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Variants in the IGF2BP2, JAZF1 and CENTD2 Genes Associated with Type 2 Diabetes Susceptibility in a Romanian Cohort

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Abstract

Diabetes mellitus (DM) is one of the leading causes of mortality and morbidity worldwide. Globally, 422 million adults were diagnosed in 2014 [1]. According to the PREDATOR study the prevalence of DM in Romania was 11.6% [2]. DM is also an important socio-economic problem with high annual losses. In 2012, the estimations of the American Diabetes Association (ADA) regarding the total cost for DM patients` management was $245 billion, of which $ 176 billion in direct medical costs (hospitals, medical staff, treatment) and $69 billion in indirect costs (inability to work, decreased productive capacity, absenteeism) [3]. The genetic factor is known to play an important role in the development of DM type 2 [4, 5]. The concordance between monozygotic twins is about 70% and 20-30% among the dizygotic twins. The lifetime risk of developing DM type 2 is approximately 40% if one parent suffers from DM type 2 and 70% if both parents have the disease [6]. Numerous genes and loci have been described in association with the susceptibility for DM type 2, such as PPARG, HNF1A, HNF4A, KCNJ11/ABCC8, GCKR, SLC30A8, SLC16A11, TM6SF2, FTO, CAPN10, TCF7L2, PPARG, IRS1, IRS2, HHEX, SLC30A8, IGF2BP2, JAZF1, CENTD2, a.o [7-10].

The current study focuses on variants within the IGF2BP2, JAZF1, and CENTD2 correlated with type 2 diabetes in a Romanian cohort. The JAZF1 gene encodes for a nuclear protein which functions as a transcriptional repressor. JAZF1 supresses lipogenesis, increases lipolysis and decreases lipid accumulation in the adipose tissue, being an important factor in lipid metabolism. It also adjusts glucose metabolism and insulin sensitivity, with a role in glucose homeostasis [11-13]. The IGF2BP2 gene is located on the long arm of chromosome 3 (3q27.2). Various studies have shown the association between pathogenic IGF2BP2 variants and the susceptibility to type 2 diabetes [11,12,14]. According to literature, the CENTD2 (ARAP1) gene is significantly associated with increased plasma glucose levels and decreased glucose-stimulated insulin release, suggesting that the diabetic effect of this locus is mediated by impairing pancreatic beta cell function [11,12].

Keywords: Diabetes mellitus type 2; Susceptibility; GWAS; IGF2BP2; JAZF1; CENTD2

Purpose

The current paper aims to study the involvement of JAZF1, CENTD2 and IGF2BP2 variants in the predisposition for DM type 2 in a cohort of Romanian men over 50 years old.

Materials & Methods

The current study included 2024 male individuals, 250 with type 2 diabetes and 1752 non-diabetic controls (22 individuals with no data available). Blood samples were collected from all individuals included in the study for genetic testing. All subjects were of self-proclaimed Romanian nationality. The study protocols were approved by the National Ethics Committee of the Romanian College of Medical Doctors. A written informed consent was obtained from all the study participants. SNP genotyping was performed at DeCODE Genetics in Reykjavik, Iceland, using the Centaurus (Nanogen) platform on 716503 SNPs (Single Nucletide

Polymorphisms). A p-value Hardy-Weinberg equilibrium threshold of 10-6 was used for data filtering. Also, markers with a minor allele frequency of less than 0.01 were excluded from the study. The statistical analysis of the results was performed using the Plink! v1.07 software.

Results

The GWAS results identified the following variants associated with type 2 diabetes (Table 1):

Table 1: The GWAS results identified the following variants associated with type 2 diabetes.

Variant	Gene	Chromosome Location	Mutant / Ancestral Allele	Variant Type	p-Value	OR
rs6766313	IGF2BP2	chr3:185749844	T / C	Intronic	0.002436	2.44
rs7790213	JAZF1	chr11: 72738204	T / C	Intronic	0.000622	1.391
rs10793039	CENTD2	chr3: 185749844	T / C	intronic	0.004664	1.314

Discussions

IGF2BP2 (Insulin-like grow factor 2 mRNA-bindind protein 2, OMIM #608289, chromosome location 3q27.2), rs6766313 [11,12]. Association of IGF2BP2 variants with DM type 2 has been documented in multiple studies [11,12,14-18]. In a research conducted by "The Diabetes Genetics Initiative of the Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes for BioMedical Research", a number of 386,731 common SNPs were analyzed on a cohort of 1464 patients with type 2 diabetes and 1467 controls [15]. For each case, blood glucose, lipid metabolism, obesity and blood pressure were recorded. In collaboration with Finland - United States Investigation of NIDDM Genetics (FUSION) and Wellcome Trust Case Control Consortium / United Kingdom Type 2 Diabetes Genetics Consortium (WTCCC / UKT2D), they identified and confirmed a locus associated with type 2 diabetes in the second intron of IGF2BP2 [16].

The evidence for rs4402960 was weak but statistically significant at the initial scan (p = 0.034) but was pronounced in the replication samples (p = 5.5 x 10-9). Strong evidence was obtained for the same SNP, phenotype and genetic model by WTCCC / UKT2D (p = 10-4) and FUSION (p = 10-4) [16]. A meta-analysis on a Finnish cohort consisting of 1,161 type 2 diabetes cases and 1,174 controls revealed an increased susceptibility for DM type 2 for all included individuales carring the rs4402960 IGF2BP2 gene variant (OR = 1.14; P = 8.6 x 10-16) [16]. Based on GWAS data obtained from 1924 diabetic cases and a control lot of 2,938 individuals, "Welcome Trust Case Control Consortium" conducted a replication study on an additional 3757 DM type 2 cases and 5346 controls and by integrating their findings with other equivalent data from other international studies. The combined evidence from all studies (p = 8.6 x 10-16 - genome-wide statistical significance - genome wide significance) established rs4402960 as a susceptibility locus for type 2 DM [17].

The IGF2BP2 rs6766313 variant identified through our study (p = 0.002436, OR = 2.44) (Table 1) is a variant of unknown clinical significance (class 3 variant, VUS), never being described before in literature [18-20]. JAZF1 (Juxtaposed with another Zinc finger gene, 1, OMIM #606246, chromosome location 7p15.2-p15.1), rs7790213. A study on a Saudi Arabian cohort, which genotyped a group of 400 patients with type 2 DM and a control group of 400 healthy individuals, investigated the association of JAZF1 (rs864745) with the susceptibility to type 2 diabetes. According to this study, the distribution frequencies of the AA, AG and GG genotypes of JAZF1 (rs864745) differ significantly among patients with type 2 DZ and the control group (p <0.05). Heterozygous (AG) and mutant homozygous (GG) genotypes were independently and significantly associated with the susceptibility for type 2 DM after adjusting for age, sex, and body mass index (OR = 2.1, p = 0.002 and OR = 1.9, p = 0.005) [21].

Our study revealed a statistical correlation (p = 0.000622, OR = 1.391) of JAZF1 rs7790213 with type 2 diabetes (Table 1), the current research being the first study describing this variant [19,20]. CENTD2 / ARAP1 (Centaurin, Delta-2, OMIM #606646, chromosome location 11q13.4), rs10793039. According to literature, CENTD2 (ARAP1) pathogenic mutations are significantly associated with increased plasma glucose values and decreased glucose-stimulated insulin release, suggesting that the diabetic effect of these variants is mediated by impairing pancreatic beta cell function [22].

The CENTD2 rs1552224 allelic variant has been reported to increase glucose levels after plasma TTGO at 30 minutes by 2.0% (p = 2 × 10-5) and by a 4.2% reduction of insulin release at 30 minutes after oral administration of glucose (p = 0.001) [22]. The results of our study identified the rs10793039 CENTD2 variant (Table 1) in a statistical correlation with DM type 2 (p = 0.004664, OR = 1.314), a variant of unknown clinical significance [19,20].

Conclusions

The present study identified several possibly important variants associated with type 2 diabetes mellitus susceptibility, which migh provide insights into the genetic architecture of this pathology. The identified variants in the JAZF1, CENTD2 and IGF2BP2 genes, genes previously reported in association with DM susceptibility, have never been described before in literature. The validity of these results for the Romanian population is to be confirmed by undergoing replication studies.

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