Transcription Factor 7-Like-2 (TCF7L2) rs7903146 (C/T) Polymorphism in Patients with Type 2 Diabetes Mellitus

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Keywords
Type 2 diabetes mellitus · Transcription factor 7-like-2 · rs7903146 polymorphism

Abstract
Introduction: Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by the incapability of pancreas to increase insulin secretion to compensate for insulin resistance in the peripheral tissues. T2DM is a multifactorial disease including several environmental factors with the presence of genetic predisposition. The transcription factor 7-like-2 gene (TCF7L2) rs7903146 (C/T) polymorphism is one of the most susceptible genes to T2DM discovered to date, with contribution to the disease through the Wnt/β-catenin signaling pathway affecting pancreatic islet development, expression of several genes involved in insulin granules exocytosis, and the incretin glucagon-like peptide 1 (GLP-1) gene. Then, TCF7L2 gene seems to affect diabetes susceptibility through B-cell dysfunction that is why we studied its association with T2DM in particular. Objectives: To investigate the potential association of the transcription factor 7-like-2 (TCF7L2) rs7903146 (C/T) gene polymorphism in patients with T2DM. Methods: A case-control study conducted on 70 T2DM patients recruited from the endocrinology clinic at Ain Shams University Hospitals, and 30 non-diabetic healthy controls age- and sex-matched with the patients. All subjects underwent full history taking; thorough clinical examination; routine laboratory investigations including hemoglobin A1c, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol; and determination of TCF7L2 gene polymorphism by qRT-PCR. Results: The minor T allele of the rs7903146 (C/T) SNP was associated with high risk of development of T2DM with an OR of 1.35 (95% CI: 0.68–2.6) and the heterozygous genotype (CT) with an OR 1.16 (95% CI: 0.49–2.7); however, they were statistically insignificant (p value >0.05). Conclusion: Our study did not confirm the presence of significant association between the TCF7L2 rs7903146 (C/T) polymorphism and T2DM; however, it pointed out the possibility of presence of high risk of development of T2DM in patients with TT genotype. Further studies with higher sample size are needed to clarify the association.

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Introduction

According to the World Health Organization (WHO), diabetes mellitus (DM) is described as a group of metabolic disorders characterized by the presence of hyperglycemia. The heterogeneous etiopathology includes defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat, and protein metabolism. The effects of DM include long-term damage, dysfunction, and failure of various organs [1].

Type 2 diabetes mellitus (T2DM) represents a global major health-care burden. According to the International Diabetes Federation (IDF), Egypt is in the World’s 8th place in terms of diabetes incidence, affecting up to 8.2 million people. By the year 2045, Egypt is expected to be in the 6th place, with about 16.7 million diabetic patients, due to the rapidly increasing and aging population, which will represent the highest incidence in the Middle East and North Africa region [2].

T2DM is a multifactorial disease that manifests itself as a result of significant interactions between environmental factors influenced by multiple genetic factors and predisposition. Recently, more than 20 genetic variants associated with T2DM have been identified; however, transcription factor 7 like-2 (TCF7L2) gene polymorphisms, especially the rs7903146(C/T) SNP, is thought to be one of the strongest candidates involved in the association with T2DM [3].

The transcription factor 7-like-2 (TCF7L2) gene encodes a transcription factor involved in the Wnt signaling pathway, which plays an important role in pancreatic islet development. TCF7L2 protein forms heterodimers with β-catenin, inducing the expression of various genes, including the insulinotropic hormone glucagon-like peptide 1 (GLP-1) gene, the insulin gene, and other genes that encode proteins involved in processing and exocytosis of insulin granules [4]. This leads to B-cell dysfunction, which is the main etiology of T2DM.

Aim of the Work

The aim of this work is to investigate the potential association of the transcription factor 7-like-2 (TCF7L2) rs7903146 (C/T) gene polymorphism in patients with T2DM.

Patients and Methods

This study is a case-control study, conducted at the Clinical Chemistry Laboratory, Clinical Pathology Department, Ain Shams University Hospitals, in the period from March 2019 to December 2019. Subjects enrolled in the study were divided into 2 groups. Group I – Patient Group (n = 70): it involved 70 T2DM patients recruited from the Endocrinology Clinic in Ain Shams University Hospitals and diagnosed according to the IDF criteria; a fasting plasma glucose level of 126 mg/dL or higher on more than 1 occasion (fasting is defined as no caloric intake for at least 8 h), or a 2-h plasma glucose level of 200 mg/dL or higher after a 75-g oral glucose load on more than 1 occasion, or hemoglobin A1c (HbA1c) level of 6.5% or higher, or a random plasma glucose level of 200 mg/dL or higher with classic symptoms of hyperglycemia. Group II – Control Group (n = 30): This group included 30 age- and sex-matched non-diabetic healthy subjects. Subjects with any of the following conditions were excluded from the study: type 1 diabetes mellitus, any other endocrine dysfunction, chronic kidney disease, chronic liver disease, alcoholism, and patients receiving medications as corticosteroids, β-blockers, or thiazide diuretics or women taking oral contraceptives. All subjects included in this study underwent full history taking: thorough clinical examination; routine laboratory investigations including HbA1c and lipid profile, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and TG; and determination of TCF7L2 gene polymorphism by qRT-PCR.

Serum lipid profile was measured by enzymatic colorimetric method and glycated HbA1c was measured by turbidimetric immunnoassay, and both were done using Roche/Hitachi Cobas® c501 System (Roche Diagnostics International Ltd., Switzerland). Genomic DNA was extracted from peripheral blood by using DNA purification Mini Kit (QIAamp®; Qiagen, Switzerland) and TaqMan® genotyping master mix (Applied Biosystems, Foster City, CA, USA) was used. The TCF7L2 rs7903146(C/T) SNP was analyzed by RT-PCR using the readymade genotyping assay kit (ThermoFisher Scientific, Waltham, MA, USA) containing sequence-specific forward and reverse primers and 2 fluorescent (VIC/FAM)-labeled TaqMan probes for distinguishing between the 2 alleles.

Statistical Analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 15.0. Quantitative data were expressed as mean ± SD for numerical parametric data. Qualitative data were expressed as frequency and percentage for non-numerical data. Student’s t test was used to assess the statistical significance of the difference between 2 study group means for parametric data. The χ² test was used when comparing between 2 independent groups of samples with respect to the categorical data. Odds ratio (OR) with 95% confidence interval (CI) was calculated for associated risk to T2DM in

Table 1. Demographic data of the patient and control groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>T2DM patients (n = 70)</th>
<th>Control (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.2±18.99</td>
<td>52.8±13.76</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>31 males (44.3)</td>
<td>15 males (50)</td>
</tr>
<tr>
<td></td>
<td>39 females (55.7)</td>
<td>15 females (50)</td>
</tr>
</tbody>
</table>

T2DM, type 2 diabetes mellitus.
Table 2. Comparative statistics of routine laboratory tests between the patient and the control groups using Student’s t test

<table>
<thead>
<tr>
<th>Routine laboratory parameter</th>
<th>T2DM patients $(n = 70)$ $\chi \pm SD$</th>
<th>Control $(n = 30)$ $\chi \pm SD$</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.5±1.6</td>
<td>5.0±0.1</td>
<td>8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>223±45</td>
<td>195±37</td>
<td>2.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>43±12</td>
<td>53±17</td>
<td>2.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>158±24</td>
<td>118±22</td>
<td>7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>160±85</td>
<td>109±50</td>
<td>5.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

T2DM, type 2 diabetes mellitus; HbA1c, hemoglobin A1c; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglycerides; $p < 0.05$, significant; $p < 0.001$, highly significant.

Table 3. Descriptive and comparative statistics between the patient and the control groups as regards TCF7L2 rs7903146 genotype frequencies using the $\chi^2$ test

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients $(n = 70)$</th>
<th>Control $(n = 30)$</th>
<th>$\chi^2$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC (%) (wild)</td>
<td>27/70 (39.6)</td>
<td>14/30 (46.7)</td>
<td>1.67</td>
<td>0.432</td>
</tr>
<tr>
<td>CT (%) (heterozygous)</td>
<td>40/70 (57.1)</td>
<td>16/30 (53.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT (%) (mutant)</td>
<td>3/70 (4.3)</td>
<td>0/30 (0.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\chi^2$, $\chi^2$ test; $p > 0.05$, non-significant.

different genotypes, alleles, and models of inheritance. Probability value (p value) indicates the level of significance, where $p < 0.001$ was considered as highly significant, $p < 0.05$ was considered significant, and $p > 0.05$ was considered insignificant.

Results

Descriptive statistics of the demographic data between T2DM patients and the healthy controls are illustrated in Table 1. Comparative statistics of routine laboratory results are presented in Table 2. Results showed that the patient group had a highly significant statistical increase in glycated HbA1c as well as serum LDL-C and serum triglyceride (TG) levels ($p < 0.001$, respectively). Moreover, a significant increase in serum TC was observed in the patient group ($p < 0.05$), whereas serum HDL-C was significantly higher in the control group than in the patient group ($p < 0.05$).

The TCF7L2 was genotyped in all studied subjects; the descriptive and comparative statistics of the genotype frequencies of the TCF7L2 rs7903146 (C/T) polymorphism are illustrated in Table 3. In T2DM patients, 39.6% had the wild-type CC genotype, 57.1% had the heterozygous CT genotype, and 4.3% had the mutant TT genotype. On the other hand, 46.7% of the controls were CC genotype, 53.3% were CT genotype, and none of the control group had TT genotype. There was no statistically significant difference observed between the patients and controls regarding the genotype frequencies ($p > 0.05$).

As for the allele frequencies, descriptive and comparative statistics in Table 4 show that the C allele was present in 67.1% of the patients and 73.3% of the controls ($p > 0.05$). The T allele was found in 32.9% of the patients and 26.7% of the controls ($p > 0.05$).

Table 5 illustrates the OR between T2DM patients and controls regarding genotypes, alleles, and dominant model of inheritance. ORs for the CC and CT genotypes were 0.71 and 1.16, respectively, while none of the patients group had the TT genotypes, which made it difficult to calculate OR, and for the C and T alleles, they were 0.74 and 1.35, respectively. As regards the dominant, OR
was 0.71. However, no statistical significant difference was observed in either the genotype, allele frequencies, or in the dominant model between patients and controls (p > 0.05, respectively).

**Discussion**

T2DM is the most common form of DM, accounting for ~90% of cases. It has a strong genetic component that is amplified by several environmental and lifestyle factors. T2DM is characterized by impaired insulin action in target tissues such as muscle, liver, and fat, that is, insulin resistance, coupled with insufficient secretion of insulin from the β-cells of the pancreatic islets. Hyperglycemia results when insulin secretion is unable to compensate for insulin resistance [5].

The TCF7L2 gene product is a transcription factor that plays an essential role in the Wnt/β-catenin signaling pathway, acting on the cell proliferation, polarization, embryogenesis, and tissue homeostasis. The Wnt pathway in turn regulates pancreatic β-cells proliferation and acts on insulin secretion. It has been discovered that changes in this pathway can alter the insulin action and resistance, facilitating the T2DM onset [6].

The discovery in 2006 by Grant et al. [7] that a common single nucleotide polymorphism (SNP) in the TCF7L2 gene region was associated with T2DM in an Icelandic case-control study has launched a new direction in diabetes research. Soon after, these results were replicated in other ethnic groups through multiple genome-wide association studies. Notably, the T risk allele of the rs7903146 confers the strongest risk of T2DM known to date in Caucasians and other ethnic groups [8].

The present study aimed to investigate the potential association of the transcription factor 7 like-2 (TCF7L2) rs7903146 (C/T) gene polymorphism in patients with T2DM. The present study was conducted on 70 T2DM patients who were recruited from the Endocrinology Clinic in Ain Shams University Hospitals and 30 non-

### Table 4. Descriptive and comparative statistics between the patient and the control groups as regards TCF7L2 rs7903146 (C/T) allele frequencies using the $\chi^2$ test

<table>
<thead>
<tr>
<th>Allele</th>
<th>Patients (n = 70)</th>
<th>Control (n = 30)</th>
<th>$\chi^2$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (%)</td>
<td>94/140 (67.1)</td>
<td>44/60 (73.3)</td>
<td>0.75</td>
<td>0.385</td>
</tr>
<tr>
<td>T (%)</td>
<td>46/140 (32.9)</td>
<td>16/60 (26.7)</td>
<td></td>
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</tbody>
</table>

$\chi^2$, $\chi^2$ test; $p > 0.05$, non-significant.

### Table 5. Statistical analysis of the genotype and allele frequencies of the TCF7L2 rs7903146 (C/T) polymorphism among patients and controls using odds ratio

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients (n = 70)</th>
<th>Control (n = 30)</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC genotype (% (wild))</td>
<td>27/70 (39.6)</td>
<td>14/30 (46.7)</td>
<td>0.71 (0.3–1.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CT genotype (% (heterozygous))</td>
<td>40/70 (57.1)</td>
<td>16/30 (53.3)</td>
<td>1.16 (0.49–1.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>TT genotype (% (mutant))</td>
<td>3/70 (4.3)</td>
<td>0/70 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alleles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C allele (%)</td>
<td>94/140 (67.1)</td>
<td>44/60 (73.3)</td>
<td>0.74 (0.37–1.45)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>T allele (%)</td>
<td>46/140 (32.9)</td>
<td>16/60 (26.7)</td>
<td>1.35 (0.68–2.6)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Dominant model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC (%)</td>
<td>27/70 (39.6)</td>
<td>14/30 (46.7)</td>
<td>0.71 (0.3–1.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CT + TT (%)</td>
<td>43/70 (61.4)</td>
<td>16/30 (53.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; $p > 0.05$, non-significant.
diabetic healthy subjects who were age- and sex-matched and fulfilling the exclusion criteria. Detection of the TC- 
F7L2 rs7903146(C/T) polymorphism was done for both the patient and control groups.

As regards the laboratory data, the comparative statistical analysis between T2DM patients and healthy controls showed a highly statistical significant difference in the LDL-C and TG levels (p < 0.001, respectively), as well as a statistical significant difference in the TC (p < 0.05), all being higher in patients than in controls, whereas HDL-C levels showed a statistical significant difference (p < 0.05), being higher in controls.

The characteristic features of diabetic dyslipidemia are high plasma TG concentration, low HDL-C concentration, and increased concentration of LDL-C particles. The lipid changes associated with DM are attributed to increased free fatty acid release from insulin-resistant fat cells. The increased flux of free fatty acids into the liver in the presence of adequate glycogen stores promotes TG production, which in turn stimulates the secretion of apolipoprotein B and VLDL-C. The impaired ability of insulin to inhibit free fatty acid release leads to enhanced hepatic VLDL-C production. The increased number of VLDL-C particles and increased plasma TG levels decrease the level of HDL-C and increase the concentration of small dense LDL-C [9].

The TCF7L2 rs7903146(C/T) polymorphism was investigated by RT-PCR, and our results showed that the frequency of the genotypic distribution of this SNP was 39.6% CC (wild genotype) in the patient group and 46.7% in the control group (p > 0.05). The CT (heterozygous) genotype was 57.1% in the patient group and 53.3% in the control group (p > 0.05). Although the TT (mutant) genotype was only found in the patient group and was not presented in the control group, it did not reach statistical significant difference (p > 0.05). This may be attributed to the small sample size included in this study. Similar results were obtained concerning the allelic distribution of the TCF7L2 rs7903146(C/T) polymorphism.

Our results came to agreement with studies performed on Arab Caucasians in Saudi Arabia by Acharya et al. [10] as well as in the United Arab Emirates by Saadi et al. [11], whose results showed no significant association of the SNP with T2DM. Another study conducted among Africans in Cameroon by Guewo-Fokeng et al. [12] showed that there was no association of the SNP with T2DM. Similar results were obtained in studies carried out by Pourahmadi et al. [13] in Iran and Chang et al. [14] in China, where the T allele was not found to have an impact on the association with T2DM.

However, in contrast to the present study, other studies replicated in European, Asian, African, and Caucasian ethnicities concluded that the presence of the T allele was associated with increased risk of T2DM. For instance, regarding European ancestry, González-Sánchez et al. [15] conducted a study in Spanish population and found a statistical significance of the occurrence of the T allele with T2DM. Anjum et al. [16] in Chinese population, Danquah et al. [17] in Ghanaian population, Ezzi di et al. [18] in Tunisian population, and Assmann et al. [19] in Brazilian population came to the same conclusion of the significance of association of the TCF7L2 rs7903146 (C/T) polymorphism and T2DM susceptibility, especially the homozygous TT genotype. A meta-analysis conducted by Lou et al. [20] on subjects from different ethnic groups showed a positive correlation of the rs7903146 C/T SNP with T2DM, and this agrees with a previous meta-analysis made by Ding et al. [21].

The underlying mechanisms of action of TCF7L2 variants in the etiology of T2DM are still uncertain, given that all the TCF7L2 SNPs identified so far are located in the intronic regions. Thus, it is necessary to clarify how the intronic variants affect TCF7L2 gene expression. In this context, Lyssenko et al. [22] found that rs7903146 T allele carriers exhibited a significant elevation of TCF7L2 mRNA expression in human pancreatic islets, which was associated with impaired insulin secretion, incretin effects, and enhanced rates of hepatic glucose production.

In 2010, Gaulton et al. [23] reported that in human islets, the chromatin state at the TCF7L2 locus is more open in chromosomes carrying the rs7903146 T allele. They measured enhancer activity in 2 β-cell lines and found that the T allele showed significantly greater enhancer activity than the C allele. The authors concluded that the T allele affects T2DM susceptibility by altering cis-regulation and local chromatin structure in human pancreatic islets. The cis-regulators are regions of non-coding DNA, which regulate the transcription of neighboring genes, and they are vital components of genetic regulatory networks, which in turn control morphogenesis, anatomical development, and other aspects of embryonic development.

Despite the fact that our study has not found a statistical significant difference between the patients and controls regarding genotype or allele frequencies, when calculating the OR, the genotypic distributions of the TCF7L2 rs7903146(C/T) polymorphism and the heterozygous (CT) were observed to carry a risk for T2DM by having an OR (95% CI) of 1.16 (0.49–2.7). Moreover, the TT genotype was observed exclusively in the patient group. In
addition, these results were strengthened by calculating the OR for the T allelic distribution with an increased risk by having an OR (95% CI) of 1.35 (0.68–2.6).

ORs and CIs were calculated for the dominant inheritance model. The dominant model is supposed to show whether the presence of the T allele, as a risk allele under investigation, increases the risk to T2DM, while the recessive model tests the essentiality of the presence of 2 copies of the T allele, that is, homozygous TT genotype, in order to increase the risk [19]; hence, it could not be calculated. Results of the present study revealed that the dominant model, that is, CC versus CT + TT, had an OR (95% CI) of 0.7 (0.3–1.7). These results may point high and increased possibility of development of T2DM in the presence of the TT genotype.

The conflicting results between the expression of the positive OR with no statistical significant difference between the patients and the controls regarding the presence of the T allele, the occurrence of the heterozygous CT, and the homozygous TT genotypes are most probably attributed to the relatively small sample size, which exerted a drawback to the statistical association.

In a meta-analysis made by Song et al. [24], the authors found that compared with those homozygous for the C allele (CC), carriers of the T allele (i.e., TT and C/T) had significantly lower levels of fasting insulin and homeostasis model assessment of insulin secretion (HOMA-%B) and higher fasting glucose and 2 h post-load glucose levels. Moreover, those carriers were associated with T2DM by having OR (95% CI) of 1.41 (1.37–1.46). Similarly, González-Sánchez et al. [15] found that the T allele was associated with a greater OR for T2DM with an OR (95% CI) of 1.29 (1.06–1.57) and Anjum et al. [16] observed an OR (95% CI) of 1.39 (1.22–1.61) for the T allele. The conflict and the variability in the results seen in the different association studies may arise due to the differences in several genetic and environmental factors, ethnic stratification, and variation in study design and sample size.

**Conclusion**

In conclusion, our study did not confirm the presence of significant association between the TCF7L2 rs7903146(C/T) polymorphism and T2DM; however, it pointed out the possibility of presence of high risk of development of T2DM in patients with TT genotype. Further studies with higher sample size are needed to clarify the association.

**Statement of Ethics**

This study has been approved by Ain Shams University, Faculty of Medicine, Research Ethics Committee, FWA 00017858. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

This study was personally supported, with no other financial support or funding.

**Author Contributions**

The first author (A.M.B.): design of the work, drafting of the work, final approval of the manuscript for publication, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The second author (A.A.S.): design of the work, drafting of the work, final approval of the manuscript for publication, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The third author (A.I.H.): interpretation of data of the work, revising it critically, final approval of the version, and agreement to be accountable for all aspects of the work. The fourth author (W.A.Y.K.): interpretation of data of the work, revising it critically, final approval of the version, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**References**

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