Type 1 diabetes in APECED: a rare manifestation in a rare disease

Alessandra Fierabracci MD PhD

διαβήτης

- Diabetes is one of the most known disorders since antiquity for the entity of its clinical manifestations, chronic hyperglycemia, polyuria and polydipsia
- Acute (ketoacidosis, hyperosmolar coma) and chronic severe complications affecting several organs may appear during the disease course

Ebers papyrus (1550 BC) refers to polyuria

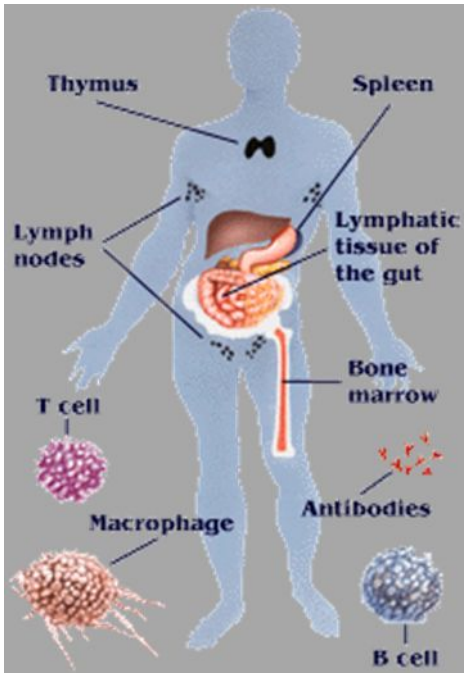
Aretaeus of Cappadocia coin the term '*διαβήτης*' *(διαβαίνειν)*

1675 Willis adds '*mellitus*'

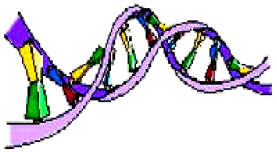
APS1

Type 1 diabetes (T1D): an autoimmune disease

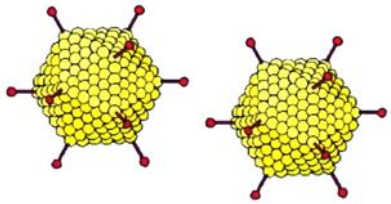
- Immune cells exert an abnormal response against pancreatic islet proteins
- Insulin-producing β cells are destroyed in genetically predisposed individulas

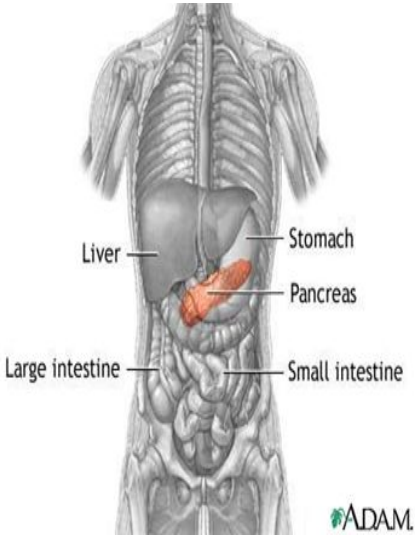


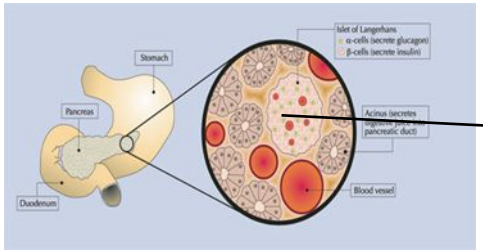
genetic background



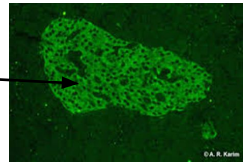
environmental factors



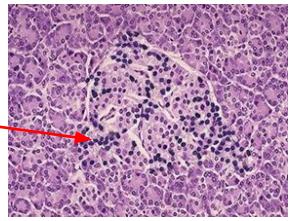




1974: discovery of Islet Cell Antibodies (ICA)



autoreactive T cells



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T1D genetic background

- T1D is a multifactorial autoimmune disease with a strong genetic component

- In both Europeans and North Americans of European ancestry susceptibility loci within the HLA complex DRB1 0401, DRB1 0402, DRB1 0405, DQA1 0301, DQB1 0302, or DQB1 0201 alleles were identified

- Oppositely, certain HLA alleles DRB1 1501, 1401, or 0701, and DQB1 0602, 0503, or 0303 alleles confer strong protection

APS1

Type 1 diabetes and autoimmune polyglandular syndromes

- T1D is frequently associated with other clinical, subclinical or potential (*i.e.* only serological) organ- or non-organ specific autoimmune diseases, contributing to the autoimmune polyglandular syndromes (APS)

- When T1D is associated with hypoparathyroidism, candidiasis and/or Addison's disease, it is part of Type 1 Autoimmune Polyglandular Syndrome (APS1)

- When it is associated with Addison's disease is part of APS2

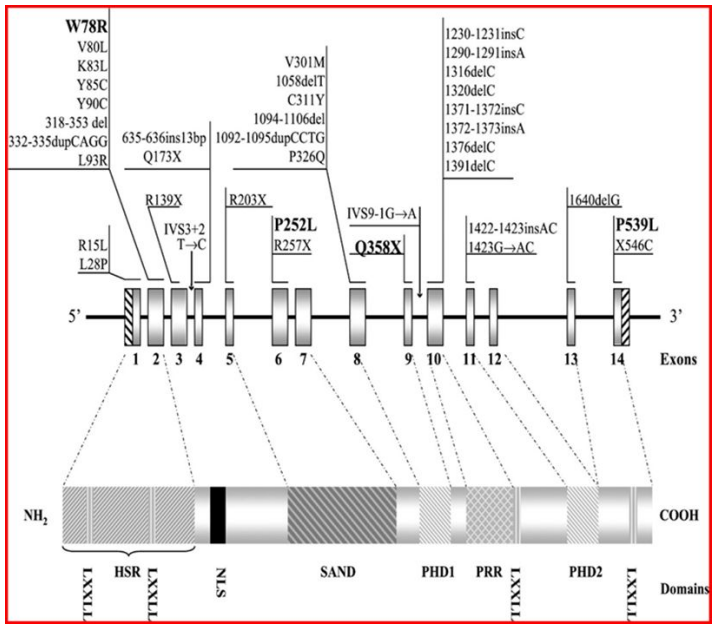
- When it is associated with autoimmune thyroiditis it is part of APS3

- When it is associated with any other autoimmune disease (chronic atrophic gastritis, celiac disease, vitiligo etc) is part of APS4

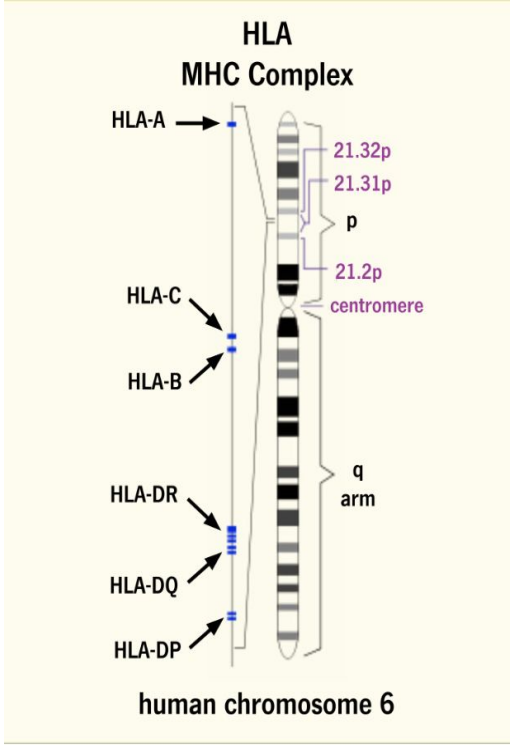
Type 1 diabetes and autoimmune polyglandular syndromes

These syndromes are related to mutations of the *AIRE* gene (APS1) or to class II *HLA* genes (APS2, APS3, APS4)

***AIRE* GENE** (chromosome 21)



Meloni A, *J Clin Invest* 2002, 87:841

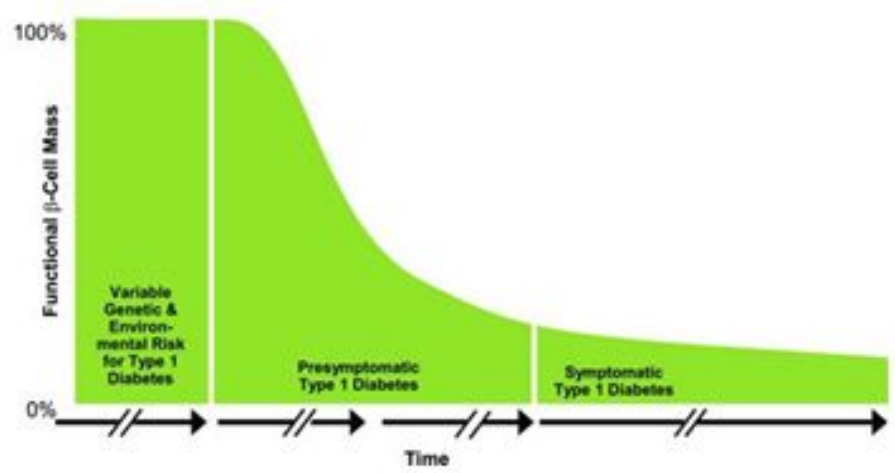


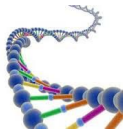
http://commons.wikimedia.org/wiki/File:HLA.svg#mediaviewer/File:HLA.svg

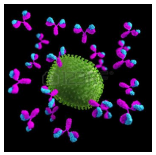
APS1

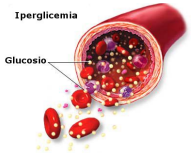
T1D PREDICTION AND PREVENTION

APS1









Genetic predisposition → **Pancreatic autoimmunity** (ICA, GADA, IA2, Znt8, insulin Ab) → **Dysglycemia** → **Diabetes onset**

PREVENZIONE PRIMARIA

- TRIGR
- BABY-DIET
- NIP
- Pre-POINT
- NIDDK
- CDA

PREVENZIONE SECONDARIA

- DPT-1
- DIPP
- CTLA-4Ig
- Anti-CD3
- intranasal insulin
- subcutaneous insulin

PREVENZIONE TERZIARIA

- Anti-CD3
- IL-2
- MSCs
- autologous HSCs
- autologous DCs
- Tregs

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ORIGINAL ARTICLE

Autoimmune polyendocrine syndrome type 1: an Italian survey on 158 patients

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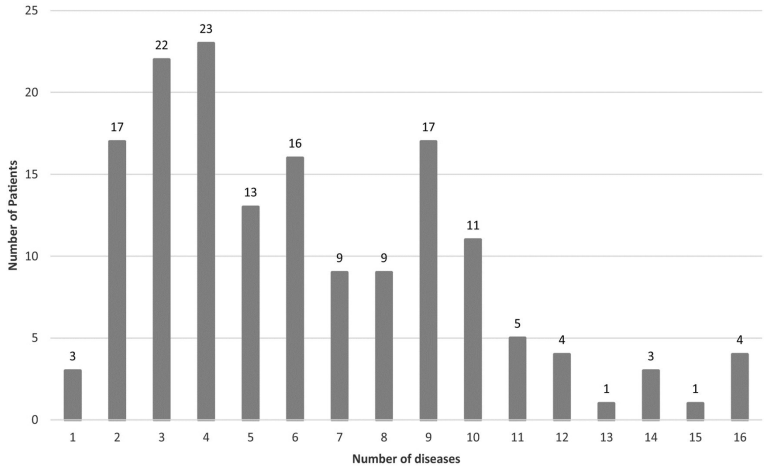
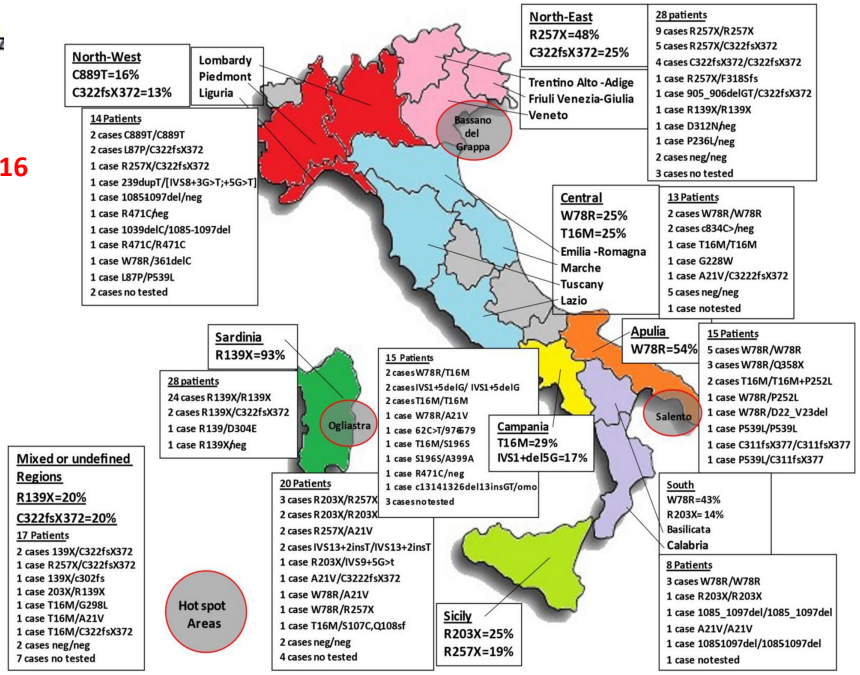
Bambino Gesù
Ospedale Pediatrico

NUMBER OF APS1 ITALIAN PATIENTS IN THE ITALIAN POPULATION WITH 1-16 ASSOCIATED MANIFESTATIONS





Main features of APS-1 presentation in patients from 20 national cohorts published from 1992 to 2018

	[6] Iranian Jewish (1992)	[24] UK (1998)	[25] USA (1998)	[26] Italy (1998)	[27] Central-East Europe (2001)	[11] Japan (2002)	[28] Slovenia (2005)	[15] Finland (2006)	[8] Poland (2006)	[9] Ireland (2006)	[29] Slovakia (2008)	[10] France (2012)	[30] Hungary (2010)	[31] Saudi Arabia (2010)	[32] Northern Ireland (2012)	[20] Norway (2016)	[17] North/South America (2016)	[33] Russia (2017)	[34] India (2017)	[35] Brazil (2018)	Total or range
No of patients	23	12	20	41	27	7	12	91	14	31	4	19	7	20	8	52	35	112	23	13	568
F/M	1.1	0.8	1.5	2.4	n/a	0.75	0.3	1	1.8	1.4	1	0.6	0.75	1.2	0.6	0.85	1.5	1.3	0.9	3.3	0.3–3.3
Mortality (%)	n/a	28	n/a	4	n/a	n/a	n/a	29	n/a	10	n/a	10	14	n/a	0	28	n/a	8	26	23	0–29
Familial disease (%)	56	61	15	17.5	15	n/a	33	32	29	42	n/a	53	57	100*	50	53	n/a	13	53	25	13–57
CMC (%)	17	100	80	83	85	85	100	100	93	80	0	89	43	90	87	77	86	75	96	69	17–100
CH (%)	96	89	100	93	92	71	83	88	100	84	50	63	71	100	87	73	85	78	91	77	50–100
AD (%)	22	83	95	73	89	43	58	84	57	68	100	79	57	40	87	63	90	67	55	15	22–100
AITD (%)	4	5	25	10	26	n/a	25	31	n/a	6	50	5	29	15	n/a	19	22	13	23	63	4–63
POF (%)	25	37	8	43	n/a	n/a	0	50	3	68	50	71	n/a	9	33	33	38	48	60	23	0–71
DM-1 (%)	4	28	n/a	3	3	n/a	8	33	33	13	n/a	5	n/a	15	25	8	11	9	9	15	3–33
GHD (%)	n/a	n/a	n/a	7	7	n/a	58	5	7	6	n/a	5	14	5	12	n/a	n/a	n/a	n/a	39	5–58
AG/PA (%)	9	22	n/a	15	15	n/a	n/a	31	7	6	27	21	n/a	5	12	15	4	8	45	n/a	4–45
CD (%)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	14	5	n/a	n/a	n/a	n/a	n/a	8	5–14
AIH (%)	n/a	17	25	20	15	n/a	8	18	43	19	n/a	11	14	15	12	4	14	11	n/a	31	4–43
AID (%)	n/a	28	5	15	18	n/a	25	22	14	13	n/a	26	n/a	n/a	n/a	23	54	25	27	8	5–54
K (%)	n/a	11	n/a	12	18	n/a	17	22	43	16	n/a	37	n/a	5	50	12	14	13	9	23	5–50
A (%)	13	22	40	37	37	n/a	33	39	21	19	25	53	n/a	45	12	31	7	34	6	16	6–53
V (%)	n/a	n/a	10	15	11	n/a	8	31	n/a	6	n/a	21	n/a	n/a	50	15	7	9	6	39	6–50
ND (%)	4	n/a	n/a	7	26	n/a	42	n/a	n/a	n/a	n/a	5	n/a	5	n/a	13	14	n/a	4	39	4–42
EH (%)	4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	72	25	37	n/a	72	n/a	28	61	n/a	n/a	n/a	4–72
As (%)	17	n/a	n/a	11	n/a	n/a	n/a	19	n/a	n/a	n/a	5	n/a	n/a	n/a	16	n/a	2	5	n/a	2–19

Frequency of T1D in APECED

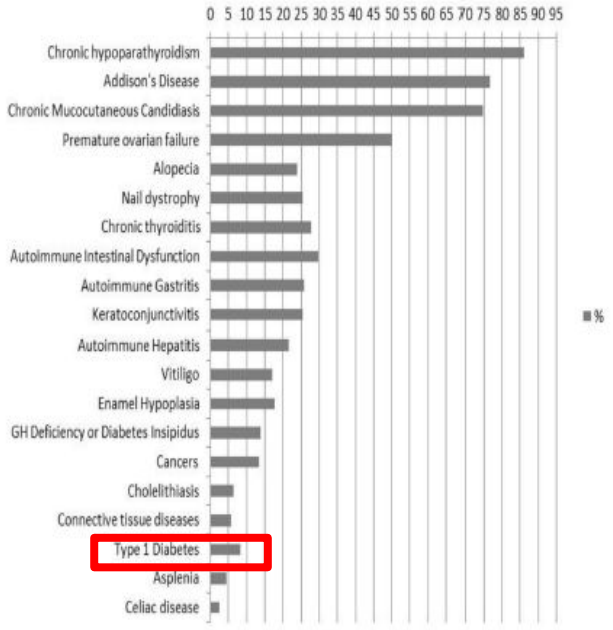
- The rate of T1D incidence varies from 3% to 33% in different series of APECED patients

- The prevalence of T1D in Finnish APECED patients is considerably elevated with respect to what is estimated in APECED patients of Eastern and Central European origin, Irish populations, or Arab families, suggesting the influence of genetic factors predisposing to T1D incidence in APECED

- Meloni et al. (2012) carried out a prospective investigation on 22 pediatric Sardinian APECED patients. Patients showed severe phenotype with, on average, seven disease manifestations. In addition to the classical triad components, autoimmune hepatitis occurred in 27% of cases with higher incidence in females (5:1). Only one patient developed T1D, and hypothyroidism was not present

Frequency and mean age of onset of T1D in the Italian APECED population

Clinical manifestations at the end of follow-up of APS-1 patients in Italy, presented as a percent of the total number of patients (n= 158). *GH* growth hormone



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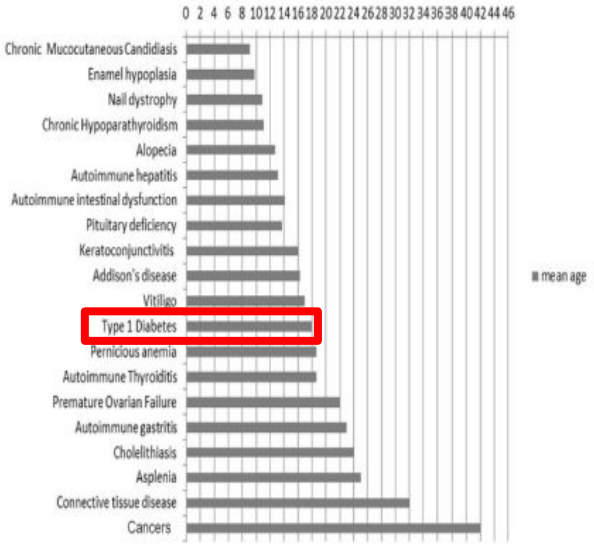
Mean age (in years) at the onset of different clinical manifestations in Italian patients with APS-1



T1D in the Italian APECED population

- Isolated T1D developed at the onset of APS-1 in 2/158 patients (1.3%) (at 18 months and 39 years of age, respectively)
- By the end of the follow-up, 13/158 (8.2%) patients developed T1D at a mean age of 18.1 ± 12.6 years (range 18 months–39 years)
- At the onset of T1D, all affected patients were positive for glutamic acid decarboxylase autoantibodies (GADAbs) and/or islet cell autoantibodies (ICA)
- Furthermore, 18/64 patients (28.1%) without T1D were found positive for ICA and/or GADAbs and during follow-up, the annual incidence of clinical T1D was 1.1%

Frequency of T1D in APECED

- Overall by excluding Finnish prevalence the average rate of T1D incidence in APECED patients is 8% similar to that reported in the Italian population

- The mean age of T1D onset in APECED is 8.5 years (range 3-13)

Low prediction of endocrine pancreas antibodies toward T1D development

APS1

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Antibodies to Glutamic Acid Decarboxylase and Insulin-Dependent Diabetes in Patients with Autoimmune Polyendocrine Syndrome Type I*

TIINAMAIJA TUOMI, PETRA BJÖRSES, ALBERTO FALORNI†, JUKKA PARTANEN, JAAKKO PERHEENTUPA, ÅKE LERNMARK, AND AARO MIETTINEN

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RASSEGNA G It Diabetol Metab 2016;36:210-219

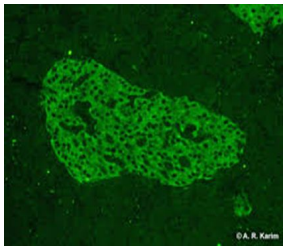
Diabete mellito di tipo 1 e poliendocrinopatie autoimmuni

Betterle C[1], Garelli S[2], Conton P[3], Presotto F[3]

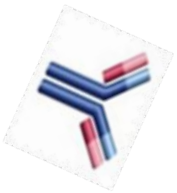
RAPID PUBLICATION | JANUARY 01 1994

GAD Autoantibodies in IDDM, Stiff-Man Syndrome, and Autoimmune Polyendocrine Syndrome Type I Recognize Different Epitopes FREE

Elisabeth Björk; Licio A Velloso; Olle Kämpe; F Anders Karlsson



Markers of pancreatic autoimmunity in APECED



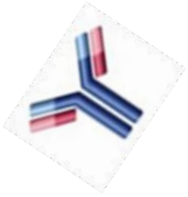
- GAD65 autoantigenic molecule is presented to the immune system through alternative pathogenetic mechanisms in APECED patients
- All sera immunoprecipitated GAD from [35S] methionine-labeled rat islet lysates
- Nevertheless, serum antibodies from SMS and APECED patients recognized the human GAD conformation on Western blot, while T1D sera did not. APECED and SMS sera inhibited the GAD enzymatic activity, but not with T1D sera
- GAD antibody specificities are an epiphenomenon of the autoimmune insulitis that does not lead to clinical disease manifestations

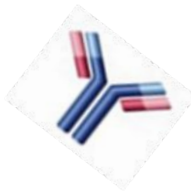
Markers of pancreatic autoimmunity in APECED

- Sera of APECED patients tested positive in addition to GADA for antibodies against a 51-kDa pancreatic islet autoantigen (Velloso 1994) which was characterized as L-amino-acid decarboxylase (AADC)

- This antigen was found unrelated to GAD since depletion from the islet lysate with GAD did not affect the amount of the 51kDa autoantigen

- APECED patients did not show clinical T1D or had altered insulin response to glucose challenge testing, suggesting that they have an autoimmune response against the islets, which is different from that causing the classical T1D





Diabetologia (1994) 37: 61–69

Diabetologia

Autoantibodies against a novel 51 kDa islet antigen and glutamate decarboxylase isoforms in autoimmune polyendocrine syndrome type I

L. A. Velloso[1], O. Winqvist[1], J. Gustafsson[2], O. Kämpe[1], F. A. Karlsson[1]

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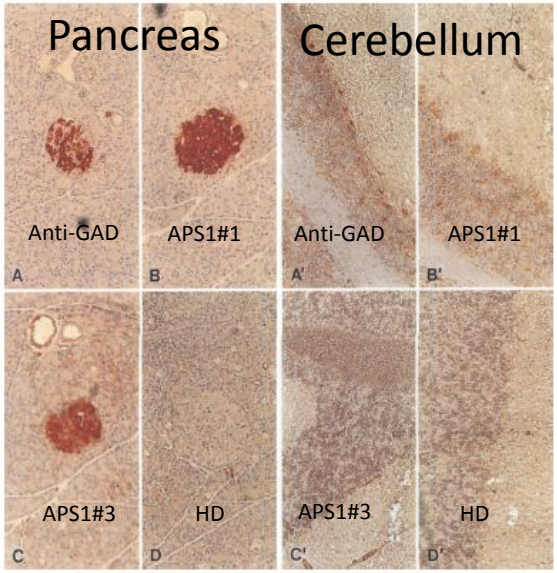

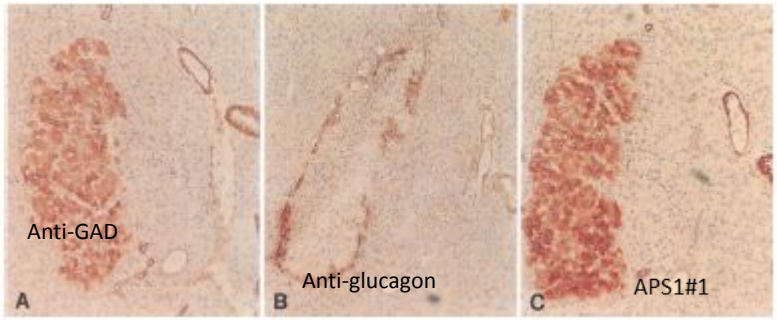

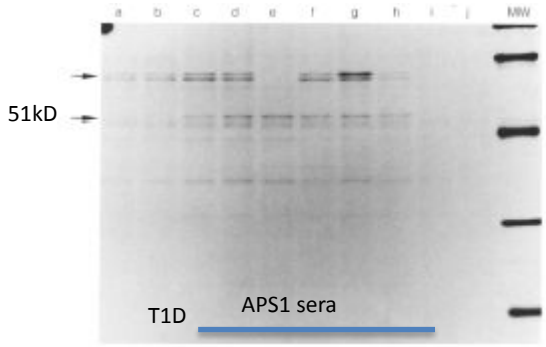

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Autoantibodies against Aromatic L-Amino Acid Decarboxylase in Autoimmune Polyendocrine Syndrome Type I*

EYSTEIN S. HUSEBYE, GENNET GEBRE-MEDHIN, TIINAMAIJA TUOMI, JAAKKO PERHEENTUPA, MONA LANDIN-OLSSON, JAN GUSTAFSSON, FREDRIK RORSMAN, AND OLLE KÄMPE

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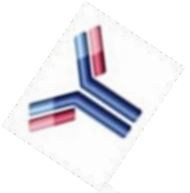
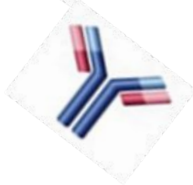
- In the study by Husebye et al. (1997) the presence of AADC Abs was assessed in APECED patients and in patients affected by T1D

- These specificities were detected in 51% of APECED patients, in none of the 138 T1D patients, nor in healthy controls





- The effect of AADC specificities in the development of T1D in APECED patients remains to be unraveled

Genetic factors and low T1D incidence in APECED

- Genetic factors were investigated to explain the low T1D incidence in APECED in spite of the high frequency of T1D-related autoantibodies
- T1D was not associated with peculiar *AIRE* gene mutations, however same HLA predisposing haplotypes than in the general population were identified *i.e.* HLA DRB1*03 and HLA DRB1*04 and the same protective haplotypes HLA DRB1*15 and DQB1*0602

International Journal of *Molecular Sciences*

Review

Type 1 Diabetes in Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy Syndrome (APECED): A "Rare" Manifestation in a "Rare" Disease

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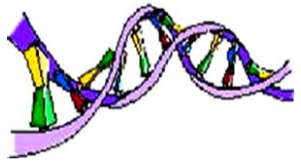
MDPI

JOURNAL ARTICLE

The Expression of Autoimmune Polyglandular Disease Type I Appears Associated With Several HLA-A Antigens But Not With HLA-DR Get access ›

PEKKA AHONEN, SAIJA KOSKIMIES, MARJA-LIISA LOKKI, ANJA TIILIKAINEN, JAAKKO PERHEENTUPA

The Journal of Clinical Endocrinology & Metabolism, Volume 66, Issue 6, 1 June 1988, Pages 1152–1157, https://doi.org/10.1210/jcem-66-6-1152



HLA haplotypes in APECED patients

JOURNAL ARTICLE

The Expression of Autoimmune Polyglandular Disease Type I Appears Associated With Several HLA-A Antigens But Not With HLA-DR Get access

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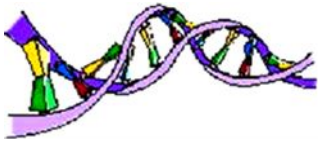
- APECED may occur sporadically or among siblings. In early studies no association was reported between APECED and the human leukocyte antigens (HLA) class I or class II (Betterle 1998, Kluger 2012)

- Subsequently the HLA-A28 haplotype was found more frequent in APECED patients than in healthy controls (Ahonen 1998). In the same study, the HLA-A3 is shown to be more frequent in APECED patients with associated ovarian failure

- Significant differences were not found by examining the HLA class I antigens in 17 patients than in normal controls, while HLA class II (DR genes) were at increased frequency of DR3 and DR5 (Betterle 1998)



Clinical Endocrinology (2011) 74, 532–535

LETTERS TO THE EDITOR

The role of heterozygous mutations of the autoimmune regulator gene (AIRE) in non-APECED autoimmunity: a comment on recent findings

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- Since T1D is at higher incidence in APECED patients from Finland, *AIRE* variants were suspected to underlie the pathogenesis of T1D in general (Fierabracci 2011)

- *AIRE* gene variants, especially in heterozygosity or sequence polymorphisms, were suspected to influence the development of certain organ-specific autoimmune disorders by affecting the establishment of tolerance at the thymus level in perinatal age

- In addition, elevated levels of IgA and activated T lymphocytes, showing immunological dysregulation, were detected in PBMC of parents of APECED patients harboring heterozygous *AIRE* mutations (Sediva 2002)

The role of *INS* gene in T1D genetic predisposition

- The insulin (*INS*) gene is associated with T1D incidence [Hirschhorn 2003].
- The locus IDDM2 mapped within the upstream region of the *INS* gene and corresponds to a minisatellite polymorphism of the variable number of tandem repeats (*VNTR*) of the chromosome 11p15.5 [Turunen 2006].
- *VNTR* plays a role in the ectopic expression of insulin in the thymus, thus inducing susceptibility to T1D [Vafiads 1997, 2001].

letter

Insulin expression in human thymus is modulated by *INS* VNTR alleles at the *IDDM2* locus

Petros Vafiadis[1], Simon T. Bennett[2], John A. Todd[2], Joseph Nadeau[3], Rosemarie Grabs[1], Cynthia G. Goodyer[1], Saman Wickramasinghe[1], Eleanor Colle[1] & Constantin Polychronakos[1]

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Class III Alleles of the Variable Number of Tandem Repeat Insulin Polymorphism Associated with Silencing of Thymic Insulin Predispose to Type 1 Diabetes

PETROS VAFIADIS, HOURIA OUNISSI-BENKALHA, MICHAEL PALUMBO, ROSEMARIE GRABS, MARYLÈNE ROUSSEAU, CYNTHIA G. GOODYER, AND CONSTANTIN POLYCHRONAKOS

Main studies referring to genes conferring genetic susceptibility to T1D in APECED patients

Reference	Number of APECED Patients	Frequency of T1D in APECED Patients	Population	Predisposing to T1D
Paquette et al. (2010)	50	16%	Finnish	IDDM2 5′ INS VNRT
Adamson et al. (2007)	33	24%	UK	class I/INS VNTR susceptibility locus in 75%
Halonen et al. (2002)	104 (index)	12.5%	12 different	DRB1*03, DRB1*04 found in 61.5% of diabetic APECED and 42.9% of non-diabetics

T1D: Type 1 diabetes; APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome; IDDM2: insulin-dependent diabetes mellitus 2; VNRT: variable number of tandem repeats.

APS1

Main studies referring to genes conferring genetic susceptibility to T1D in APECED patients

- Paquette et al. [2010] found that IDDM2 is prevalent in the diabetic Finnish APECED patients versus the nondiabetics, adding evidence that loss of Aire function is not exclusive of T1D-development in APECED.

- Previously, the same authors examined T1D-discordant APECED siblings, from a French Canadian family, having the same *AIRE* mutation (Ward 1999). The T1D-affected sibling was found to possess a 5' INS VNTR I/I genotype while the unaffected sibling had a I/III genotype suggesting the involvement of this locus in APECED-associated T1D.

- This hypothesis was confirmed in another pair of APECED siblings discordant for T1D.

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ORIGINAL PAPER

Joni A. Turunen · Maija Wessman · Carol Forsblom · Riika Kilpikari · Maija Parkkonen · Nora Pöntynen · Tanja Ilmarinen · Ismo Ulmanen · Leena Peltonen · Per-Henrik Groop

Association analysis of the *AIRE* and insulin genes in Finnish type 1 diabetic patients

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The potential interaction of *AIRE* and *INS* genes in the development of T1D was originally unraveled in Finnish APECED patients (Turunen 2006). They examined a series of 733 Finnish patients and 735 controls and failed to detect an association of any of the five common *AIRE* SNPs selected from the public database (single nucleotide polymorphism database (dbSNP)) (rs2776377, rs878081, rs1800520, rs933150, and rs1800522) or the corresponding *AIRE* haplotypes.

The 23HphI polymorphism in the *INS* gene was significantly associated with T1D in the Finnish population (p = 6.8 1012) (Hirschhorn 2003).

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Conclusions

- T1D rarely occurs in APECED with different frequencies among the different ethnic groups

- T1D in APECED has peculiar immunological features

- T1D in APECED is a T1D endotype with peculiar response to Immunotherapeutic approaches?

Review article

Type 1 diabetes and inborn errors of immunity: Complete strangers or 2 sides of the same coin?

Check for updates

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