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EC MICROBIOLOGY
Short Communication

Interleukin-17A Serum Concentrations - No Association with *IL17A* Gene Polymorphisms in the Bacillus Calmette-Guerin Osteitis Cohort

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Received: May 28, 2018; **Published:** August 30, 2018

Abstract

Serum Interleukin-17A concentration was measured in 127 former Bacillus Calmette-Guerin (BCG) osteitis patients at 21 - 49 years of age, and the concentrations varied from < 1.22 pg/ml to 1973.5 pg/ml. The concentrations did not differ between those who were carriers of the minor allele A of the *IL17A* rs4711998 polymorphism and who were not, and between those who were potential carriers of the haplotype GTA of the *IL17A* rs4711998, rs8193036 and rs2275913 polymorphisms and who were not. In conclusion, we found no evidence on the association between the genotypes or haplotypes of three polymorphisms of the IL17A gene and serum IL-17A concentrations in former BCG osteitis patients.

Keywords: *Bacillus Calmette-Guerin; Interleukin-17; Osteitis; Single Nucleotide Polymorphisms; Vaccination*

Abbreviations

BCG: Bacillus Calmette-Guerin; IL-17A: Interleukin-17A (Protein); *IL-17A*: *Interleukin17A* (gene); SNP: Single Nucleotide Polymorphism

Introduction

Interleukin-17 (IL-17) family promotes the host's defense against mycobacterial infections. In our previous study, the polymorphism rs2275913 of the *IL17A* gene was associated with an increased osteitis risk after Bacillus Calmette-Guerin (BCG) vaccination as newborns [1]. The variant genotypes were significantly more common in 132 former BCG osteitis patients than in 405 population-based controls aged two to three months in a birth cohort study. However, we were not able to document significant differences in serum IL-17A concentrations between those who had the variant and those who had the wild genotype [1]. In the further analyses, the minor allele A of the *IL17A* rs4711998 polymorphism and the haplotype GTA of the *IL17A* rs4711998, rs8193036 and rs2275913 polymorphisms were significantly more common in the former BCG osteitis patients than in 99 population-based controls from the FIN data of the 1000 Genomes Project [2]. The software that are available for haplotype analyses estimate the frequencies of haplotypes in the cohorts taking into account the population data, but they do not identify the individual cases who have the haplotype in question [3]. Therefore, only the potential carriers of the haplotypes constructed theoretically can be assessed.

The aim of the present study was to evaluate serum IL-17A concentration in those former BCG osteitis patients who were carriers of the minor allele A of the *IL17A* rs4711998 polymorphism compared to those who were not, and in those former BCG osteitis patients who were potential carriers of the haplotype GTA of the *IL17A* rs4711998, rs8193036 and rs2275913 polymorphisms compared to those who were not.

As published previously, the *IL17A* rs2275913 polymorphism [1] and the *IL17A* rs4711998 and rs8193036 polymorphisms [2] were studied in 132 former BCG osteitis patients aged 21 - 49 years from across Finland. BCG osteitis was diagnosed and treated in infancy after newborn BCG vaccination. The genotyping was performed with the high-resolution melting analysis (Roche Diagnostics Light Cycler 480, Basel, Switzerland) at the University of Turku, Finland [1,2]. Serum IL-17A concentration was measured in blood samples of the former BCG osteitis patients using the Bio-Plex Pro Human IL-17A kit with the detection limit of 1.22 pg/ml (Bio-Rad, Helsinki, Finland) at the University of Turku, Finland [1,4].

Exploratory data analyses showed that serum IL-17A concentrations were non-normally distributed. The independent samples Mann-Whitney U test was used in the comparisons of serum IL-17A concentrations between the carriers and non-carriers of the minor allele A of the *IL17A* rs4711998 polymorphism and between the potential carriers and non-carriers of the GTA haplotype of the *IL17A* rs4711998, rs8193036 and rs2275913 polymorphisms.

The Ethics Committee of the Tampere University Hospital district (Pirkanmaa) accepted the study, and a written informed consent was obtained from all participating subjects, including a permission for genetic studies on susceptibility to mycobacterial infections. The samples were studied in the laboratory as coded without any identification data included.

Serum IL-17A concentration was measured in 127 cases with good-quality samples available, and the concentrations varied from < 1.22 pg/ml to 1973.5 pg/ml. The median was 21.0 pg/ml (interquartile range (IQ) 12.8 - 48.0) in the 52 carriers of the minor allele A of the *IL17A* rs4711998 polymorphism and 29.9 pg/ml (15.6 - 63.4) in the 76 non-carriers ($p = 0.122$). The median was 33.4 pg/ml (IQ 13.9 - 56.0) in the 78 subjects who were potential carriers of the GTA haplotype of the *IL17A* rs4711998, rs2275913 and rs8193036 polymorphisms and 24.7 pg/ml (12.6 - 65.9) in those 50 who were not potential carriers ($p = 0.662$).

Thus, there was no significant association between IL-17A concentration and the polymorphism rs4711998 of the *IL17A* gene in former BCG osteitis patients, although the minor allele A was significantly more common in them than in population controls [2]. In fact, the result was similarly negative, when serum IL-17A concentrations were compared in the same cohort in relation to the *IL17A* rs2275913 polymorphism, though the presence of that polymorphism had a significant association with BCG osteitis risk [1].

Further, there was no significant association between IL-17A concentration and the GTA haplotype of the *IL17A* rs4711998, rs2275913 and rs8193036 polymorphisms. This GTA haplotype was significantly associated with BCG osteitis risk in our previous study applying the HaploView software [2,3]. The HaploView like other similar software estimates the frequency of the haplotype in the cohort from a certain population but does not identify the individual patients [3]. The frequency of the GTA haplotype in the present BCG osteitis cohort was 0.291, which means that the real number of GTA carriers would be 40 among our 127 cases. The number of potential GTA carriers who in theory might have the haplotype was 78, and serum IL-17A concentration did not differ between them and those 50 who cannot have the GTA haplotype. Thus, our negative result was only a rough estimate.

We measured the serum IL-17A concentration when the former BCG osteitis patients were 21 - 49 years old, although they presented with BCG osteitis in infancy. Thus, serum IL-17A concentration does not reflect the situation during or immediately after BCG osteitis. In the present cohort, the IL-17A concentrations were many times higher than in two to three months old healthy infants whose serum samples were studied in the same laboratory by the same method [4]. There was a significant association between the *IL17A* rs2275913 genotypes and serum IL-17A concentration in that cohort of healthy infants [4]. Therefore, we expected that serum IL-17A concentrations would have been associated with the *IL17A* gene polymorphisms also in the present study.

Conclusion

The result of the present study was negative. We found no evidence on the association between the genotypes or haplotypes of three polymorphisms of the *IL17A* gene and serum IL-17A concentrations in former BCG osteitis patients.

Acknowledgements

Tampere Tuberculosis foundation supported financially this study.

Conflicts of Interests

Nothing to declare.

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Volume 14 Issue 9 September 2018