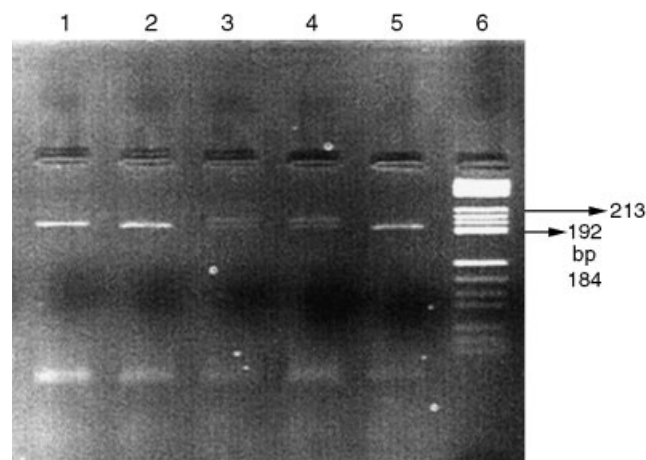


Fig. 2. Analysis of TAP2-379 polymorphism by restriction with *BstUI*.

- 1, 2, 5 : Val/Val (192 bp/192 bp)
 3, 4 : Ile/Val (212 bp/192 bp)
 6 : DNA Marker (pBR322 *HaeIII* digest)

decrease in Asp/Asp and Gly/Gly and an increase in Asp/Gly frequency were noticed in the patient group.

Similarly, TAP2-379 and TAP2-665 gene polymorphism analysis showed significant differences between the two groups ($\chi^2 = 33.2$, df: 2, $P < 0.001$ and $\chi^2 = 104$, df: 2, $P \leq 0.001$, respectively). In TAP2-379 position, there was a significant increase in the Ile/Val genotype and decrease in the Ile/Ile genotype in the patient group and in TAP2-665 position, a decrease in Thr/Thr genotype frequency and an increase in Thr/Ala and Ala/Ala genotypes were noticed in the patient group.

Among the included TAP1 and TAP2 gene polymorphisms, no statistically significant difference in genotype frequency between patient and control groups was noted only in the TAP2-565 polymorphism ($\chi^2 = 1.1$, df: 2, $P \leq 1$). Genotype frequencies for TAP1 and TAP2 gene polymorphisms are shown in Table 2.

DISCUSSION

This is the first study to investigate the role of TAP gene polymorphisms in the pathogenesis of bronchiectasis in our country. In this report, we demonstrated that there were statistically significant differences in four out of five studied genotype frequencies of TAP1 and TAP2 gene polymorphisms between children with idiopathic bronchiectasis and healthy controls. These findings suggest that genetic factors may have a role in the etiopathogenesis of bronchiectasis.

Patients with bronchiectasis present with cough, sputum expectoration, wheezing, and chest pain; crackles, rhonchi, and clubbing of the fingers are some physical examination findings.¹ The estimated prevalence of bronchiectasis is not exactly known, but was reported to be 1.06/10,000 in the report by Clark et al.¹¹, 1: 5,900 in Auckland¹², and 4:10,000 in Alaska¹³; the exact rate is not known in our country. In a previous report from our hospital, among 204 children with bronchiectasis, the etiology could not be determined in 49% of the cases.¹⁴ Although the exact pathogenesis of bronchiectasis is unknown in these cases, genetic factors can be considered to play an important role. Furthermore, the high rate of consanguineous marriage in our country suggests that genetic factors may play a role in the formation of bronchiectasis in children.

Symptomatic TAP deficiency is a rare syndrome and only 18 patients have been reported in the literature to date,^{4,15-17} the most recent two siblings being from Turkey.¹⁷ The characteristics of the disease are recurrent bacterial infections of the upper respiratory tract, like chronic purulent rhinitis often complicated by nasal septum perforation, nasal polyps, sinusitis and otitis media, and involvement of the lower respiratory tract as bacterial pneumonia and eventually bronchiectasis. *Haemophilus influenzae*, *Streptococcus pneumoniae*,

TABLE 1—Primer Sequences and Restriction Enzymes Used for the Analysis of the Polymorphisms

	PCR Primers	Restriction enzyme	Digestion products
TAP1-333	F 5'-CACCTgAgTgATTCTCT-3' R 5'-ACTGACTCTGCCAAGTCT-3'	Sau3AI (37°C, 4 h)	Ile—118, 74, 28, 15 bp Val—146, 74, 15 bp
TAP1-637	F 5'-CCCTATCCAgCTACAACC-3' R 5'-AACGCCACTGCCTGTCGCT-3'	AccI (37°C, 4 h)	Gly—183 bp Asp—132, 51 bp
TAP2-379	F 5'-GAACGCGCCTTGTACCTGCTC-3' R 5'-ACCCCCAAGTGCAGCAC-3'	BstUI (60°C, 16 h)	Ile—212 bp Val—192, 20 bp
TAP2-565	F 5'-ggAgCAAgCTTACAATTgTAAGgATACC-3' R 5'-CTGTTCTCCGGTTCTGTGAGGAACAACAGT-3'	ScaI (37°C, 4 h)	Ala—162 bp Thr—132 bp, 30 bp
TAP2-665	F 5'-ggTgATTgCTCACAggCTgCCg-3' R 5'-CACAGCTCTAGGGAAACTC-3'	MspI (37°C, 4 h)	Ala—227 bp Thr—207 bp, 20 bp

Staphylococcus aureus, *Klebsiella species*, *Escherichia coli*, and *Pseudomonas aeruginosa* are the micro-organisms commonly isolated from their respiratory tract. The chronic bacterial infections and the bronchiectasis may progressively lead to respiratory failure and death.² The presence of bronchiectasis in TAP deficiency syndrome and the high prevalence of idiopathic bronchiectasis in our patients led us to consider that TAP deficiency may have been contributory in those patients.

TAP genes are located between DQB1 and DPA1 loci on human chromosome 6 and exhibit genetic polymorph-

ism. TAP1 and TAP2 proteins are homologous and facilitate the transport of peptides across the membrane of the ER in an adenosine triphosphate-dependent manner and have an important role in the T-cell mediated immunity. Two dimorphic sites have been found in the TAP1 gene and four dimorphic sites in the TAP2 gene.¹⁸ However, the TAP gene polymorphism has been shown to be functionally effective only in rats.¹⁹ Studies in humans have shown contradictory results. One study suggested that human TAP1 polymorphism influenced the antigenic peptide transport in human lymphoblastoid and tumor cells,²⁰ whereas another in vitro study could show no functional efficacy of the human TAP polymorphism.²¹ Nevertheless, in several studies, the TAP gene polymorphism has been suggested to be associated with some disorders like type I diabetes mellitus, Sjögren syndrome, Graves disease, Hashimoto disease, diffuse panbronchiolitis, hepatitis C virus infection, sarcoidosis, human immunodeficiency virus (HIV)-I infection, and human alveolar echinococcosis disease.^{3,5-9} In our report, we determined for the first time that the TAP gene polymorphism can be associated with bronchiectasis, although it is well known that polymorphisms in human TAP genes have not been reconciled with any functional variation and that the role of TAP genes in disease susceptibility is not clear.²²

One limitation of our study is linkage disequilibrium of TAP genes. As TAP genes are located between the HLA-DQ and DP loci centromeric to HLA-DR, a strong linkage disequilibrium has been found between TAP genes and HLA class II genes in different reports.²³⁻²⁶ However, in one recent study, no evidence of linkage disequilibrium was found between TAP1 and TAP2 or between TAP genes and HLA-DR, -DP, and -DQ in an Eastern Andalusian population in southern Spain.¹⁷ As we did not have the opportunity to make a linkage disequilibrium analysis, we cannot exclude the possibility that TAP polymorphism association could be secondary to linkage disequilibrium between TAP and HLA class II genes. Therefore, our data should be cautiously interpreted with this probability in mind.

TABLE 2—The Comparison of TAP1 and TAP2 Polymorphism Genotype Frequencies in Patient and Control Group

TAP polymorphism	Control group (n = 100)		Bronchiectasis (n = 44)		χ^2
	(n = 100)	(%)	(n = 44)	(%)	
TAP1-333					
Genotypes					
Ile/Ile	75	75	26	59	7.97
Ile/Val	21	21	17	39	
Val/Val	4	4	1	2	
TAP1-637					
Genotypes					
Asp/Asp	82	82	31	70	27
Asp/Gly	4	4	12	27	
Gly/Gly	14	14	1	2	
TAP2-379					
Genotypes					
Ile/Ile	25	25	1	2	33.2
Ile/Val	1	1	7	16	
Val/Val	74	74	36	82	
TAP2-565					
Genotypes					
Thr/Thr	1	1	0	0	—
Thr/Ala	4	4	2	5	
Ala/Ala	95	95	42	95	
TAP2-665					
Genotypes					
Thr/Thr	99	99	13	30	104
Thr/Ala	1	1	15	34	
Ala/Ala	0	0	16	36	

As a curative treatment of TAP deficiency is not yet available, the only option is supportive treatment. The major objectives of therapy for patients with TAP deficiency syndrome are early recognition, aggressive treatment of respiratory infections, and prevention of bronchiectasis.² When diagnosis is made, intravenous or oral antibiotics, chest physiotherapy, vaccinations for respiratory pathogens, and avoidance of exposure to tobacco are options of treatment in these patients.⁴

In conclusion, although the number of tested patients was small, our investigation demonstrated preliminary data that the TAP gene polymorphism may have a role in the pathogenesis of bronchiectasis. In order to prove this finding, further powered studies with larger numbers of patients and controlled data for linkage disequilibrium with other genes in MHC class II region are needed. TAP deficiency syndrome should be kept in mind in patients with bronchiectasis whose etiology remains unknown despite extensive investigations, especially in communities where consanguinity of parents is common. Early diagnosis will enable initiation of early supportive treatment which will improve life quality and decrease morbidity.

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