Functional characterization of a novel KLF11 mutation identified in a family with autoantibody-negative type 1 diabetes

Ushijima K.1, Kawamura T.2, Ogata T.3, Yokota I.4, Sugihara S.5, Narumi S.1, Fukami M.1
The Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes
1National Research Institute for Child Health and Development, 2Osaka City University School of Medicine, 3Hamamatsu University School of Medicine,
4Shikoku Medical Center for Children and Adults, 5Tokyo Women's Medical University Medical Center East

Introduction

• KLF11 is a transcription factor that is ubiquitously expressed in human tissues, including islet cells and exocrine pancreas.
• KLF11 knock-out mice showed lower serum insulin levels than wildtype mice, indicating that decreased KLF11 expression level causes impaired glycemic regulation3).
• To date, two KLF11 mutations (p.A347S, p.T220M) have been identified in three families clinically diagnosed with type 2 diabetes2).

Our case

<table>
<thead>
<tr>
<th>Age at diagnosis (yr)</th>
<th>WT (n=4)</th>
<th>A347S (n=4)</th>
<th>H418Q (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Sister</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Mother</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

They were diagnosed with autoantibody-negative type 1 diabetes (T1D).

Methods

Mutation detection:
Exome sequencing and Sanger sequencing

Evaluation of the KLF11 variants:
3D structure modeling
Western blotting
Immunofluorescence
Luciferase assay
- CHO cells
- Transient transfection
- 6xGC-luc* *six tandem repeats of a KLF11-binding site

Results

Luciferase assay: 6xGC box

Discussion

• For the first time, we identified the KLF11 mutation-carrying family with antibody-negative “T1D”.
• In our study, H418Q-KLF11 had a dominant-negative effect, which could possibly explain severer phenotypes observed in our patients than in previously reported patients.
• KLF11 is known to cause transcriptional repression by direct interaction with the scaffold corepressor protein Sin3A3,4). A347S-KLF11 is defective in corepressor binding, although do not interfere the binding between WT-KLF11 and corepressors.
• Contrastingly, the binding between WT-KLF11 and corepressors was interfered by H418Q-KLF11, probably through competitive bindings to the corepressors.

Conclusion

KLF11 mutation with the dominant-negative effect is likely to be associated with the T1D-like phenotype.

References:
4) Fernandez-Zapico ME et al. EMBO J, 2003

Conclusion

KLF11 mutation with the dominant-negative effect is likely to be associated with the T1D-like phenotype.