SINDROMI POLIENDOCRINE AUTOIMMUNI

Sindromi poliendocrine autoimmuni Definizione

Qualunque combinazione di due o più malattie endocrine autoimmuni nello stesso soggetto. In senso più esteso, sono comprese anche le combinazioni di una malattia endocrina autoimmune con manifestazioni autoimmuni non endocrine: es. gastrite atrofica, vitiligine, morbo celiaco

Sindromi poliendocrine autoimmuni Definizione II

Si differenziano in forme:

COMPLETE: presenza di segni clinici delle manifestazioni autoimmuni che caratterizzano ciascuna sindrome

INCOMPLETE: presenza dei soli segni biochimici della malattia autoimmune (es. autoanticorpi) in almeno una delle manifestazioni caratterizzanti

Sindromi poliendocrine autoimmuni
Classificazione

Vengono classificate in base alla presenza di una (o più) malattie caratterizzanti, cioè malattie senza le quali non si può porre diagnosi di quella particolare sindrome

Sindromi poliendocrine autoimmuni
Abbreviazioni

APS: Autoimmune Polyendocrine Syndrome

PGA: Polyglandular Autoimmune syndrome

SPA: Sindrome Poliendocrina Autoimmune

Sindrome poliendocrina autoimmune di tipo I (SPA I)

Definita dalla presenza di almeno due delle tre seguenti malattie:

Ipoparatiroidismo

Morbo di Addison

Candidiasi cronica

Oppure da una sola in familiari di pazienti già diagnosticati con SPA I

Characteristics of autoimmune polyendocrine syndromes

Feature	APS1	APS2	IPEX
Main components	Addison's disease	Addison's disease	Autoimmune enteropathy
	Hypoparathyroidism	Type 1 diabetes	Neonatal diabetes mellitus
	Mucocutanous candidiasis	Autoimmune thyroid disease	Eczema
Frequency of diabetes	~ 20%	~ 50%	> 60%
Onset	Childhood	Adolescence, adulthood	Infancy
Gene and inheritance	*AIRE*, autosomal recessive	Polygenic (MHC and others)	*FOXP3*, X-linked
Female:Male ratio	Equal	Female>Male	X-linked (male only)
Pathogenesis	Autoreactive T cells escape negative selection	Unknown	Defect Treg leading to T cell activation and proliferation
Immunologic phenotype	High titer autoantibodies to intracellular enzymes, interferons and Th17 cytokines, candida susceptibility	Antibodies to affected organs; anti-21OH (Addison's disease), GAD, IA2 (type 1 diabetes)	Lymphocytosis, eosinophilia, over production of cytokines, hyper IgE
Other common manifestations	Oophoritis, malabsorption, hepatitis, asplenism, alopecia, vitiligo, keratitis, enamel dysplasia	Autoimmune gastritis, celiac disease, vitiligo, oophoritis	Autoimmune thyroid disease, eczema haemolytic anemia, thrombocytopenia, lymphadenopathy

Husebye & Anderson 2011

Genes associated with Addison's disease, type 1 diabetes and autoimmune thyroid disease.

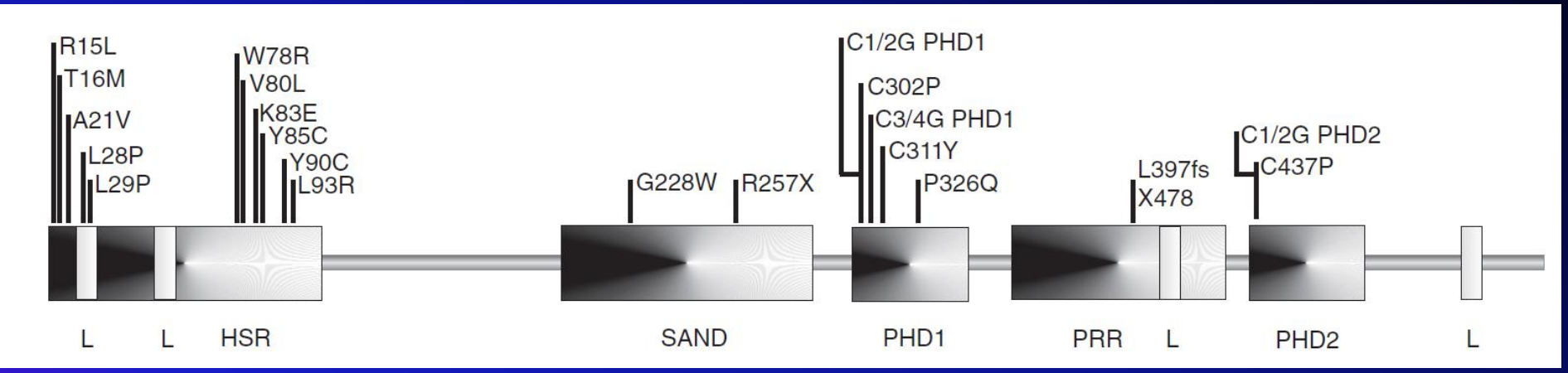
Gene class	Addison's disease	Type 1 diabetes	Autoimmune thyroid disease
	Gene or variant	Gene or variant	Gene or variant
Organ specific genes	?	*VNTR* of the Insulin promoter	*TSH Receptor* (for Graves' disease)
Immune related genes			
MHC class I		*HLA-B*	*HLA-C* and *HLA-B*
MHC class II	*DR3-DQ2*	*DR3-DQ2*	*DRB1*
	*DR4(DRB1*0404)-DQ8*	*DR4*(DRB1*0401 or DRB1*0404)-*DQ8*	*DQA1*
Non-MHC	*CTLA-4*	*CTLA-4*	*CTLA-4*
	PTPN22	*PTPN22*	*PTPN22*
	NALP1	*NALP1*	
		IL2Rα (CD25)	

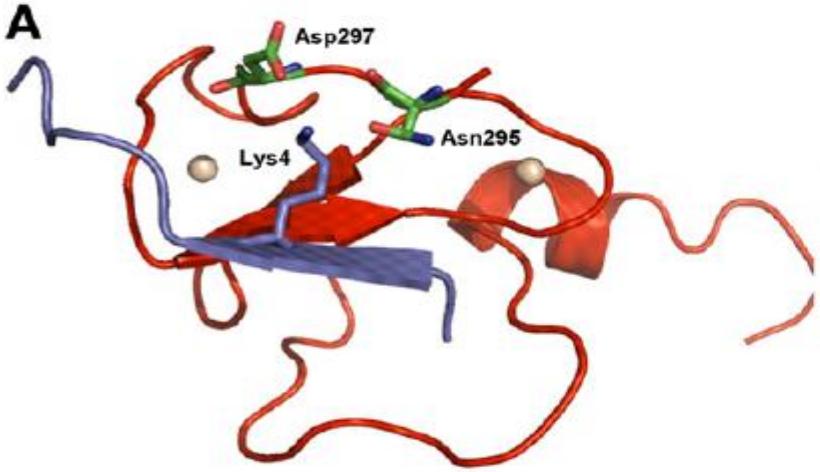
Husebye & Anderson 2011

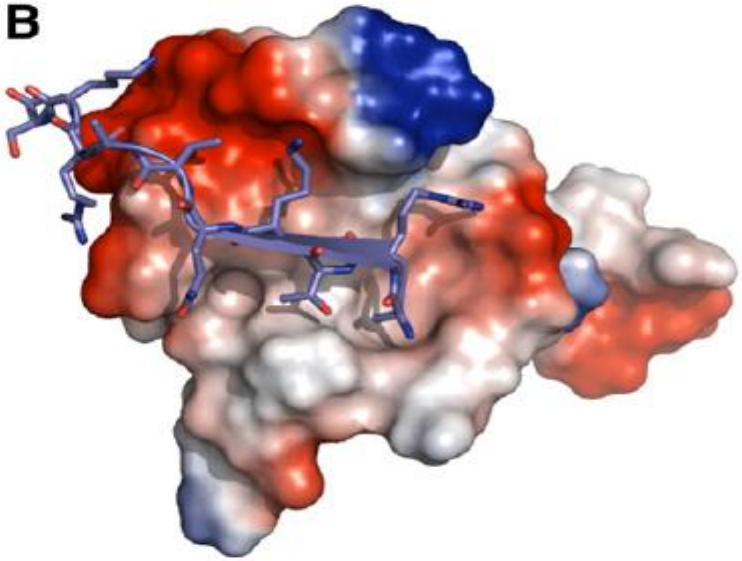
Sindrome poliendocrina autoimmune di tipo I (SPA I)

✓ **Età insorgenza**	**Pediatrica**
✓ **Trasmissione genetica**	**Autosomica recessiva – Cromosoma 21 (q22.3) geneAIRE (AutoImmune Regulator) NON ASSOCIATA CON HLA**
✓ **Componenti endocrine**	**Addison (70-80%)**
	Ipoparatiroidismo (80%)
	Tireopatie autoimmuni (10%)
	Diabete di tipo 1 (2-4%)
	Ipogonadismo (12-17%)
✓ **Componenti extraendocrine**	**Candidiasi cronica (75-85%)**
	Anemia perniciosa (15%)
	Vitiligine (8-9%)
	Epatite cronica attiva (11%)
	Alopecia (28-32%)
	Malassorbimento (22%)

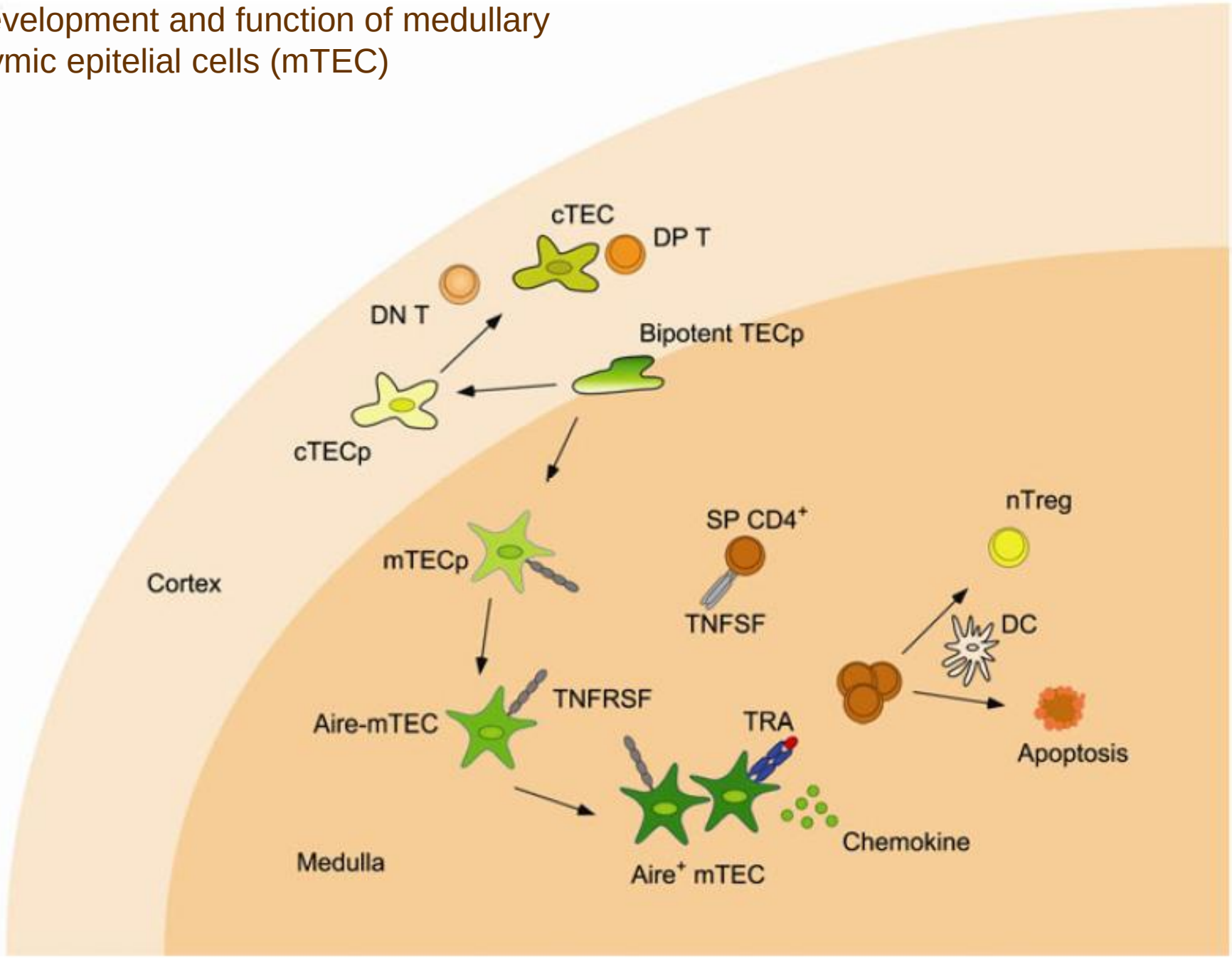
Aire

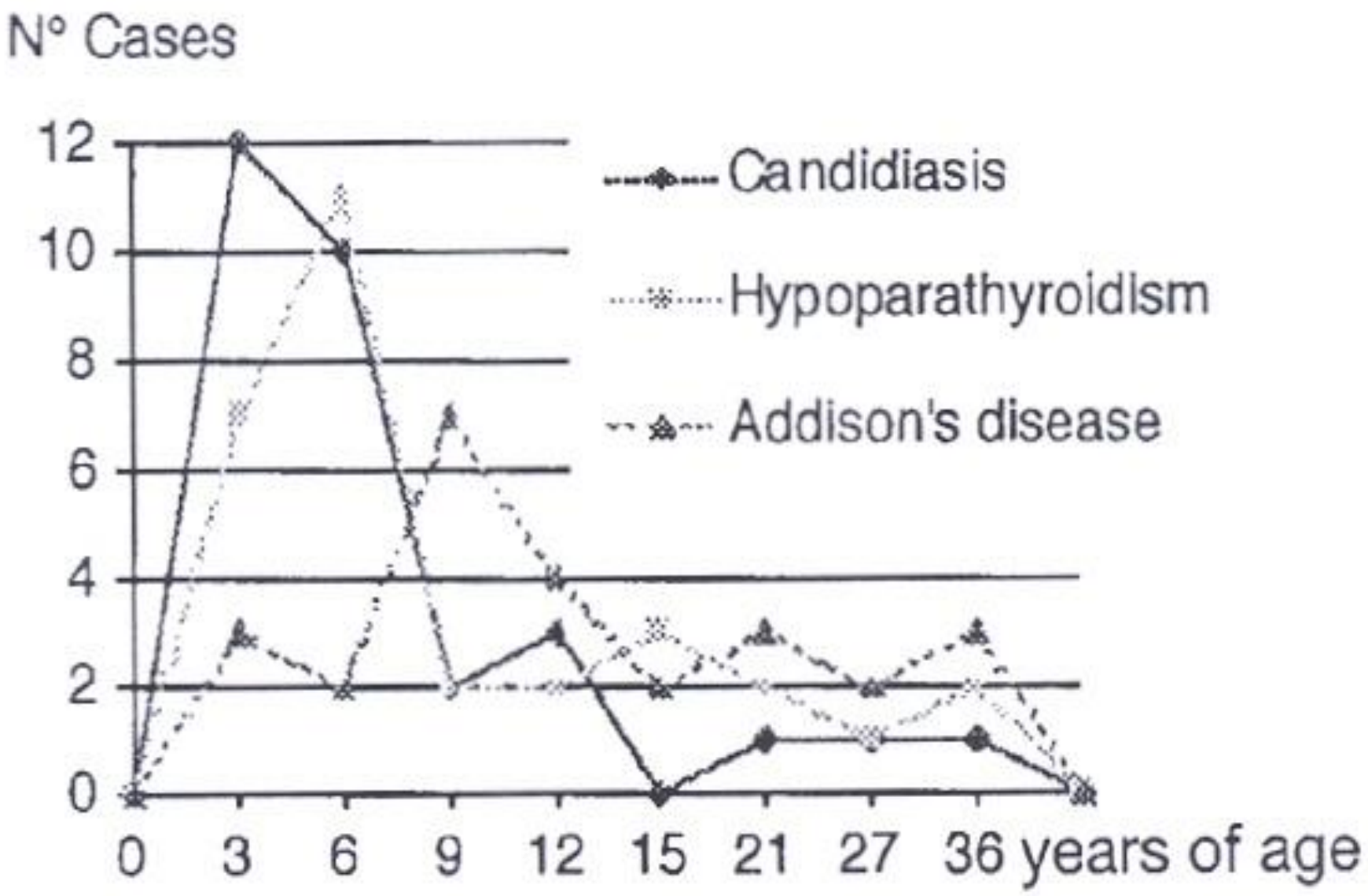

R15L
T16M
A21V
L28P
L29P
W78R
V80L
K83E
Y85C
Y90C
L93R
G228W
R257X
C1/2G PHD1
C302P
C3/4G PHD1
C311Y
P326Q
L397fs
X478
C1/2G PHD2
C437P
L
L
HSR
SAND
PHD1
PRR
L
PHD2
L


A
Asp297
Asn295
Lys4


B

Development and function of medullary thymic epitelial cells (mTEC)





Timing of major clinical features in APS type 1.

Hot-spots di SPA I in Italia

TABLE 8. Haplotype analysis in 10 Italian patients with APS type 1

Patients	Mutations Allele 1/Allele 2	Sex	Major clinical diseases
1. F.T.	R257X/R257X	F	CC + CHP + AD
2. F.L.	R257X/R257X	F	CC + CHP + AD
3. A.E.	R257X/R257X	M	CC + CHP + AD
4. C.A.	R257X/R257X	M	CC + CHP + AD
5. C.G.	R257X/R257X	M	CC + CHP + AD
6. C.G.	del 13/R257X	F	CC + CHP + AD
7. C.E.	del 13/R257X	F	CC + CHP + AD
8. T.P.	del 13/del 13	F	CC + CHP + AD
9. DG.F.	del 13/del 13	M	CC + CHP + AD
10. S.M.	R139X/R139X	F	CC + CHP + AD

Betterle et al. Endocrine Reviews 2002

Steroid-cell autoantibodies in autoimmune Addison's disease and related disorders

	21OHAb	ACA	StCA	17αOHAb	sccAb
Isolated Addison	85-90%	80-90%	15-25%	10-15%	10-15%
APS I	85-90%	80-90%	60-80%	50-70%	60-80%
Addison + POF	85-90%	80-90%	90-95%	50-70%	70-80%
Isolated POF	-	-	<2%	<2%	<2%
Healthy controls	<1%	<1%	<1%	<2%	<2%

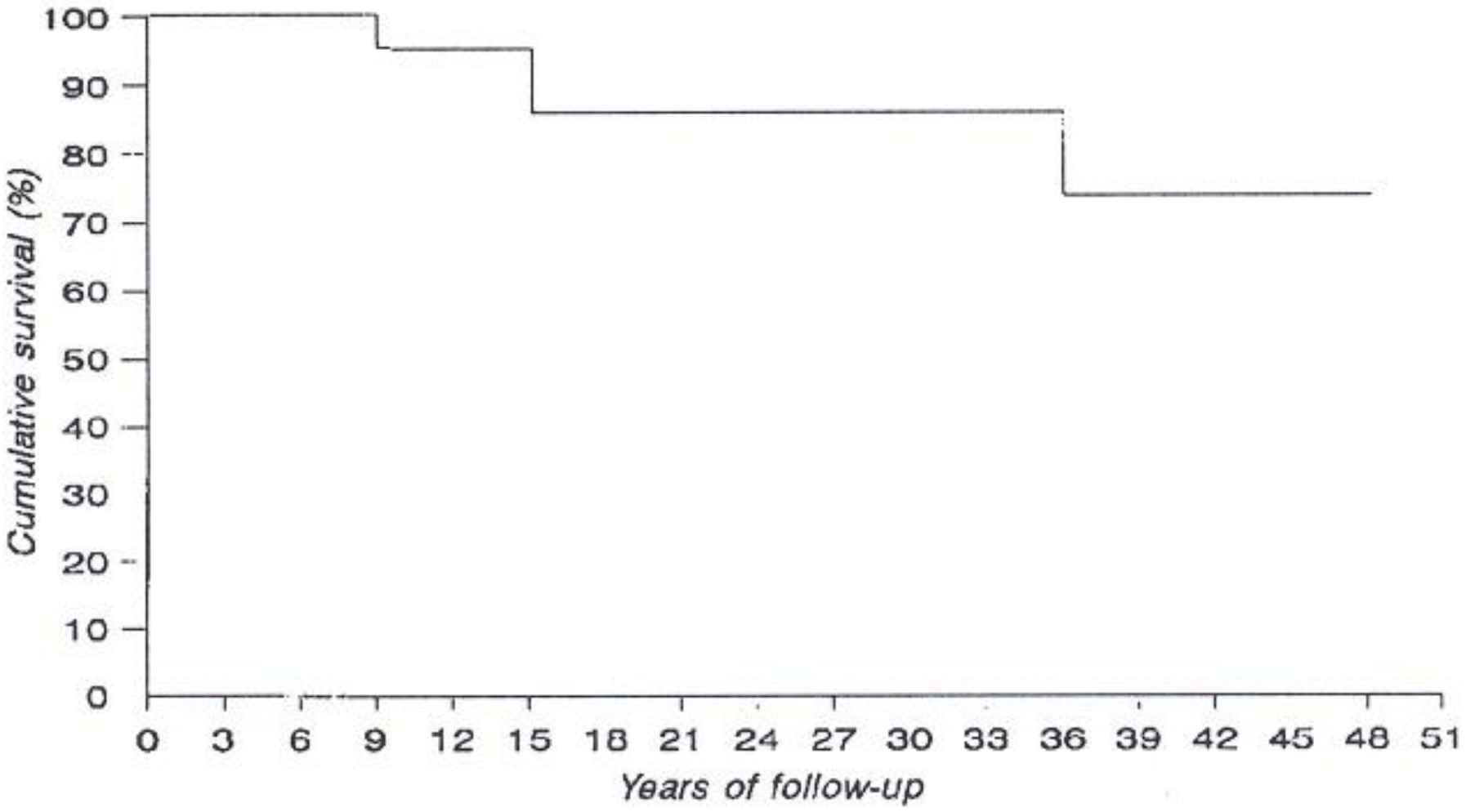
Falorni & Laureti, 2000; Perniola R et al, 2001; Falorni et al, 2002

Frequenza di altri autoanticorpi in APS I

GAD65Ab	IA-2Ab	TPOAb	TGAb	ANA	LKM-Ab
45-50%	35-40%	20-30%	20-30%	60-70%	15-20%

Falorni & Laureti, 2000; Perniola R et al, 2001

SURVIVAL RATE OF APS I PATIENTS



CAUSE DI MORTE IN 13 PAZIENTI APS I

3 EPATITE FULMINANTE
2 CARCINOMA DELLA MUCOSA ORALE
2 SETTICEMIA
1 CRISI ADDISONIANA
1 CHETOACIDOSI DIABETICA
1 INCIDENTE
1 MORTE IMPROVVISA PER IPOPARATIROIDISMO
1 INSUFFICIENZA RENALE
1 CAUSA SCONOSCIUTA

J Clin Endocrinol Metab, November 2008, 93(11):4389–4397

Autoantibodies against Type I Interferons as an Additional Diagnostic Criterion for Autoimmune Polyendocrine Syndrome Type I

Antonella Meloni,* Maria Furcas, Filomena Cetani,* Claudio Marcocci, Alberto Falorni,* Roberto Perniola,* Mikuláš Pura,* Anette S. Bøe Wolff, Eystein S. Husebye, Desa Lilic,* Kelli R. Ryan, Andrew R. Gennery, Andrew J. Cant, Mario Abinun, Gavin P. Spickett, Peter D. Arkwright, David Denning, Colm Costigan, Maria Dominguez, Vivienne McConnell, Nick Willcox, and Anthony Meager**

TABLE 1. Summary of anti-IFN antibodies and *AIRE* mutations in APS-I patients

AIRE mutations		Ref.	n	Neutralizing antibodies against IFN-α2	Neutralizing antibodies against IFN-ω
Truncations/extensions					
R139X	hom		12	≥+ or –	≥++ or +
R139X/not detected			1	+++	+++
R257X	hom	15, 16	57	54 ≥ +; 3[a] –	56 ≥ +; 1[a] –
C322fsX372	hom	15	10	+++ to –	100% ≥ +
p.IVS7 + 1G→A,[b]	hom	15	2	+++ or –	≥++
C311fsX376	hom		1	+++	+++
R257X/H415fsX422		15	2	+++	+++
L417fsX422	hom	15	1	++	++
R257X/X546C + 59 aa		15	4	+++	+++ to ++
Totals				8/151[c] negative	1/151[c] negative initially
Missense mutations					
R8C + S135Q[d]			1	–	++
R8C + L97P			1	+++	+++
W78R	hom		3	+++	+++
W78R + V22-D23del			1	+++	+++
W78R + P252L			1	+++	+++
W78R + Q358X			3	+++	+++
Y85C	hom	29	1	++ (ELISA)	ND
R92W + truncations		25	2	+++ to ++	+++ to ++
G228W + wt family 1			5	+++ to +	+++ to +
Grandmother			1	–	++
C311Y + R257X			2	+ or –	++
C446G + R257X			1	–	++
P539L	hom		1	++	++
Totals				5/23[c] negative	0/22[c] negative

–, ≤1:60; +, >1:120; ++, >1:10,000; +++, >1:50,000. aa, Amino acids; hom, homozygous; ND, not done; wt, wild type.

[a] One initially negative patient was strongly positive against both IFNs in both subsequent bleeds (16).

[b] Also called c.879 + 1G→A.

[c] Totals include additional compound heterozygotes omitted here for clarity.

[d] Also called c.402delC.

J Clin Endocrinol Metab, November 2008, 93(11):4389–4397

Autoantibodies against Type I Interferons as an Additional Diagnostic Criterion for Autoimmune Polyendocrine Syndrome Type I

Antonella Meloni,* Maria Furcas, Filomena Cetani,* Claudio Marcocci, Alberto Falorni,* Roberto Perniola,* Mikuláš Pura,* Anette S. Bøe Wolff, Eystein S. Husebye, Desa Lilic,* Kelli R. Ryan, Andrew R. Gennery, Andrew J. Cant, Mario Abinun, Gavin P. Spickett, Peter D. Arkwright, David Denning, Colm Costigan, Maria Dominguez, Vivienne McConnell, Nick Willcox, and Anthony Meager**

TABLE 2. Anti-IFN antibodies in newly tested APS-I patients with truncations or missense mutations in both *AIRE* alleles

		Neutralizing antibodies[a]			
		Anti-IFN-α2		Anti-IFN-ω	
AIRE mutation	APS-I triad/total patients tested	No. positive/total	Titer × 10^{-3}	No. positive/total	Titer × 10^{-3}
Length variants					
Sardinia					
R139X hom	7/12	12/12	>512–14	12/12	>512–14
R139X/C322fsX372	1/2	2/2	500–5	2/2	256–180
Unaffected relatives[b]		0/33	All <0.04	0/33	All <0.04
Apulia					
C311fsX376 hom	0/1	1/1	>256	1/1	200
Unaffected relatives[b]		0/1	<0.04	0/1	<0.04
UK and Ireland					
R257X and/or C322fsX372	8/14	14/14[c]	>512–7	14/14[c]	>512–0.6
Totals	16/29	29/29		29/29	
Missense *AIRE* mutations					
Apulia					
W78R hom	2/3	3/3	>256–64	3/3	135–25
W78R/P252	1/1	1/1	128	1/1	110
W78R/V22-D23del	0/1	1/1	256	1/1	110
W78R/Q358X	3/3	3/3	>256–70	3/3	256–70
P539L hom	1/1	1/1	50	1/1	12
Unaffected relatives[b]		0/10	All <0.04	0/10	All <0.04
Rome family 1					
G228W/wt	1/6	5/6	331–0.06	6/6	1024–4.5
Unaffected relatives		0/4	All <0.04	0/4	All <0.04
Totals	8/15	14/15		15/15	
Grand totals	24/44	43/44		44/44	

J Clin Endocrinol Metab, November 2008, 93(11):4389–4397

Autoantibodies against Type I Interferons as an Additional Diagnostic Criterion for Autoimmune Polyendocrine Syndrome Type I

Antonella Meloni,* Maria Furcas, Filomena Cetani,* Claudio Marcocci, Alberto Falorni,* Roberto Perniola,* Mikuláš Pura,* Anette S. Bøe Wolff, Eystein S. Husebye, Desa Lilic,* Kelli R. Ryan, Andrew R. Gennery, Andrew J. Cant, Mario Abinun, Gavin P. Spickett, Peter D. Arkwright, David Denning, Colm Costigan, Maria Dominguez, Vivienne McConnell, Nick Willcox, and Anthony Meager**

TABLE 3. Neutralizing antibodies against IFN-α2 and IFN-ω as diagnostic markers for APS-I; comparisons with disease and healthy controls

Donor group	Patient numbers tested			
	This paper	Previously (Ref.)	Anti-IFN-α2	Anti-IFN-ω
APS-I				
APS-I total	45	123 (15, 16, 25)	166/174	173/174[a]
APS-I but without full APS-I triad	20	≥27 (15, 16, 25)	≥43/47	47/47
APS-I with <2 *AIRE* mutations detected initially	1	6 (15, 16, 25)	4/7	4/7
Controls				
Healthy controls	49 (supplemental Table A)	70 (17)	0/119	0/119
Unaffected APS-I relatives	48 (Table 2)	10 (16)	0/58	0/58
Subtotals			0/177	0/177
Disease controls				
APS-2	27	9 (16, 25)	0/36	0/36
AD alone	49	11 (16, 25)	0/60	0/60
HP alone		2 (16)	0/2	0/2
CMC alone ± hAT	19 (Supplemental Table A)	3 (16)	0/22	0/22
IDDM		(17)	0/29	0/29
Thyroid autoimmunity		(17)	0/25	0/25
Pemphigoid		(17)	0/67	0/67
Di George syndrome	48		0/48	0/48
Neurological		(17)	0/124	0/124
Neoplastic		(17)	0/70	0/70
Postviral		(17)	0/94	ND
Rheumatological				
OA, giant cell arteritis, polymyalgia rheumatica, RA		(30)	0/70	0/70
SLE			1/50[b]	0/50
Subtotals			1/695	0/601
Grand totals			1/874	0/780
Sensitivity			95.4%, 166/174[a]	99.4%, 173/174[a]
Specificity			99.9%, 873/874	100%, 780/780
Predictive values				
Positive			99.4%, 166/167	100%,173/173
Negative			99.1%, 873/881	99.9%, 780/781

Autoantibodies against Type I Interferons as an Additional Diagnostic Criterion for Autoimmune Polyendocrine Syndrome Type I

Antonella Meloni,* Maria Furcas, Filomena Cetani,* Claudio Marcocci, Alberto Falorni,* Roberto Perniola,* Mikuláš Pura,* Anette S. Bøe Wolff, Eystein S. Husebye, Desa Lilic,* Kelli R. Ryan, Andrew R. Gennery, Andrew J. Cant, Mario Abinun, Gavin P. Spickett, Peter D. Arkwright, David Denning, Colm Costigan, Maria Dominguez, Vivienne McConnell, Nick Willcox, and Anthony Meager**

J Clin Endocrinol Metab, November 2008, 93(11):4389–4397

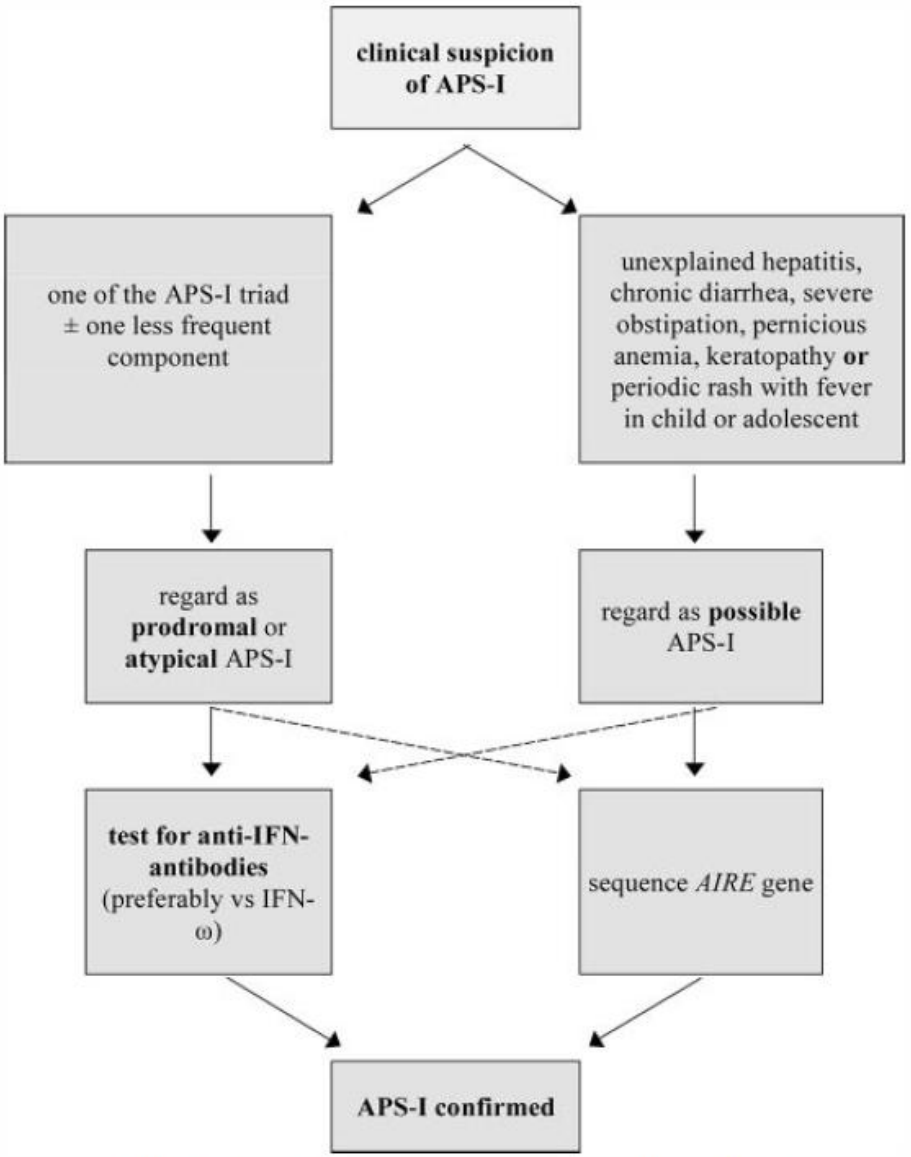
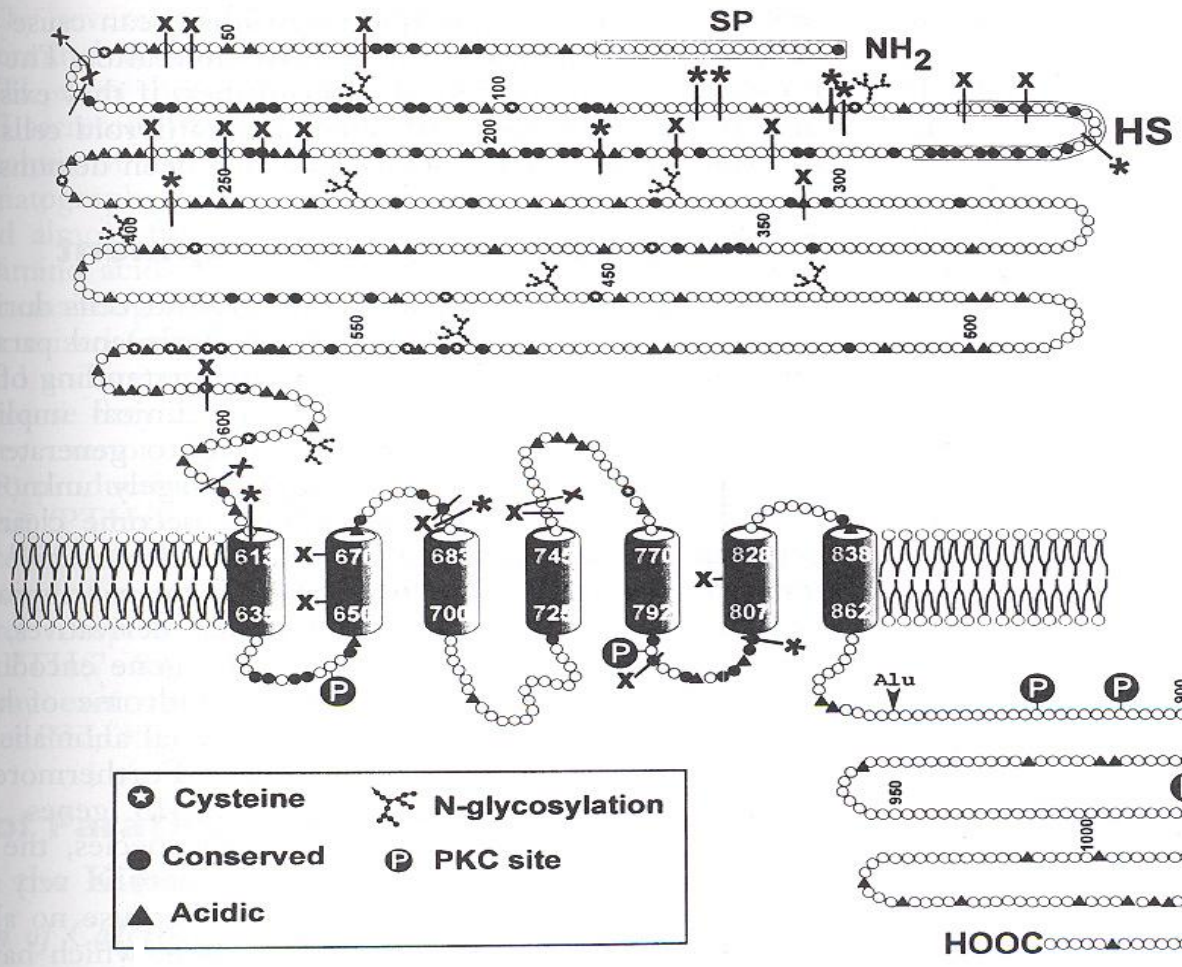


FIG. 3. Diagnostic options for atypical or prodromal APS-I.

IL RECETTORE DEL CALCIO E' UN AUTOANTIGENE NELL'IPOPARATIROIDISMO



X – Inactivating	* – Activating
Pro39Ala	Ala116Thr
Ser53Pro	Asn118Lys
Pro55Leu	Glu127Ala
Arg62Met	Phe128Leu
Arg66Cys	Thr151Met
Thr138Met	Gln191Lys
Gly143Glu	Gln245Arg
Asn178Asp	Phe612Ser
Arg185Gln	Gln681His
Asp215Glu	Phe806Ser
Tyr218Ser	
Pro221Ser	
Arg227Leu(Gln)	
Glu297Lys	
Cys582Tyr	
Ser607Stop	
Ser657Tyr	
Gly670Arg	
Arg680Cys	
Pro747F-shift	
Pro748Arg	
Arg795Trp	
Val817Ile	
Thr876Alu	

Attivazione di fosfolipasi C

Blocco della stimolazione della produzione di cAMP → **Rapido aumento del calcio intracellulare** → **Riduzione della secrezione di PTH**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Autoimmune Polyendocrine Syndrome Type 1 and NALP5, a Parathyroid Autoantigen

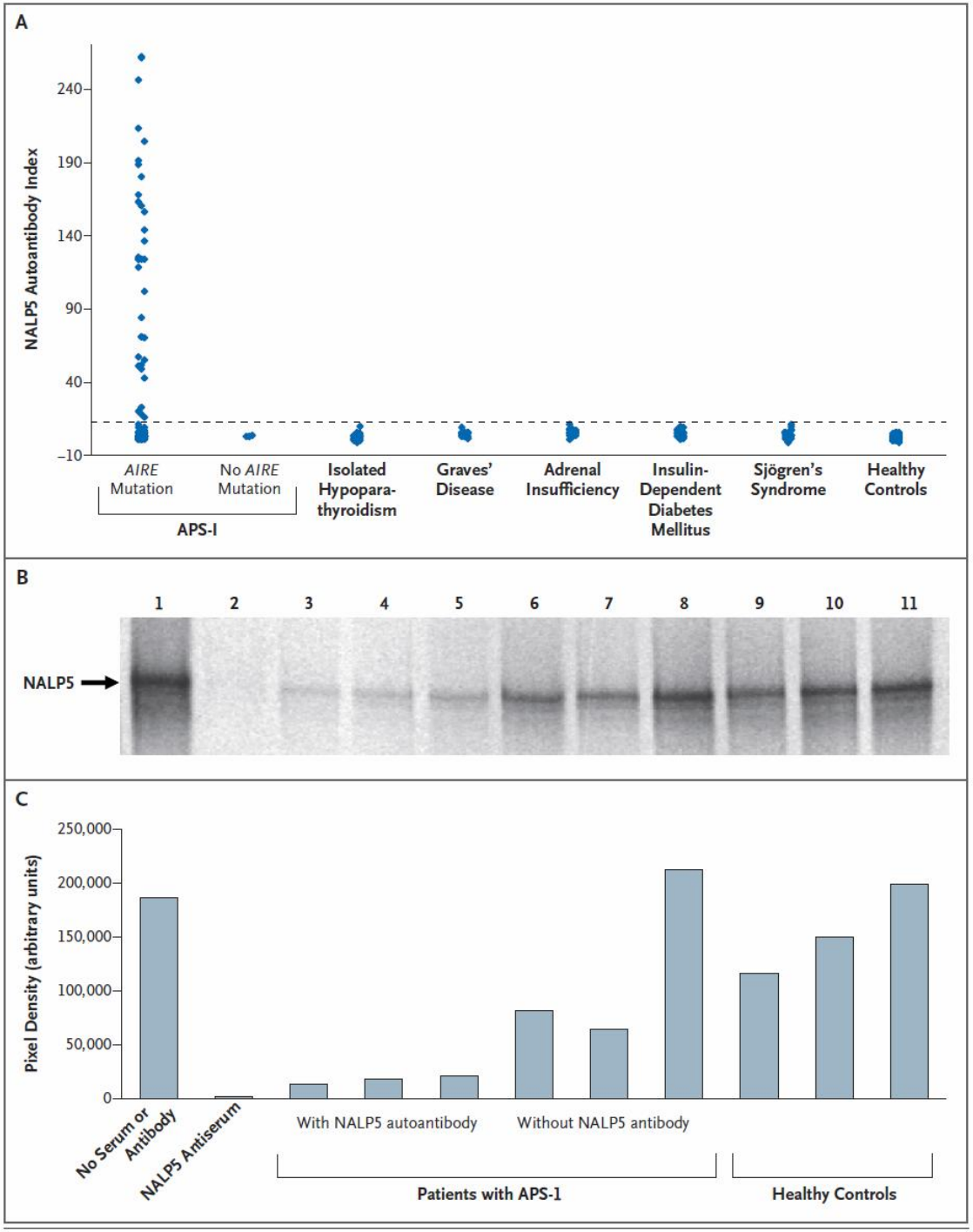
Mohammad Alimohammadi, M.D., Peyman Björklund, Ph.D., Åsa Hallgren, B.Sc., Nora Pöntynen, M.Sc., Gabor Szinnai, M.D., Noriko Shikama, Ph.D., Marcel P. Keller, Ph.D., Olov Ekwall, M.D., Ph.D., Sarah A. Kinkel, B.Sc., Eystein S. Husebye, M.D., Ph.D., Jan Gustafsson, M.D., Ph.D., Fredrik Rorsman, M.D., Ph.D., Leena Peltonen, M.D., Ph.D., Corrado Betterle, M.D., Ph.D., Jaakko Perheentupa, M.D., Ph.D., Göran Åkerström, M.D., Ph.D., Gunnar Westin, Ph.D., Hamish S. Scott, Ph.D., Georg A. Holländer, M.D., and Olle Kämpe, M.D., Ph.D.

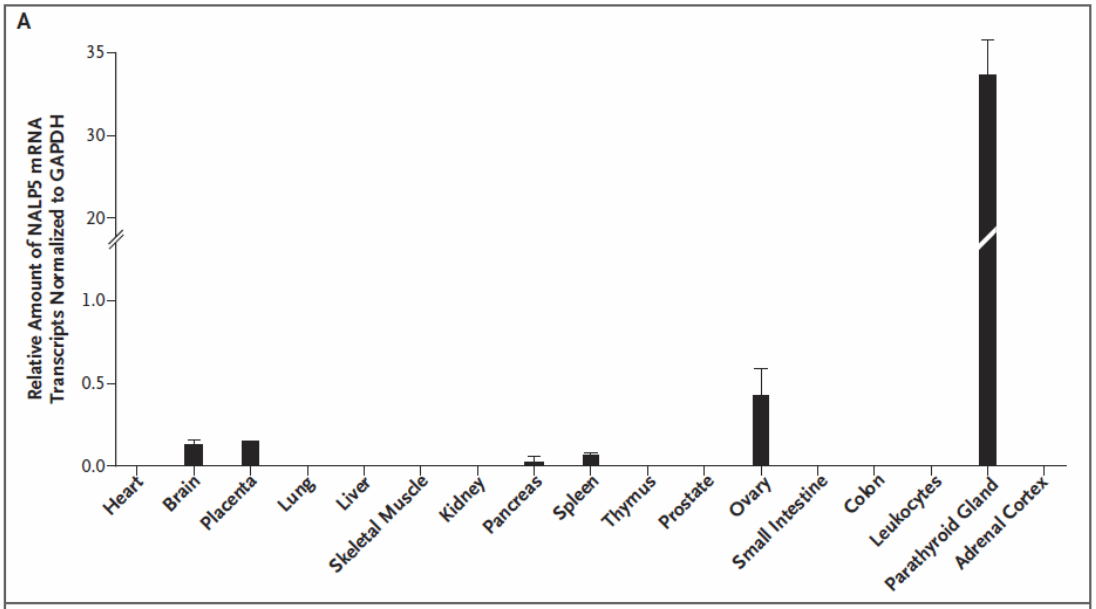
N Engl J Med 2008;358:1018-28.

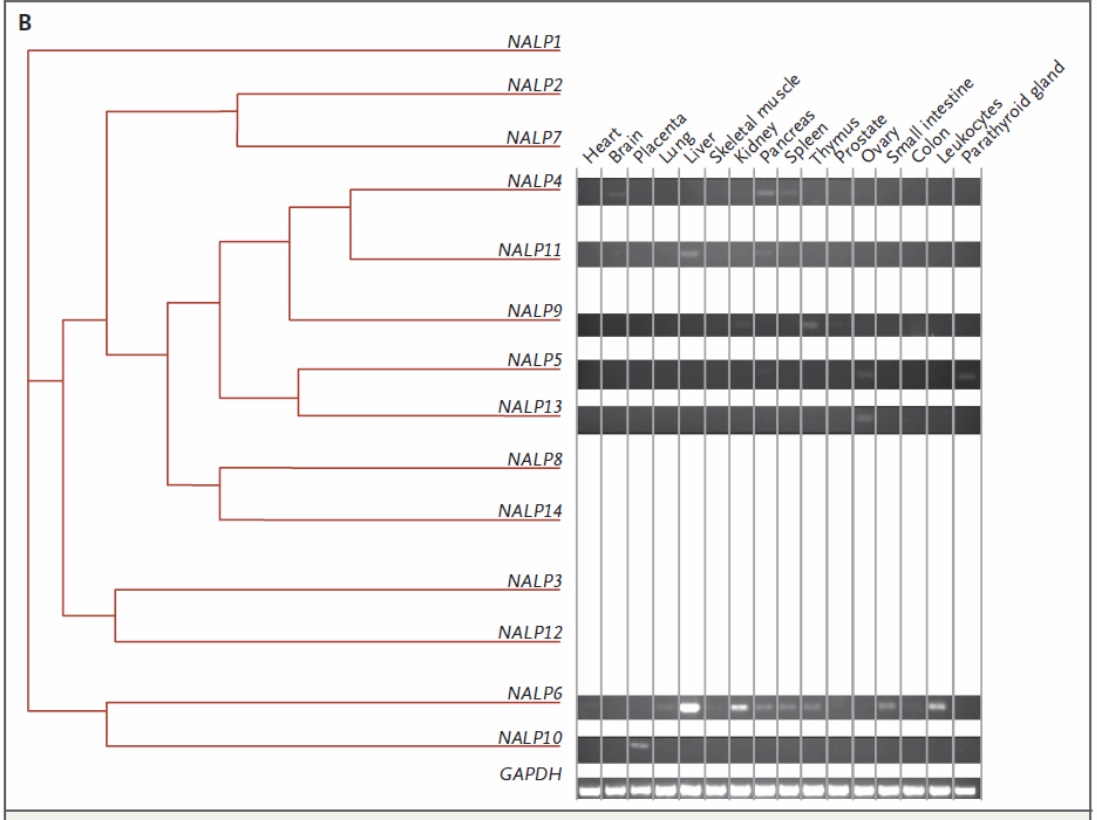
Table 1. Associations between Clinical Manifestations of Autoimmune Polyendocrine Syndrome Type 1 (APS-1) and the Presence of NACHT Leucine-Rich-Repeat Protein 5 (NALP5) Autoantibodies.*

Manifestation	APS-1	APS-1 and NALP5 Autoantibodies		P Value
		With Manifestation	Without Manifestation	
		number/total number (percent)		
Hypoparathyroidism	73/87 (84)	36/73 (49)	0/14	<0.001
Hypogonadism	28/87 (32)	19/28 (68)	17/59 (29)	<0.001
Adrenal insufficiency	69/87 (79)	29/69 (42)	7/18 (39)	0.81
Type 1 diabetes mellitus	11/87 (13)	2/11 (18)	34/76 (45)	0.10
Vitiligo	17/87 (20)	7/17 (41)	29/70 (41)	0.99
Alopecia	30/87 (34)	11/30 (37)	25/57 (44)	0.52
Hepatitis	15/87 (17)	8/15 (53)	28/72 (39)	0.31
Malabsorption	22/87 (25)	10/22 (45)	26/65 (40)	0.66
Pernicious anemia	14/87 (16)	5/14 (36)	31/73 (42)	0.64
Candidiasis	83/87 (95)	34/83 (41)	2/4 (50)	0.72

* Fisher's two-tailed exact test was used to compare the data between the two groups of patients with autoantibodies against NALP5 and the P values reported. Although a significant correlation was found for hypogonadism, NALP5 autoantibodies are not specific for this manifestation, since 29% of the patients without hypogonadism also have autoantibodies against NALP5.


A
NALP5 Autoantibody Index
240
190
140
90
40
−10
AIRE Mutation
No AIRE Mutation
APS-I
Isolated Hypoparathyroidism
Graves' Disease
Adrenal Insufficiency
Insulin-Dependent Diabetes Mellitus
Sjögren's Syndrome
Healthy Controls
B
1 2 3 4 5 6 7 8 9 10 11
NALP5
C
Pixel Density (arbitrary units)
250,000
200,000
150,000
100,000
50,000
0
No Serum or Antibody
NALP5 Antiserum
With NALP5 autoantibody
Without NALP5 antibody
Patients with APS-1
Healthy Controls


A
Relative Amount of NALP5 mRNA Transcripts Normalized to GAPDH
35
30
20
1.0
0.5
0.0
Heart
Brain
Placenta
Lung
Liver
Skeletal Muscle
Kidney
Pancreas
Spleen
Thymus
Prostate
Ovary
Small Intestine
Colon
Leukocytes
Parathyroid Gland
Adrenal Cortex


B
NALP1
NALP2
NALP7
NALP4
NALP11
NALP9
NALP5
NALP13
NALP8
NALP14
NALP3
NALP12
NALP6
NALP10
GAPDH
Heart
Brain
Placenta
Lung
Liver
Skeletal muscle
Kidney
Pancreas
Spleen
Thymus
Prostate
Ovary
Small intestine
Colon
Leukocytes
Parathyroid gland

Sindrome poliendocrina autoimmune di tipo II (SPA II)

✓ **Età insorgenza**	**Adulta**
✓ Trasmissione genetica	Poligenica
	HLA DR3-DQ2; MICA 5.1
✓ **Componenti endocrine**	**Addison (100%)**
	Tireopatie (60%)
	Diabete di tipo 1 (50%)
	Ipogonadismo (35%)
✓ Componenti extraendocrine	Anemia perniciosa (0.5-1%)
	Vitiligine (4-5%)
	Alopecia (0.5-1%)
	Morbo celiaco (0.5-1%)

Sindrome poliendocrina autoimmune di tipo III (SPA III)

✓ Età insorgenza	Adulta
✓ Trasmissione genetica	Poligenica
	HLA DR3-DQ2; MICA 5.1
✓ Componenti endocrine	Tireopatie (100%)
	Diabete di tipo 1 (50%) (3A)
	Ipogonadismo (3-4%)
✓ Componenti extraendocrine	Gastrite atrofica (50%) (3B)
	Anemia perniciosa (0.5-1%)
	Vitiligine (4-5%)
	Alopecia (0.5-1%)
	Morbo celiaco (4-5%)

Sindrome poliendocrina autoimmune di tipo III (SPA III)

Presenza di patologia tiroidea autoimmune

Tiroidite autoimmune, mixedema idiopatico, Morbo di Graves-Basedow

+

Diabete mellito tipo 1

Ipofisite autoimmune

Menopausa precoce

SPA 3A

Sindrome poliendocrina autoimmune di tipo III (SPA III)

Presenza di patologia tiroidea autoimmune

Tiroidite autoimmune, mixedema idiopatico, Morbo di Graves-Basedow

+

Gastrite cronica atrofica
Anemia perniciosa
Morbo celiaco
Malattia infiammatoria cronica intestinale
Epatite autoimmune
Cirrosi biliare primitiva

SPA 3B

Sindrome poliendocrina autoimmune di tipo III (SPA III)

Presenza di patologia tiroidea autoimmune

Tiroidite autoimmune, mixedema idiopatico, Morbo di Graves-Basedow

+

Vitiligine
Alopecia

Miastenia gravis
Sclerosi multipla

SPA 3C

Sindrome poliendocrina autoimmune di tipo III (SPA III)

Presenza di patologia tiroidea autoimmune

Tiroidite autoimmune, mixedema idiopatico, Morbo di Graves-Basedow

+

LES
Artrite reumatoide
Sclerosi sistemica
Sindrome di Sjogren
Vasculiti
Sindrome da antifosfolipidi

SPA 3D

Sindrome poliendocrina autoimmune di tipo IV (SPA IV)

Qualunque associazione che non rientri nelle prime 3 forme:

es. Diabete + morbo celiaco
Addison + POF
Tireopatie + vitiligine
Diabete + gastrite atrofica
ecc…

AUTOANTIGENI IN SPA

IPOPARATIROIDISMO	**Recettore del Calcio**
	NALP5
ADDISON	**21-idrossilasi**
	L-amino-acido-decarbossilasi
POI	**17-idrossilasi**
	Colesterolo desmolasi (P450scc)
DIABETE TIPO 1	**Insulina**
	GAD65
	IA-2
	Zn-T8
VITILIGINE	**Tirosina idrossilasi**
TIROIDITI AUTOIMMUNI	**Tireoperossidasi**
	Tireoglobulina
	Cotrasportatore Na-I
	Recettore del TSH
MORBO CELIACO	**Transglutaminasi**
MALASSORBIMENTO IN APS I	**Triptofano idrossilasi**
GASTRITE ATROFICA	**H+/K+-ATPasi**
ANEMIA PERNICIOSA	**Fattore intrinseco**
APS 1	**IFNα2 – IFNω**

POEMS Syndrome

(*P*lasma cell dyscrasia with polyneuropathy, *O*rganomegaly, *E*ndocrinopathy, *M* protein, *S*kin changes)

- Diabete mellito nel 50% dei casi
- Insufficienza gonadica primitiva nel 70% dei casi
- Discrasia delle plasmacellule
- Lesioni ossee sclerotiche
- Polineuropatia.
- Epatomegalia
- Splenomegalia
- Linfoadenopatie
- Iperpigmentazione

Si considera che sia secondaria all'azione di immunoglobuline circolanti. Possibile coinvolgimento di IL-1β, IL-6, TNF-α e proteina M. Elevati livelli di VEGF correlano con la gravità del quadro clinico.