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Atopic phenotype associations with rs7927894 inter gene polymorphism on chromosome 11q13.5 in Czech adult patients with atopic dermatitis

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Abstract

Aim: Aim of the study was phenotype-genotype association analysis of rs7927891 polymorphism in adult patients with Atopic Dermatitis (AD).

Material and methods: Finally, 90 patients were enrolled to the study, 31 men (30 ± 10 years) and 59 women (31 ± 11 years). Among them, 65% of men and 75% of women reported positive family history of atopic phenotype.

Results: We did not observe significant differences in genotype distribution and/or allelic frequencies between AD men and women in polymorphism rs792894. But, the CT genotype of polymorphism rs7927894 on chromosome 11q13.5 was more than 4times more frequently observed in AD women with elevated levels of the total IgE above 158 IU/ml. In AD men, a significant association of polymorphism rs7927894 on chromosome 11q13.5 with atopic phenotype/predisposition was found: the genotypes CC and TT are 6 times more frequent in AD men with other atopic phenotype (asthma, atopic rhinitis) compared to AD men without it. The TT genotype of the polymorphism was 4 times more frequent in men with positive family history of atopic phenotypes.

Conclusion: We identified significant risky genotypes for some AD phenotypes in rs7927894 polymorphism in patients with AD, differently for adult AD men and women.

Introduction

Atopic Dermatitis (AD), or eczema, is one of the most common chronic inflammatory skin diseases with prevalence rates of up to 20% in children and 3% in adults. It commonly starts during infancy and frequently precedes or co-occurs with asthma and rhinitis. It is characterized by dry skin, intense pruritus, and a typical age-related distribution of inflammatory lesions with frequent bacterial and viral superinfections. Profound alterations in skin barrier function and immunologic abnormalities are considered key components affecting the development and severity of AD, but the exact cellular and molecular mechanisms remain incompletely understood [1].

Atopic dermatitis (AD) has high heritability. Apart from filaggrin (*FLG*), the genes influencing AD are largely unknown. An association signal was recently identified at 11q13.5 (rs7927894), downstream of *C11orf3* [2-4]. The polymorphism rs7927894 is located in an intergenic region 38 kb downstream of *C11orf30* (chromosome 11 open reading frame 30) and 68 kb upstream of *LRRC32* (leucine rich repeat containing 32). *C11orf30* and *LRRC32* are found to be ubiquitously expressed, including in tissues relevant to atopic dermatitis such as skin and peripheral blood mononuclear cells. The potential involvement of *C11orf30* in multiple inflammatory and malignant epithelial diseases (atopic dermatitis, Crohn's disease and adenocarcinoma) strongly suggests a role for *C11orf30* in epithelial immunity, growth and/or differentiation [3] Approximately 13% of individuals of European origin are homozygous for rs7927894 [T], and their risk of developing atopic dermatitis was calculated to be 1.47 times higher that of non-carriers [5].

In this study we performed genotype-phenotype study for rs7927894 single nucleotide polymorphism on chromosome 11q13.5 in a group of 90 adults with atopic dermatitis.

Material and methods

Patients

Total of 90 patients with AD, diagnosed and treated at the 1st Department of Dermatology of St Ann's Faculty Hospital Brno were recruited to the study. The patients were diagnosed according to the generally accepted criteria Hanifin and Rajka [6].

Demographic data are presented in Table 1 and 2. None phenotypic differences between man and women (M/W) were significant.

All these patients were genotyped for rs7927894 by conventional PCR method with restriction analysis.

This study was approved by the Committee for Ethics of Medical Experiments on Human Subjects, Faculty of Medicine, Masaryk

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Table 1. Descriptive characteristics- personal history.

Sex M/ W (N=90)	32%/68%
Age M/ W (years)	30 ± 10/ 31 ± 11
Personal history of atopic phenotype (s) M/W	65%/47%
Personal history of aero allergy M/W	90%/73%
Personal history of food allergy	29%/41%
Personal history of other complex disease (not atopy) M/W	23%/39%
Personal history of diabetes mellitus	0%/5%
Personal history of cardiovascular diseases	11%/18%
Personal history of GIT diseases M/W	8%/12%
Personal history of thyreopathy	0 %/7%

M/W-men/women

Table 2. Descriptive characteristics-family history.

Family history of atopy M/W	65 % /75%
Family history of other than atopic diseases M/W	71%/80%
Family history of psoriasis M/W	3 % /19%
Family history of thyreopathy M/W	10%/45%
Family history of diabetes mellitus M/W	53/59%
Family history of cancer M/W	36 %/60%
Family history of cardiovascular disease M/W	36%/66%

M/W-men/women

University, Brno (no. 64/93, 1993) and was performed in adherence to the Declaration of Helsinki Guidelines. Participants gave their written informed consent which has been archived.

Genotyping

Genotyping was performed using PCR and restriction analysis.

Genomic DNA was purified from peripheral blood leukocytes by the standard method using the phenol-chloroform extraction and the proteinase K digestion of cells.

Genotype in rs7927894 polymorphism on chromosome 11q13.5 was detected using PCR reaction (primers 5´- TGT TAA GAA TCC CCA CCT CAC T-3´ and 5´-GCC TCA GTT TCC TCA TGG TAA G-3´) with HINFI restriction analysis. The genotypes were distinguished as CT (9, 85, 106,182 / 9, 85, 288 bp), CC (9, 85, 106,182/9, 85, 106,182 bp) and TT (9, 85, 288/9, 85, 288 bp).

The genotypes were determined by 2% agarose Serva electrophoresis.

Statistics

Statistical analysis was performed using STATISTICA software (StatSoft, version 11). One-tailed Fisher exact test was used for all categorical data, Mann–Whitney U-test and Kruskall-Wallis test for continuous data. Four different modes of inheritance were tried: allele-based additive model (one allele vs. the other), genotype-based dominant (more common homozygote vs. rarer allele carrier), codominant/recessive (rarer homozygote vs. common allele carrier) and overdominant model (both homozygotes vs. heterozygote).

Results

We did not observe significant differences in genotype distribution and/or allelic frequencies in the detected polymorphism between men and women (data not presented).

No significant genotype/phenotype association was found when AD men and women have been evaluated all together.

After division of the group of patients to men and women, some differences have been observed: in AD women, the CT genotype of polymorphism rs7927894 on chromosome 11q13.5 was more frequently detected in AD women with elevated levels of IgE (OR=4.76, 95% CI 1.19-18.98, P=0.02, Table 3). In AD women, we found a significant association of polymorphism rs7927894 on chromosome 11q13.5 with atopic phenotype: the genotypes CC and TT are 6 times more frequent in AD men with other atopic phenotype compared to AD men without it (OR=6.22, 95% CI 1.212-31.938, P=0.03). At the same time, the TT genotype was 4x more frequent in AD men with positive family history of atopic phenotypes (OR=4.286, 95% CI 0.444-41.364, P=0.05, Table 4).

Discussion

In addition to *FLG*, two European GWAS on atopic dermatitis established four susceptibility loci (*C11orf30*, *OVOL1*, *ACTL9*, and *RAD50/IL13/KIF3A*) [2-3]. Single nucleotide polymorphism rs7927894 appears to mark a genuine eczema susceptibility locus [7]. Recently, polymorphism C11orf30-rs2155219 was found to double the risk of poly-sensitization (specific IgE/4 allergens) [8].

According to our study, the TT genotype in rs7927894 of was 4 times more frequent in AD patients with positive family history of atopic phenotypes, but only in men. Austrian study refers a significant association of the rs7927894 variant on chromosome 11q13.5 with atopic dermatitis. But, genotype-phenotype study analysis revealed no significant association of rs7927894 with early age of onset of the disease, concomitant asthma and allergic rhinoconjunctivitis, total serum IgE levels and family history of atopy [9] which is not in agreement with our results. Different results could be caused by strictly separated statistical analysis of AD men and women data performed in our study.

Other polymorphic sites have been discovered in other QWAS studies [10-11], probably many of them in linkage disequilibrium and with some inter population differences.

We identified significant risky genotypes for some AD phenotypes in rs7927894 polymorphism in patients with AD, differently for adult AD men and women.

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Table 3. rs7927894 (11q13.5) genotype and IgE levels in AD women.

rs7927894 (11q13.5)	No elevated IgE (<158 IU/ml)	Elevated IgE (v ≥ v158 IU/ml)	Row Totals
CC	11 (61%)	17 (41%)	28
CT	3 (17%)	20 (49%)	23
TT	4 (22%)	4 (10%)	8
All Grps	18	41	59

Table 4. rs7927894 (11q13.5) genotype and family history of atopy in AD men.

rs7927894 (11q13.5)	Family history of atopy	No family history of atopy	Row Totals
CC	7 (35%)	4 (36%)	11
CT	7 (35%)	7 (64%)	14
TT	6 (30%)	0 (0%)	6
All Grps	20	11	31

komplexních chorob/ stavů", **MUNI/A/1549/2014** and of the project "Faktory ovlivňující průběh a léčbu u chronických a závažných kožních diagnóz", **MUNI/A/1557/2014** with the support of the Specific University Research Grant, as provided by the Ministry of Education, Youth and Sports of the Czech Republic in 2015.

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