Differences in genetic predisposition to Graves’ disease (GD) and Graves’ orbitopathy (GO) between young and elderly patients.

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Introduction
Graves’ disease is a complex disorder. Genetic predisposition modified by environmental factors is responsible for the pathogenesis of GD. Young patients are susceptible to environmental factors for a shorter time than older patients, thus the impact of genetic factors may be higher than environmental factors in patients with young age of GD diagnosis. Differences in the disease phenotype between younger and older patients may suggest a different genetic predisposition to the disease. The association between genetic markers and the age at the diagnosis was reported in type 1 diabetes, rheumatoid arthritis and multiple sclerosis.

Orbitopathy (GO) and GD hyperthyroidism have the common autoantigen TSHR which plays a key role in triggering the onset of the disease. Taking into account the diverse nature of the GO phenotype, especially in young patients and lack of the relation of time of the GO with development of hyperthyroidism, the pathogenesis of GD and GO may differ with different genetic backgrounds. Current studies suggest a correlation between polymorphism in cytokines involved in orbit inflammation and GO, but not GD. It has been confirmed that GO risk increases with age and is considerably higher in smokers.

The aim of the study was to assess genetic predisposition to GD and GO in young patients (age of diagnosis ≤ 30 years of age) in which the time of environmental effects was shorter than in older patients.

Methods
735 GD patients and 1216 healthy controls from Poland were included in the study. 338 of the patients had orbitopathy NOSPECS ≥ 2. Association analyses were performed after correcting for the genetic variants in genes encoding proteins involved in immune response (HLA DRB1, TNF, CTLA4, CD40, NFKB, PTPN22, IL4 and IL10). RTSH and the age of diagnosis of GD and GO. Patients were stratified by the age of diagnosis of GD and GO.

Results
Our analysis demonstrated an association between HLA DRB01*03 and the age of GD diagnosis. Patients with age 330 years at GD diagnosis had higher frequency of the HLA DRB01*03 allele. The genotype containing at least one DRB01*03 allele occurred almost twice as often in younger patients (Tab. 1). Young carriers of the DR3 polymorphism were more common then the older ones both in familial and sporadic GD. This results suggest the existence of different genetic conditions for the development of GD in young people.

No association was observed between DRB01*03 allele and the duration of pharmacotherapy, GD relapse rate, number of radiodiagnosis treatment courses, thyroid receptor (TR) Ab level and gender.

Table 1. HLA DRB01*03 genotypes in patients with GD stratified by the age at GD diagnosis.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>GD (n=735)</th>
<th>GD &lt;30 (n=338)</th>
<th>OR (95% CI), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1/3*01</td>
<td>50 (20)</td>
<td>18 (8)</td>
<td>0.85 (0.54-1.34)</td>
<td></td>
</tr>
<tr>
<td>DRB1/3*03</td>
<td>156 (67)</td>
<td>93 (33)</td>
<td>2.21 (1.53-3.19)</td>
<td></td>
</tr>
<tr>
<td>DRB1/3*12</td>
<td>7 (3)</td>
<td>2.00 (0.19-21.38)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* carriers of minor alleles

We found a significant association between orbitopathy and HLA DRB01*03 and TSHR gene rs179247 polymorphisms. We observed an higher frequency of the HLA DRB01*03 allele in young patients (p=0.010). Tab. 2.

In younger patients without orbitopathy the A allele of TRSH gene rs179247 occurred significantly more often in comparison with those with GO (P=0.013). In younger patients group there was a statistically significant difference in genotype distribution (P=0.038). The presence of an AA homozygous locus was associated with a significant reduction in the risk of GO incidence as compared to patients with AG or GG genotypes (P=0.019)

In our study the allele A carriers were dominant in the group of patients with orbitopathy (N=145 vs N=90), especially in younger patients group (N=64 vs N=28). Orbitopathy was not present in 88% of young AA homozygote carriers (N=30 vs N=5) (Fig. 1).

These findings showed the association between the presence of the allele A and lesser risk of GO in young GD patients.

Fig. 1. Incidence of GD patients with age at GD diagnosis ≤30 years and with the AA genotype TSHR is 179247.

In the group of all patients or only older patients (age at diagnosis >30 years) the frequency of alleles present and genotype distributions of polymorphisms HLA DRB1 and TSHR rs179247 did not differ in patients with or without GO.

Conclusions
1. Polymorphism of HLA DRB01*03 is associated with an early age at diagnosis of GD.
2. Carriers of the HLA DRB01*03 allele are significantly more common in young patients with GO.
3. The allele A of the TSHR polymorphism is associated with a lower risk of GO in young patients with GD.

Bibliography