Diabetes mellitus. 2015;18(3):46-50

Полиморфизм гена *UBE2E2* и риск развития сахарного диабета 2 типа

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В последние годы убиквитин-протеасомный путь стал рассматриваться в качестве ключевого механизма белкового обмена. Ученые установили, что данный механизм играет важную роль в синтезе инсулина, имеет огромное значение для β-клеток поджелудочной железы и связан с возникновением инсулино-зависимых заболеваний, наиболее значимым из которых является сахарный диабет 2 типа (СД2), а также такими метаболическими заболеваниями, как ожирение и атеросклероз. Ген UBE2E2 кодирует убиквитин-связанный белок E2E2, который играет важную роль в синтезе и секреции инсулина. Ген UBE2E2 экспрессируется в поджелудочной железе, печени, жировой ткани и в инсулин-секретирующих клетках. Согласно ряду исследований, однонуклеотидные полиморфизмы гена UBE2E2 (rs6780569, rs7612463, rs9812056) связаны с повышенным риском развития СД2 у жителей Японии, Кореи и Китая. Интерес ученых к гену UBE2E2 обусловлен недавними результатами исследований, свидетельствующими о его взаимосвязи с различными заболеваниями.

Ключевые слова: *сахарный диабет 2 типа; UBE2E; однонуклеотидный полиморфизм; генетическая предрасположенность*

Polymorphism of gene UBE2E2 and the risk of developing T2DM

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During the past years, the ubiquitin-proteasome pathway has emerged as crucial machinery for protein turnover. It has been identified as an important factor for insulin synthesis. It plays a critical role inside the β-cell and naturally has been linked with various insulin-related diseases, most notably T2DM, but also with other metabolic diseases and symptoms such as obesity and atherosclerotic plaque. UBE2E2 gene encodes an ubiquitin-conjugating enzyme E2E2, which plays an important role in the synthesis and secretion of insulin. UBE2E2 is a protein that is expressed in pancreas, liver and adipose tissue, as well as in an insulin-secreting cell line. Some studies have indicated that SNPs on UBE2E2 (rs6780569, rs7612463, rs9812056) were associated with the risk of T2DM in Japanese, Korean and Chinese populations. UBE2E2 gene is beginning to draw interest from researchers due to its newly discovered relations with various diseases.

Keywords: *type 2 diabetes mellitus; UBE2E2; single nucleotide polymorphism; genetic predisposition*

DOI: 10.14341/DM2015346-50

Type 2 diabetes mellitus (T2DM) is increasingly becoming a serious medical and social problem in modern healthcare [1]. The high percentages of disability and mortality resulting from this disease has made T2DM treatment and prevention a priority for the national health systems of all countries.

In 2011, 366 million people worldwide were estimated to have T2DM, and this number is projected to increase to 552 million in 2030 [2]. A total of 4.6 million deaths have been attributed to T2DM over the past XX years, which accounts for 8.2% of global all-cause mortality (International Diabetes Federation, 2011).

Although the mechanisms by which T2DM develops have not been fully elucidated, many studies have shown that T2DM is a genetic disease; thus, it is not only caused by environmental factors [3].

A family history of the disease is known to be a major risk factor for T2DM. Patients with T2DM having a strong positive family history of diabetes are frequently seen in clinical practice. Subjects who have one parent with T2DM have an approximately 30%–40% lifetime risk of developing T2DM, and those who have both parents with T2DM have an approximately 70% lifetime risk of developing the disease [4-6]. In addition, the risk of developing T2DM is increased approximately 2–4-fold in individuals who have a sibling with T2DM compared with the general population [7]. On the basis of these findings, many researchers have tried to fully clarify the genetic risk factors of T2DM.

To date, more than 75 T2DM susceptibility genes have been identified, mostly through genome-wide association studies (GWAS) [8, 9]. The initial studies, and indeed, the majority of these studies, have been performed in European populations. However, recent studies have also assessed the development of T2DM in Japanese, Korean and Chinese populations. The association between the *UBE2E2* locus and T2DM was first identified in a Japanese GWAS of T2DM.

Diabetes mellitus. 2015;18(3):46-50

UBIQUITIN

Recently, the ubiquitin–proteasome pathway has emerged as a crucial pathway for protein turnover. This pathway is involved in the regulation of multiple cellular processes such as proliferation, differentiation, signal transduction, transcriptional regulation and stress response [10, 11].

Ubiquitin is a small protein that is covalently linked to other cellular proteins, thus targeting them for degradation in proteasomes [12, 13]. Ubiquitination is considered to be a post-translational modification, along with phosphorylation [14, 15]. The ubiquitination reaction involves the sequential participation of three kinds of enzymes: a ubiquitin-activating enzyme (*E1*), a ubiquitin-conjugating enzyme or ubiquitin-carrier enzyme (*UCB* or *E2*), and a ubiquitin-protein ligase (*E3*) [16]. Recent studies have indicated that inhibition of proteasomes may indirectly decrease the biosynthesis of insulin [12].

The ubiquitin–proteasome system regulates membrane channels, such as the active channel of direct current and ATP-sensitive potassium channels, and plays a role in the regulation of proinsulin transcription; however, the mechanisms for these are still unclear [13]. In addition, the ubiquitin–proteasome system is also the degradative machinery of endoplasmic reticulum-associated degradation, which eliminates misfolded proteins. The ubiquitin–proteasome system also decreases the accumulation of amyloid protein in the β-cells of the pancreas, which are usually found in the islets of Langerhans in the pancreases of patients with T2DM because of islet amyloid polypeptide deposition [14, 15].

Several genes involved in the ubiquitin–proteasome system were shown to be downregulated in a mouse pancreatic β cell line with impaired insulin secretion, suggesting that defects in this system may lead to impaired secretion [16].

UBE2E2 is expressed in the pancreas, liver, and adipose tissue, as well as in an insulin-secreting cell line [9,17], and encodes ubiquitin-conjugating enzyme E2 E2 (*UBE2E2*), which plays an important role in the synthesis and secretion of insulin. The ubiquitin–proteasome system identifies protein substrates, and then catalyses protein degradation, and influences protein quality, gene transcription and cell function [11].

The identification of the functions of *UBE2E2* have only just begun in the β cells of the pancreas, and it is likely that many aspects of this work are closely dependent on the system.

Structure of the *UBE2E2* gene

In 1997, Kimura et al. isolated *UBE2E2*, a new human E2 enzyme with a unique N-terminal extension,

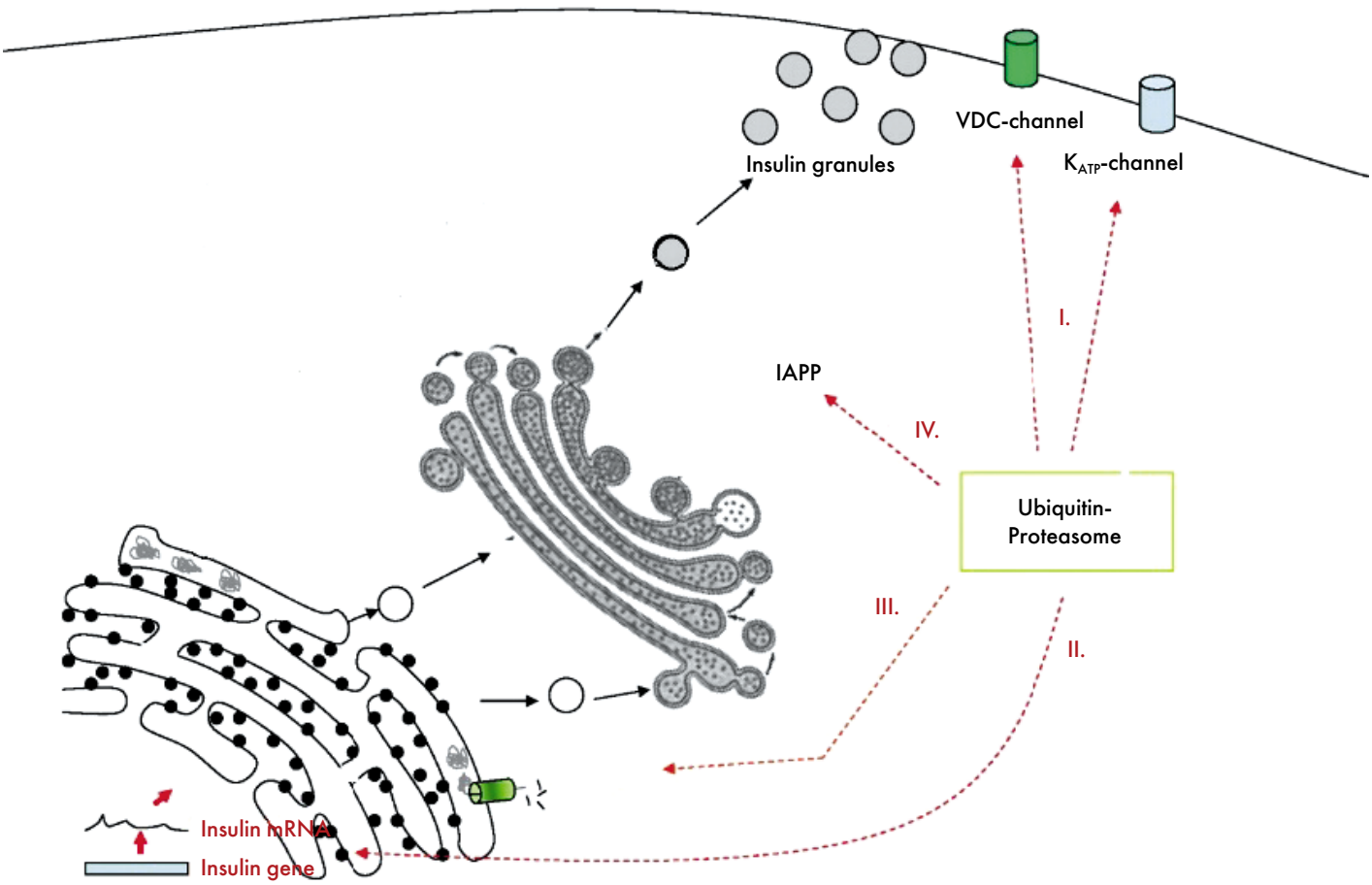

Рис. 1. The roles of ubiquitin-proteasome system in pancreatic β-cells.

Diabetes mellitus. 2015;18(3):46-50

Table 1

Splice-variants *UBE2E2*

Name	Transcript ID	bp	Protein	Biotype	CCDS	RefSeq	Flags
UBE2E2-001	ENST00000396703	2748	201 aa	Protein coding	CCDS2637	NM_152653 NP_689866	TSL:1GENCODE basic
UBE2E2-003	ENST00000425792	1248	201 aa	Protein coding	CCDS2637	-	TSL:2GENCODE basic
UBE2E2-004	ENST00000452894	665	164 aa	Protein coding	-	-	CDS 3' incompleteTSL:3
UBE2E2-201	ENST00000613545	282	94 aa	Protein coding	-	-	TSL:5GENCODE basic
UBE2E2-002	ENST00000335798	1330	92 aa	Nonsense mediated decay	-	-	TSL:1
UBE2E2-005	ENST00000427371	579	89 aa	Nonsense mediated decay	-	-	TSL:3

Table 2

The exons and introns *UBE2E2*

No.	Exon / Intron	Start	End	StartPhase	EndPhase	Length
5' upstream sequence						
1	ENSE00001525976	23,203,293	23,203,464	-	-	172
	Intron 1-2	23,203,465	23,208,691			5,227
2	ENSE00001525974	23,208,692	23,208,875	-	2	184
	Intron 2-3	23,208,876	23,217,261			8,386
3	ENSE00001648562	23,217,262	23,217,312	2	2	51
	Intron 3-4	23,217,313	23,499,607			282,295
4	ENSE00001730682	23,499,608	23,499,740	2	0	133
	Intron 4-5	23,499,741	23,532,553			32,813
5	ENSE00003670823	23,532,554	23,532,701	0	1	148
	Intron 5-6	23,532,702	23,589,733			57,032
6	ENSE00001525971	23,589,734	23,591,793	1	-	2,060
3' downstream sequence						

from a human β-cell library. Fluorescence in situ hybridization experiments demonstrated that the gene is located on 3p24.2 [18].

According to current data, *UBE2E2* is located on chromosome 3 at 23,203,020-23,591,793. The Homo sapiens *UBE2E2* gene has 17,246 single nucleotide polymorphisms (SNPs) and six transcripts (splice variants). The exons and introns involved are shown in Table 1.

Table 2 provides data on exons and introns in this gene.

ASSOCIATION OF *UBE2E2* WITH VARIOUS DISEASES

Specific variants in the *UBE2E2* gene have been identified as being associated with the risk of non-small cell lung cancer, as well as the risk of T2DM (rs6780569, *rs7612463* and *rs9812056*). Dmitriev et al. showed that the *UBE2E2* gene is involved in carcinogenesis ($p < 0.05$), and *UBE2E2* has been proposed as being one of the biomarkers of lung adenocarcinoma metastasis. Along with *UBE2E2*, a set of 19 markers was proposed that would allow the diagnosis of most cases of non-small cell lung cancer with a sensitivity and specificity higher than 80% (up to 100%) [19].

In recent years, several studies have explored the relationship between *UBE2E2* polymorphisms and T2DM. Some of these studies have indicated the presence of an association between SNPs in *UBE2E2* (*rs6780569*, *rs7612463* and *rs9812056*) and the risk of T2DM in Japanese and Korean populations [20,21].

Toshimasa Yamauchi with co-authors did not find significant associations between these *UBE2E2* polymorphisms and T2DM in a European population ($p > 0.05$) comprising 6980 subjects in the study group and 8615 subjects in the control group. However, because of the fact that they failed to identify any strong signals in *UBE2E2* in this European study population, the authors did not exclude the possibility that *UBE2E2* may be associated with T2DM in this European population. This discrepancy in European populations may be because of genetic heterogeneity or different linkage disequilibrium structures that exist among Europeans caused by differences in geographical location and genetic origin [21]. This association does not necessarily mean that the substitution of nucleotides in the related polymorphisms has a direct effect on the phenotype. Therefore, it is likely that some causal variants may be present elsewhere in the same or nearby genes depend-

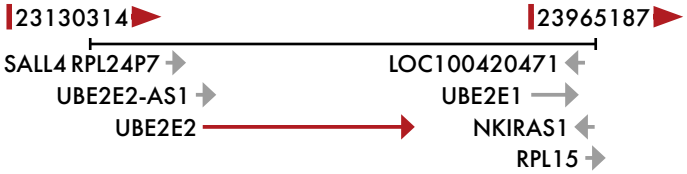

Fig. 2. Chromosome 3 - NC_000003.11.

ing on the subject's ethnicity. The authors also showed that rs7612463 in *UBE2E2* was associated with T2DM in a Japanese population (study group: 3622 subjects, control group: 2356 subjects). In addition, GWAS have revealed that subjects with the risk allele rs7612463 (CC + CA) exhibited a significantly lower level of homeostasis in β-cells (homeostatic model assessment HOMA-B), than those who did not have the risk allele (AA), which suggests a role of this variant in the reduction of insulin secretion in T2DM [21].

However, Iwata et al. assessed 14 polymorphisms (patients with T2DM: 724 subjects, control group: 763 subjects), including rs7612463 in *UBE2E2*, and did not find any SNPs that were significantly associated with T2DM in a Japanese population (P = 0.207). On the other hand, this study lacked statistical power because of the lack of replication [22].

In a recently published study, Alharbi et al. (2014) did not find a significant relationship between *rs7612463* in *UBE2E2* and the development of T2DM in a Saudi Arabian population (study group: 376 subjects, control group: 380 subjects) [23].

Furthermore, we conducted a case–control study to investigate the effect of the leading *UBE2E2* SNP on T2DM risk in a Han population in north-eastern China. A total of 1957 participants were enrolled, including 964 patients with T2DM and 993 controls. AC was associated with increased risk of total cholesterol (mmol/l-1; P = 0.031) and triglycerides (mmol/l-1; P = 0.039). Our results showed that *rs7612463* is associated with T2DM, and homozygotes with the AA genotype had lower risk of T2DM in this Chinese population. In addition, heterozygotes may have lower risk of T2DM because of insulin resistance [24].

To date, several studies have tried to link genetic variants with the risk of gestational diabetes mellitus (GDM). Kim et al. showed associations between two *UBE2E2* genetic variants (*rs6780569* and *rs7612463*) and risk of GDM in a Korean population (1104 cases and 967 controls) [25]. Interestingly, however, although the ubiquitin–proteasome pathway is a known factor that controls the insulin signal [25], genetic variants of *UBE2E2* showed no associations with HOMA-B or HOMA-insulin resistance, and only showed an association with fasting plasma glucose. This may be because of pathological differences between patients with GDM and patients with T2DM; further research is needed [26].

Future prospects

research into the *UBE2E2* gene is of great interest in many countries. However, the relationships between different SNPs of the *UBE2E2* gene and T2DM have not always been found to be statistically significant, as shown in studies in Japanese, Korean, Chinese, Saudi Arabian and European populations. These conflicting data may be associated with the heterogeneity of the SNPs of this gene, and it is likely that some causal variants may be present elsewhere in the same or nearby genes depending on the subject's ethnicity. Further, there may be some pathological differences in the development of different types of diabetes mellitus, such as GDM and T2DM.

The role of ubiquitin in insulin signalling is not yet fully understood, and thus, future research should aim to reveal the mechanism of influence of *UBE2E2* and its various SNPs in T2DM and atherosclerosis.

Competing interests

The authors have declared that no competing interests exist.

Funding

This work was funded by the National Natural Science Foundation of China (81172742 and 81473053), project 937 (2014 CB542401) the Natural Science Foundation of Heilongjiang Province (ZD201220).

The funders had no role in study design, data collection and analysis, decision on publish, or preparation of the manuscript.

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