Identification of a Novel -99A>T IAPP Gene Mutation in A North Indian Type-2-Diabetes Patient with Hypertension

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Abstract

Several studies conducted worldwide supports that mutations in activator domains of promoter region (-91 to -222 bp) of IAPP gene can lead to increased Islet amyloid deposition, β cells destruction and insulin resistance. Considering it a pilot study we conducted to identify amylin promoter mutation and its association in patients diagnosed having both type-2-diabetes and hypertension. Strikingly we identified a novel −99A>T mutation in a 35 year old female patient with BMI of 26.4 kg/m² and family history of diabetes and hypertension. To elucidate whether the identified mutation disrupts the binding site for transcription factors, potential binding sites in the vicinity of this mutation was screened for using the TESS master (Transcription Element Search System) a computer program on TRANSFAC, EMBL, CBIL databases. This −99A>T mutation produced a sequence 5ˈ˗ATTGG˗3ˈ (corresponding to −101 to −97 of IAPP gene promoter) and its complementary sequence 3ˈ˗TAACC˗5ˈ formed a putative binding site for CAAT box binding transcription factors (CTF) like CBP, CP-1, C/EBPa. All these CTFs are well established transcription activators, their role in initiation and maintaining efficiency of eukaryotic transcription is also very well established. This activator domain −99A>T mutation of IAPP gene can possibly increase gene transcription, production, deposition of Islet amyloid ultimately leading to pathogenesis of type-2-diabetes.

Case Description

A 37-year-old North-Indian woman with type-2-diabetes mellitus was enrolled in a clinical study to establish association of promoter mutation -132G>A of IAPP (Amylin) gene and hypertension associated with type-2-diabetes mellitus. Patient was diagnosed having type2 diabetes mellitus at the age of 29 years and was diagnosed having hypertension 3 weeks prior to the study enrolment. Her family history was limited to her mother having diabetes. Patient had a BMI of 26.4 kg/m² at enrolment and being treated with insulin, statins and ACE-inhibitor.

The baseline investigations including blood glucose, blood urea, serum creatinine, fasting lipid profile of patient were done. Results of metabolic chemistry were within reference intervals except for increased levels of postprandial glucose (Postprandial 218 mg/dL; reference interval, <180 mg/dL), total cholesterol (218 mg/dL; reference interval, 150-200 mg/dL), triglycerides (445.75 mg/dL; reference interval, 50-200 mg/dL). The HBA1C value was 12.2% (reference interval, <6.0%). Patient had no micro and macro-vascular complications. All other laboratory results including serum electrolytes, serum lipoproteins, total protein, albumin, are shown in Table 1. Genomic investigation of patient was done and strikingly we identified a novel mutation −99A>T in IAPP (Amylin) proximal promoter region. The mutated sequence produced a putative binding site for CAAT box binding transcription factors (CTF) like CBP, CP-1, C/EBPa. All these CTFs are well established transcription activators, their role in initiation and maintaining efficiency of eukaryotic transcription is also very well established. This activator domain −99A>T mutation of IAPP gene can possibly increase gene transcription, production, deposition of Islet amyloid ultimately leading to pathogenesis of type-2-diabetes.

Discussion

Islet amyloid polypeptide (IAPP) also called as Amylin is a 37 amino acid peptide is a major subunit of amyloid found in insulinomas and pancreatic islet amyloid of patients with type 2 diabetes mellitus [1]. The structural and functional feature of amylin suggests that it has a hormonal control over carbohydrate metabolism in partnership with insulin and other glucoregulatory factors. Immunolocalisation studies of its secretory granules confirmed that amylin is synthesised in, and probably co-secreted from the β-cells of the Islets of Langerhans [2]. Apart from its pathological role in type-2-diabetes [3,4], amylin also plays a vital role in glycemic regulation by various mechanisms like delaying gastric emptying, stimulating satiety centre in hypothalamus, thereby delaying the rate of appearance of glucose in blood and preventing post-prandial spikes in blood glucose levels [5]. The human amylin gene IAPP which encodes the complete polypeptide is located in short arm of chromosome12; (12p12.1). IAPP has a proximal promoter region, exon1, intron1, exon2, intron2, exon3 (coding region-approximately 187 bp) and 130 nucleotides following the stop codon [6]. Amylin is probably generated by proteolytic processing similar to that of pro-insulin and other islet pro-hormones. DNA cloning studies in humans and rats had proved that amylin is generated from a precursor called proamylin with a signal peptide within itself which undergoes proteolytic cleavage to form a small pro-hormone-like sequence called proamylin which is further cleaved proteolytically to form mature amylin [2]. Like insulin, amylin is also secreted in response to plasma glucose by β-cells, it has been studied that Insulin gene and IAPP gene exhibit sequence similarity in their promoter region, so the activation of any promoter is capable of driving a activating signal to other heterologous promoter in a tissue-specific manner [7]. So an activator mutation in promoter either of gene will positively affect the transcription of other. This supports that hyperinsulinemia goes hand-in-hand with hyperamylinemia. Previous mutation studies on IAPP gene promoter reported −132G>A mutation in type 2 diabetes patients with a frequency of 0.8% in New Zealand Maori population [6], 10% in Spanish population [8], 4% in Danish Caucasians [9].

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The IAPP promoter mutation −99A>T identified in our study was found in activator domain (located between -91 to -222 bases upstream of exon1) of the IAPP promoter producing a potential binding site for transcription activators like CCAAT box binding transcription factors which may lead to increased transcription of IAPP gene ultimately leading to increased islet amyloid production, deposition and β-cell destruction, hypertension through stimulation of RAAS.

**Table 1:** Selected patient laboratory results with corresponding reference intervals.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>218</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>442.75</td>
<td>&lt;100</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>42.56</td>
<td>30-60</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>112.31</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>137</td>
<td>136-145</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.83</td>
<td>3.5-5.3</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>101</td>
<td>98-106</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>17.85</td>
<td>10-50</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.56</td>
<td>0.5-1.3</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>7.48</td>
<td>6.4-8.3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.4</td>
<td>3.5-5.2</td>
</tr>
</tbody>
</table>

**Conclusion**

The novel mutation −99A>T identified in our study was found in activator domain (located between -91 to -222 bases upstream of exon1) of the IAPP promoter producing a potential binding site for transcription activators like CCAAT box binding transcription factors which may lead to increased transcription of IAPP gene ultimately leading to increased islet amyloid production, deposition and β-cell destruction, hypertension through stimulation of RAAS.

**References**

11. http://www.cbl.upenn.edu/cgi-bin/tess/tess