THE MOLECULAR GENETIC ETIOLOGY BY WHOLE EXOME SEQUENCE ANALYSIS IN CASES WITH FAMILIAL TYPE 1 DIABETES MELLITUS WITHOUT HLA HAPLOTYPE PREDISPOSITION OR INCOMPLETE PREDISPOSITION

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INTRODUCTION

- Family history is observed in approximately 10% of the cases with type 1 diabetes mellitus (T1DM)
- The most important gene that determines susceptibility is the human leukocyte antigen complex (HLA) on chromosome 6
- In HLA genes; specific combinations of alleles at DR3, DR4, DRB1, DQA1 and DQB1 locus either predispose or protective for T1DM

AIM

- to investigate the molecular genetic etiology by whole exome sequence (WES) analysis in cases with familial T1DM who had no HLA haplotype predisposition or incomplete predisposition

RESULTS

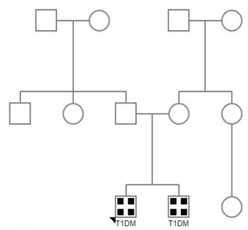
- Four cases (13.3%) had consanguineous marriage between their parents out of 30 patients (female / male: 17/13)
- Mean age: 14.9±6 years
- Diabetes duration: 7.56±3.84 years
- As a result of filtering all exome sequence analysis data of 2 cases with DQ2 (-) and DQ8 (-), 7 cases with DQ2 (+) and DQ8 (-), and 1 case with DQ2 (-) and DQ8 (+), 7 different variants in 7 different genes were detected in 5 cases

The pathogenicity of the detected variants were determined according to the “American College of Medical Genetics and Genomics (ACMG)” criteria

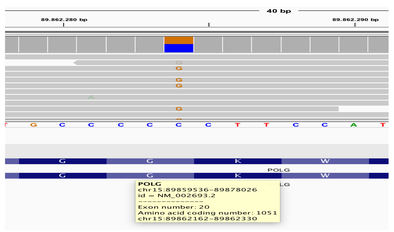
- These 7 variants detected were evaluated as high-score VUS (Variants of unknown/uncertain significance)

Cases	Gene	HGVS-Code (DNA code)	HGVS-Protein (amino acid exchange)	Zygosity	Mutation type	Classification	Pathology associated
Case 1	**CIITA**	c.286G>A	p.Ala96Thr	Heterozygous	Missense	VUS	Autoimmune diseases
Case 2	**KCNJ11**	c.153G>A	p.Glu51Glu	Heterozygous	Synonym	VUS	T2DM, monogenic diabetes
Case 3	**CASP10**	c.922+36delT	-	Heterozygous	Intronic	VUS	Autoimmune lymphoproliferative syndrome, T1DM
Case 4	**BLVRA**	c.166C>T	p.Q56*	Heterozygous	Nonsense	Franklin: Likely pathogenic Varsome: Pathogenic	Hyperbiliverdinemia, T2DM
Case 5	**POLG**	**c.3151G>C**	**p.G1051R**	**Heterozygous**	**Missense**	**Franklin: Pathogenic Varsome: Likely pathogenic**	**Progressive external ophthalmoplegia, mitochondrial DNA depletion syndrome (MINGE, ALPERS), mitochondrial recessive ataxia syndrome, Alpers-Huttenlocher Syndrome, Ataxia Neuropathy Syndrome, myoclonic epilepsy myopathy sensory ataxia (MEMSA), Childhood myocerebrohepatopathy syndrome (MCHS), T1DM**
Case 5	**AKT2**	c.709-3C>G.		Heterozygous	Splice area	Franklin VUS (Leaning Pathogenic) NNSPLİCE pathogenic MT DC	T2DM
Case 5	**FBN1**	c.31C>G	p.L11V L11Q L11R	Heterozygous	Missense	Varsome VUS Franklin VUS (leaning pathogenic)	Marfan Syndrome Stiff Skin Syndrome, Marfan lipodystrophy Syndrome, Geleophysical dysplasia 2, Acromicric dysplasia Weill-Marchesani Syndrome, T1DM, T2DM

Case 5
Two-year-old boy
Diagnosed with DKA at 18 months of age
No consanguinity marriage in his family
AIA and AntiGAD positive
HLA-DQ2 (+) vs. HLA-DQ8 (-)
In the segregation study conducted for the mutation in the POLG gene detected in case 5, this mutation was detected in the mother of the case and his brother with T1DM



Pedigree of Case 5



METHOD

- Patients had at least one first degree relatives with T1DM were included
- **In the first step**, HLA DRB1, DQA1 and DQB1 loci were investigated with polymerase chain reaction-sequence specific oligonucleotide (PCR SSO) method
- **In the second step,** the presence of variants that could explain the clinic in cases where both tissue types were negative in HLA typing [DQ2 (-) / DQ8 (-)] and only one of the HLA types was found positive [(DQ2 (+) / DQ8 (-), and DQ2 (-) / DQ8 (+)] was investigated by WES analysis

CONCLUSIONS

- In a previously study, T1DM has been reported in monozygotic twins with POLG mutation
- In another study, POLG mutation was shown to be responsible for diabetic polyneuropathy in patients with T1DM
- In this study, 7 different variants in 7 different genes were detected in 5 patients by whole-exome sequence analysis in familial T1DM patients with no or weak HLA tissue type susceptibility
- We thought that the heterozygous c.3151G>C mutation detected in the POLG gene in our case was associated with the current T1DM phenotype

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