A Functional IRF5 Variant Predicts Prognosis in Patients with Systemic Sclerosis


SSc: High mortality and morbidity but variable course

- Systemic sclerosis (SSc) → high mortality and morbidity.
- Standardized mortality ratios in female and male patients with SSc are 3.8 and 2.7, respectively*.
- Highly variable course: Milder form with limited internal organ involvement → widespread internal organ involvement.
- Predictive biomarkers can aid clinicians in providing more focused monitoring and treatment.

First SSc-genome wide association study
1st SSc-GWAS → Three non-MHC susceptibility loci*:
- Interferon regulatory factor 5 (IRF5)†
- Signal transducer and activator of transcription 4 (STAT4)‡
- T-cell receptor zeta (CD247)

†Dieude et al. Arthritis Rheum 2009;60:225-233

Objective

To investigate the impact of the non-MHC susceptibility loci on survival and severity of interstitial lung disease (ILD) in SSc patients.

Study population

- Overall study population: 1443 patients with systemic sclerosis
  - Discovery cohort → n=914
    * Recruited from Genetics versus Environment in Scleroderma Outcomes Study (GENISOS)
    * Scleroderma Family Registry and DNA Repository
  - Replication cohort → n=529
    * Johns Hopkins Scleroderma Cohort

All patients were of European ancestry.

Disclosure

- I have no relevant financial relationships to disclose.
Survival Analysis

- Cox proportional hazards regression model was utilized
- Vital status was determined by the CDC National Death Index and the Social Security Death Index
- The best fitting model was additive genetic inheritance mode which was used for all reported comparisons

Study population

<table>
<thead>
<tr>
<th></th>
<th>Discovery cohort (n=914)</th>
<th>Replication cohort (n=529)</th>
<th>Combined cohort (n=1443)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (± SD)</strong></td>
<td>45.3 (13.6)</td>
<td>45.9 (13.5)</td>
<td>45.6 (13.6)</td>
</tr>
<tr>
<td><strong>Disease duration</strong></td>
<td>9.7 (8.7)</td>
<td>9.6 (8.5)</td>
<td>9.7 (8.6)</td>
</tr>
<tr>
<td><strong>Diffuse skin involvement %</strong></td>
<td>37.1</td>
<td>32.9</td>
<td>35.6</td>
</tr>
<tr>
<td><strong>Deceased %</strong></td>
<td>15.9</td>
<td>14.7</td>
<td>15.5</td>
</tr>
<tr>
<td><strong>Anti-topoisomerase I %</strong></td>
<td>17.5</td>
<td>15.9</td>
<td>17.0</td>
</tr>
</tbody>
</table>

Association of susceptibility loci with survival in discovery cohort (n=914)

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRF5</td>
<td>rs4728142</td>
<td>0.76 (0.6, 0.96)</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>rs12537284</td>
<td>0.94 (0.69, 1.29)</td>
<td>0.726</td>
</tr>
<tr>
<td></td>
<td>rs10488631</td>
<td>0.95 (0.68, 1.33)</td>
<td>0.760</td>
</tr>
<tr>
<td>STAT4</td>
<td>rs3821236</td>
<td>1.01 (0.77, 1.32)</td>
<td>0.943</td>
</tr>
<tr>
<td>CD247</td>
<td>rs2056626</td>
<td>1.23 (0.93, 1.57)</td>
<td>0.091</td>
</tr>
</tbody>
</table>

Association of susceptibility loci with survival in replication cohort (n=529)

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRF5</td>
<td>rs4728142</td>
<td>0.73 (0.54, 0.99)</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>rs12537284</td>
<td>0.84 (0.55, 1.29)</td>
<td>0.434</td>
</tr>
<tr>
<td></td>
<td>rs10488631</td>
<td>0.59 (0.35, 0.98)</td>
<td>0.042</td>
</tr>
<tr>
<td>STAT4</td>
<td>rs3821236</td>
<td>1.45 (1.02, 2.05)</td>
<td>0.036</td>
</tr>
<tr>
<td>CD247</td>
<td>rs2056626</td>
<td>1.01 (0.74, 1.39)</td>
<td>0.926</td>
</tr>
</tbody>
</table>

Association of susceptibility loci with survival in the combined cohort (n=1443)

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>MAF</th>
<th>Discovery p-value</th>
<th>Replication p-value</th>
<th>HR (95% CI)</th>
<th>Combined P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRF5</td>
<td>rs4728142</td>
<td>0.49</td>
<td>0.031</td>
<td>0.047</td>
<td>0.75 (0.61, 0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>rs12537284</td>
<td>0.17</td>
<td>0.726</td>
<td>0.494</td>
<td>0.99 (0.71, 1.38)</td>
<td>0.391</td>
</tr>
<tr>
<td></td>
<td>rs10488631</td>
<td>0.15</td>
<td>0.760</td>
<td>0.002</td>
<td>0.74 (0.53, 0.92)</td>
<td>0.006</td>
</tr>
<tr>
<td>STAT4</td>
<td>rs3821236</td>
<td>0.23</td>
<td>0.943</td>
<td>0.006</td>
<td>1.1 (0.86, 1.38)</td>
<td>0.495</td>
</tr>
<tr>
<td>CD247</td>
<td>rs2056626</td>
<td>0.38</td>
<td>0.001</td>
<td>0.606</td>
<td>1.1 (0.8, 1.24)</td>
<td>0.287</td>
</tr>
</tbody>
</table>

Association of susceptibility loci with survival

- None of the investigated SNPs were associated with age at disease onset
- Adjustment for age at disease onset:
  - IRF5 rs 4728142 → survival: (HR: 0.79, 95%CI: 0.66-0.95, p=0.012)
  - Adjustment for disease type and serology (ACA and ATA):
    - IRF5 rs 4728142 → survival: (HR: 0.81, 95%CI: 0.66-0.99, p=0.043)
IRF5 rs 4728142 was associated with survival in the discovery and replication cohorts.

Are the susceptibility loci associated with severity of ILD?

- % predicted FVC → as a continuous variable was used as the outcome measure
- The relationship between the susceptibility loci and severity of ILD was investigated in the Scleroderma Family Registry and GENISOS cohorts by linear regression analysis

IRF5 rs4728142 predicts severity of ILD in SSc*

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Regression coefficient</th>
<th>P value</th>
<th>Adjusted P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRF5</td>
<td>rs4728142</td>
<td>2.57 (0.38, 4.76)</td>
<td>0.022</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>rs12537284</td>
<td>1.27 (-1.64, 4.18)</td>
<td>0.391</td>
<td>0.390</td>
</tr>
<tr>
<td></td>
<td>rs10486631</td>
<td>0.73 (-2.51, 3.97)</td>
<td>0.657</td>
<td>0.658</td>
</tr>
<tr>
<td>STAT4</td>
<td>rs1821236</td>
<td>-1.08 (-3.83, 1.67)</td>
<td>0.441</td>
<td>0.420</td>
</tr>
<tr>
<td>CD247</td>
<td>rs2056626</td>
<td>0.16 (-2.17, 2.49)</td>
<td>0.889</td>
<td>0.845</td>
</tr>
</tbody>
</table>

*Adjusted for disease duration

Summary

- IRF5 rs 4728142 minor allele is associated with longer survival and milder ILD
- Minor allele frequency: 49% → common variant → making it potentially suitable for biomarker development

Position of IRF5 rs4728142

IRF5 rs4728142 and IRF5 gene expression in monocytes

- Located in the promoter region of IRF5 gene
- Is IRF5 rs4728142 associated with differential gene expression levels of IRF5?
- IRF5 gene expression was examined conditional on IRF5 SNPs in monocytes
IRF5 rs4728142 is associated with differential levels of IRF5 gene expression in patients (p=0.034) and controls (p=0.016)

Limitations

• Not all IRF5 polymorphisms were investigated in comprehensive manner → Other IRF5 genetic polymorphisms might also contribute to the severity of disease in SSc

• IRF5 rs4728142 SNP might be associated with other important disease manifestations such scleroderma renal crisis, severity of GI involvement and pulmonary hypertension

Conclusions

• Minor allele of a SNP in the IRF5 promoter region (rs4728142), associated with lower IRF5 transcript levels, was predictive of better survival and milder ILD in patients with SSc.
• Further support for importance of genes involved in type I IFN pathway in pathogenesis of SSc
• Potentially important implications for biomarker development and identification of therapeutic targets

Thank you

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Patients with systemic sclerosis and unaffected controls