The association of HLA class II, CTLA-4 and PTPN22 genetic polymorphisms and β-cell autoantibodies in development of type I diabetes in patients with autoimmune thyroid disease

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OBJECTIVES

Co-occurrence of type 1 diabetes (T1D) and autoimmune thyroid disease (AITD) denote variant of autoimmune polyglandular syndrome type 3 (APS3v).
Thyroid autoimmunity in T1D was widely studied, but a few studies examined β-cell autoimmunity among AITD patients.

The aim of the study was to investigate β-cell autoimmunity and genetic polymorphism of HLA class II, CTLA-4 and PTPN22 genes with susceptibility for development of T1D, in AITD patients.

METHODS

The study comprised of 158 unrelated AITD patients (127 with autoimmune thyroiditis, AT and 31 with Graves disease, GD) aged 4.3-25.9 years, 69 APS3v patients aged 5.2 – 19.4 years and 94 healthy subjects aged 4.7-21.5 years (control group).

Islet cell cytoplasmic (ICA), glutamic acid decarboxylase (GADA) and thyrosin phosphatase islet (IA-2) autoantibodies as well as HLA-DRB1, DQB1 genotypes, A49G and C60T polymorphisms of CTLA4 gene and R620W mutation of PTPN22 gene were analyzed.

RESULTS

Clinical and demographic characteristics and distribution of HLA-DRB1 and DQB1 genotypes, CTLA-4 (49AG and CT60) and PTPN22 R620W gene polymorphism in 17 patients with AITD and β-cells autoimmunity

patient	*diagnosis*	*sex*	*Age at diagnosis (years)*	*ICA (ref <1 IF)*	*GAD (ref <10 IU/ml)*	*IA-2 (ref <15 IU/ml)*	*TgAt (ref <20 IU/ml)*	*TPOAt (ref <10 IU/ml)*	*Genotype HLA DRB1-DQB1/DRB1-DQB1*	*Genotype CTLA4 49AG*	*Genotype CTLA4 CT60*	*Genotype PTPN22 R620W*
1	AT	F	13.54	1.0	0	**16.7**	755	269	11-03(DQ7)/14-05***	A/A	A/G	C/T
2	AT	F	11.34	0.5	**22.7**	0.0	147	>2000	04-03(DQ8)/11-03(DQ7)**	G/G	G/G	C/C
3	**AT**	**F**	**11.80**	**3**	**676**	**258.6**	**44.2**	**>2000**	**04-03(DQ8)/07-02****	**G/G**	**G/G**	**C/C**
4	AT	F	19.04	0	**17.7**	0.0	0	159	NT	NT	NT	NT
5	AT	F	11.55	1	**23.7**	0.0	2000	93.3	04-06/13-06***	G/G	G/G	C/C
6	AT	M	13.75	1	0	**21.0**	0	46	04-03(DQ8)/11-03(DQ7)**	A/G	G/G	C/T
7	AT	F	12.31	0.5	0	**22.3**	28.2	1191	04-03(DQ8)/15-06**	A/A	A/G	C/C
8	**AT**	**F**	**8.02**	**3**	**0**	**1245.0**	**140**	**40**	**03-02/13-06****	**G/G**	**G/G**	**C/T**
9	AT	F	7.79	**2**	0	0.0	0	15	11-03(DQ7)/13-06***	A/G	A/G	C/C
10	**AT**	**F**	**11.39**	**1**	**68.6**	**226.0**	**25**	**>2000**	**04-03(DQ8)/11-03(DQ7)***	**G/G**	**G/G**	**C/T**
11	AT	F	13.16	**1.5**	0	0.0	177.2	>2000	03-02/13-06**	A/A	A/G	C/C
12	**AT**	**F**	**10.08**	**3**	**859**	**136.1**	**0**	**>2000**	**01-05/07-02*****	**A/A**	**A/A**	**C/C**
13	AT	F	12.18	0	**27.4**	0.0	155	96	03-02/14-05**	A/G	A/G	C/C
14	AT	F	17.28	1	**1193**	0.0	642.6	1112	03-02/16-05**	A/A	A/A	C/T
15	**AT**	**M**	**8.11**	**1.5**	**149**	**0.0**	**584**	**>2000**	**03-02/04-03(DQ8)***	**A/G**	**A/G**	**C/C**
16	GD	F	15.38	**1.5**	0	0	27	279	01-05/08-04***	G/G	G/G	C/C
17	**GD**	**F**	**6.50**	**3.5**	**2509**	**1882**	**71.1**	**>2000**	**03-02/03-02****	**A/A**	**A/G**	**C/C**

M – male; F – female; ICA – *Islet Cell Cytoplasmic Autoantibody, GAD - Glutamic Acid Decarboxylase Autoantibody; IA-2 - Insulinoma-2 Associated Autoantibody;*. NT – not tested; AT - autoimmune thyroiditis; GD – Graves disease,
*high risk HLA haplotypes,** medium risk HLA haplotypes, *** low risk HLA haplotypes; orange – patients who developed T1D during investigation period (2,5 years),

β-cell autoimmunity was found in 10.76% (17/158, 2 male and 15 female) AITD patients, significantly more frequently than in controls (0%, 0/94; p=0.001), with higher prevalence found in AT (11.81%, 15/127) than GD (6.45%, 2/31) patients.
All three β-cell autoantibodies were positive in three patients, and three patients were positive to two autoantibodies. All six of them developed T1D during the investigation period of 2.5 years.
No difference in high risk HLA haplotypes for development of T1D was found between AITD patients with β-cell autoimmunity (1/16, 6.3%) and patients with APS3v (14/69, 20.3%; p=0.283) or controls (0/94, 0%; p=0.147), while the difference between the APS3v group and controls was statisticaly significant (p<0.001). The frequency of medium risk HLA genotypes for development of T1D were not significantly different between patients with AITD and β-cell autoimmunity (10/16; 62.5%) and patients with APS3v (43/69; 62.3%, p=0.578). On the other hand, HLA genotype HLA-DRB1*04-DQB1*03/DRB1*X-DQB1*X was found significantly more often in patients with AITD and β-cell autoimmunity (5/16, 31.3%) and APS3v (21/69; 30.4%) compared to controls (7/94; 7.5%, p=0.015 and <0.001 respectively). The frequency of other medium risk genotypes for development of T1D was not different between the groups. Low risk HLA haplotypes for development of T1D were found more frequently in controls (65/94; 69.9%) than in patients with AITD and β-cell autoimmunity (5/16; 31.3%, p=0.003) or APS3v (12/69; 17.4%; p<0.001).
Disease associated G/G genotype of CTLA4 A49G gene was significantly more common in AITD patient with β-cell autoimmunity than in controls (p=0.024), while PTPN22 and CT60 CTLA-4 gene polymorphisms were not significantly different in AITD patients regardless of β-cell autoimmunity.

CONCLUSION

Our results showed that patients with AITD are prone to develop β-cell autoimmunity and T1D, especially those with multiple islet cell autoantibodies.

REFERENCES

Bright GM et al. J Pediatr 1982;100:8–14.
Moriguchi M et al. Metabolism 2011;60:761-6.
Maugendre D et al. Eur J Endocrinol 1997;137:503-10.
Hiromatsu Y et al. Diabetic Med 2005;23:211-5.
Kawasaki E et al. J Autoimmun 1995;8:633-43.
Yamaguchi Y et al. Diabetes 1991;40:319-22.
Chaillous L et al. Diabetologia 1994;37:491–9.
Hallengren B et al. J Intern Med 1996;239:63–8.
Lethagen AL et al. J Clin Endocrinol Metab 2002;87:1177-83.
Marwaha RK et al. Indian J Med Res 2013;137:82–6.
Aksoy DY et al. Exp Clin Endocrinol Diabetes 2006;114:412-6.
Wiebolt J et al. Eur J Endocrinol 2011;164:789-94.

We declare no conflict of interest

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