POLYENDOCRINOPATHIES AUTOIMMUNES

D. Dubois-Laforgue

Polyendocrinopathies AI

PEA monogéniques: autoimmunité diffuse

- PEA-1 (APECED)
- Syndrome IPEX

PEA polygéniques: PEA-2, 3, 4

Association de MAI spécifiques d'organe

Polyendocrinopathie AI de type 1 (PEA1) ou APECED

Autoimmune Poyendocrinopathy Candidiasis Ectodermal Dystrophy

- Rare: 1/9 000 à 1/500 000
- Autosomique récessive: mutations du gène AIRE (>100)
- Manifestations cliniques: précoces (< 10 ans)
  - Candidose cutanéo-muqueuse: 75-93%
  - Hypoparathyroïdie AI: 70-96%
  - Maladie d'Addison: 63-92%

  } **2/3**

Tableau qui se complète avec l'âge

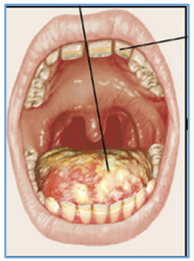
CMC: 50% 5 ans, 70% 10 ans, 94% 20 ans

HP: 33% 5 ans, 66% 10 ans, 85% 30 ans

AD: 40% 10 ans, 78% 30 ans

Formes mineures

PEA-1: manifestations cliniques



Keratitis

Chronic candidiasis
Squamous cell carcinoma
Dental enamel dysplasia
77%

Interstitial lung disease

Autoimmune hepatitis
20%

Exocrine pancreatitis
Type 1 diabetes
5-15%

60% Ovarian failure

10% Testicular failure

Alopecia

Pituitary failure

Hypothyroidism **25%**

Hypoparathyroidism

AIRE-deficient thymus

Adenocortical failure

Asplenia **20%**

Chronic atrophic gastritis **30%**

Tubulo-interstitial nephritis **10%**

Malabsorption **25%**

Vitiligo **20%**

Vaginal candidiasis

Chronic nail candidiasis

Kisand, J Clin Immunol 2015

PEA1: anomalie de la tolérance centrale

AIRE: contrôle l'expression d'Ag au niveau de l'épithélium thymique

Pas d'expression d'Ag ➔ pas de délétion des LT autoréactifs

Anomalies de la maturation thymique (Treg)

Défaut TH17
⬇ IL17F, IL22

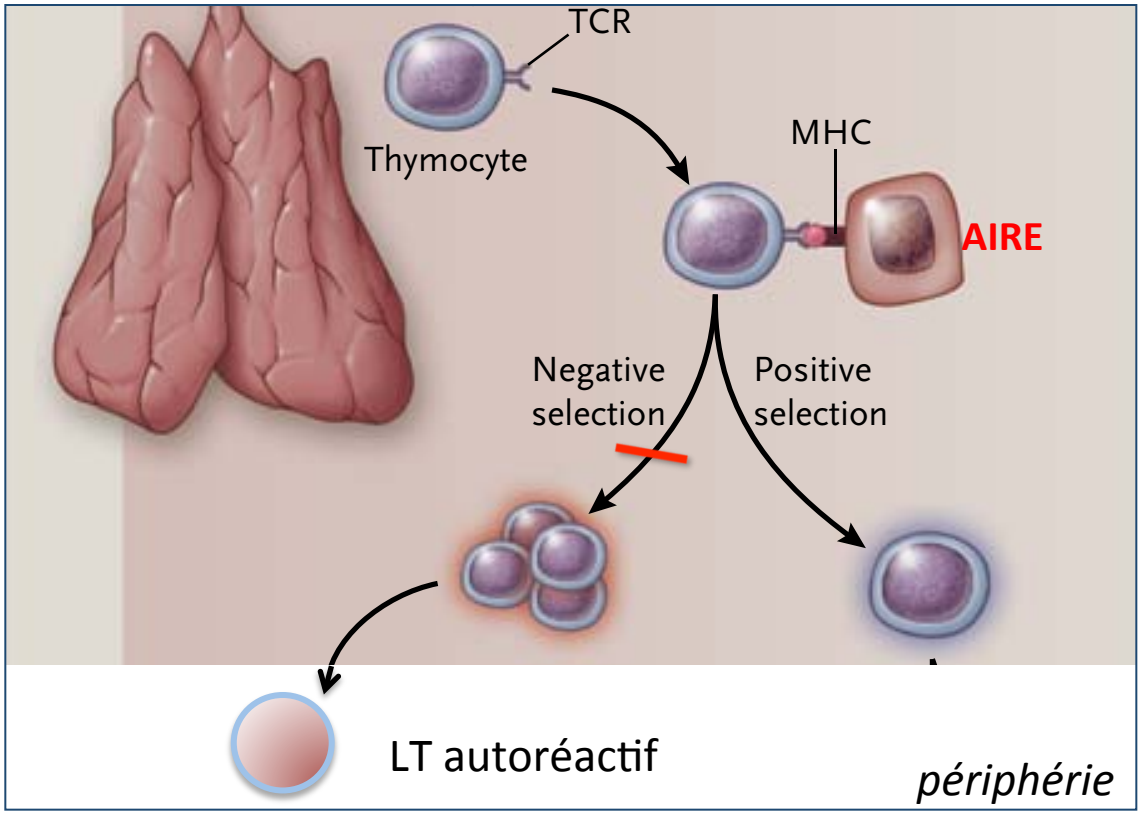


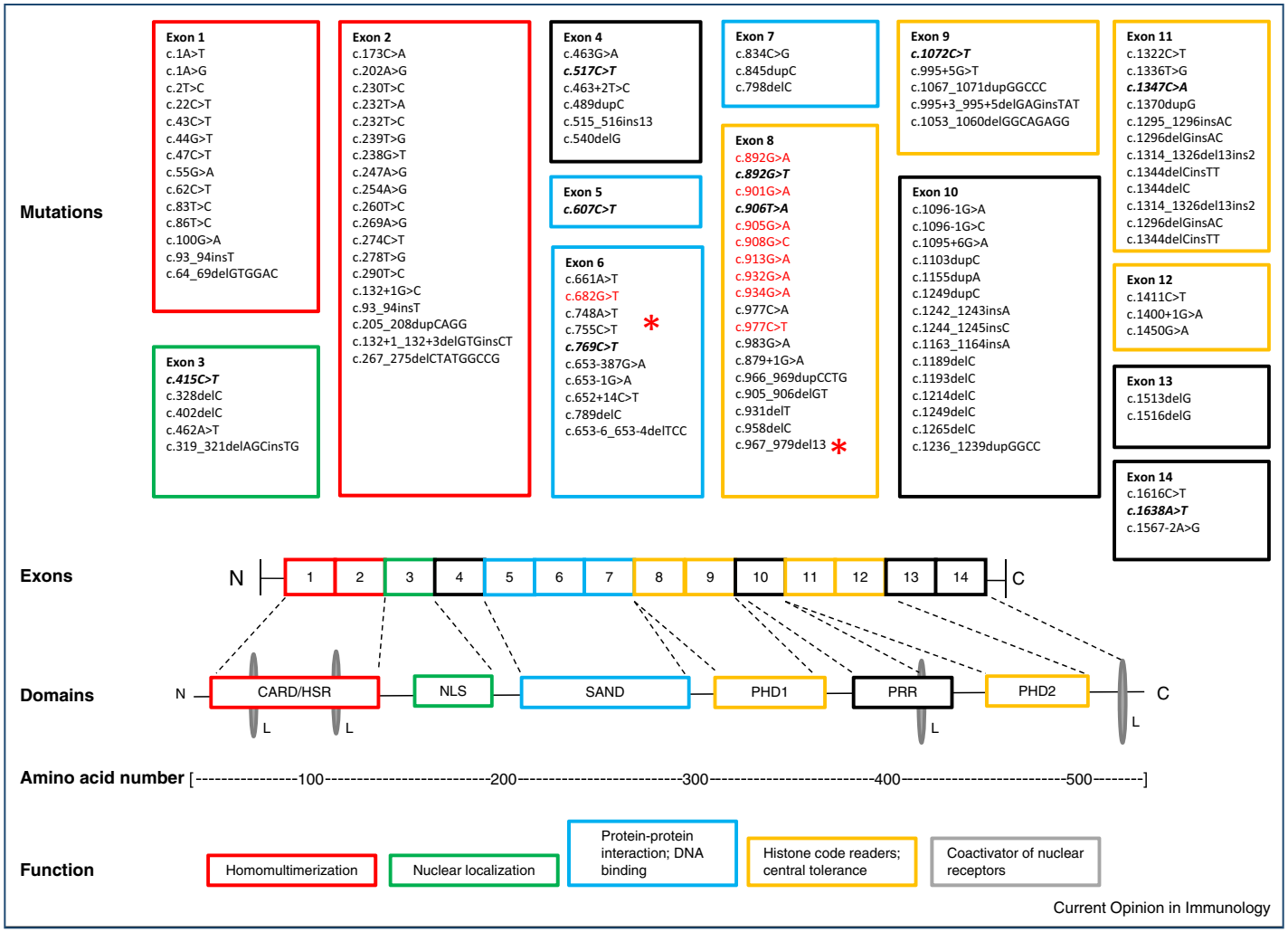
Table 1 APECED autoantibodies, their prevalences (%) and diagnostic value **Marqueurs sérologiques**

Autoantibody targets	%	Associated with	Expressed in	References
IFN-ω[a]	100	**AIRE−/−**	secreted	[16]
IFN-α	95	**AIRE−/−**	secreted	[16]
IFN-β	22		secreted	[16]
IFN-λ	14		secreted	[16]
IL-22	91	CMC	secreted	[29, 69]
IL-17F	75	CMC	secreted	[29, 69]
IL-17A	41		secreted	[29, 69]
steroid 21-hydroxylase (CYP21A2)	55–69	**AD**	adrenal	[19, 23, 94, 98, 148]
steroid 17-α-hydroxylase (CYP17A1)	24–58	AD OF	adrenal	[94, 23, 97, 145]
side chain cleavage enzyme (CYP11A1)	38–68	OF	adrenal, ovary, testis	[19, 94, 99, 148]
NACHT leucine-rich-repeat protein 5 (NALP5)	32–49	HP	ovary, parathyroid, breast, testis	[22, 23, 132, 145, 148]
calcium-sensing receptor (CaSR)	86	HP	parathyroid pancreas, kidney	[133]
thyroglobulin (TG)	15–21	HT	thyroid	[23, 87, 157]
thyroid peroxidase (TPO)	15–36	HT	thyroid	[23, 87, 157]
islet antigen-2 (IA-2)	7	**T1D**	pancreas,	[87, 94]
glutamic acid decarboxylase (GAD65)	27–42	GID	pancreas, brain	[19, 23, 87, 94, 145, 148]
testis-specific gene 10 protein (TSGA10)	8		testis, brain	[140]
tudor domain containing protein 6 (TDRD6)	49		testis, brain	[139]
intrinsic factor (IF)	15–30	**PA**	stomach	[71, 87]
aromatic L-amino acid de-carboxylase (AADC)	39–68	AIH VIT	kidney, intestine, brain, liver, pancreas	[19, 94, 137, 138, 145, 158, 159]
cytochrome P450 1A2 (CYP1A2)	6–8	**AIH**	liver	[23, 104, 106, 107]
CYP2A6		AIH	liver	[23, 104, 108]
tryptophan hydroxylase (TPH)	28–61	GID, AIH	multiple	[19, 94, 116, 137, 145, 158]
histidine decarboxylase (HDC)	37	GID	brain, stomach, lung	[115]
tyrosine hydroxylase (TH)	44–50	AL, ED	brain, adrenal	[94, 119, 137]
SOX9/SOX10	15–22	VIT	nervous system, breast	[120]
potassium channel-regulating protein (KCNRG)	6	**ILD**	lung, cervix	[123]
bactericidal/permeability-increasing fold-containing B1 (BPIFB1)	10	**ILD**	lung, stomach, esophagus, cervix	[125]
Defensin, alpha 5 (DEFA5)	27	GID	Paneth cells	[118]

AD Addison's disease, *AIH* autoimmune hepatitis, *AL* alopecia, *CMC* chronic mucocutaneous candidiasis, *ED* enamel dysplasia, *GID* gastro-intestinal dysfunction, *HP* hypopathyroidism, *HT* hypothyroidism, *IFN* interferon, *IL* interleukin, *ILD* interstitial lung disease, *OF* ovarian failure, *PA* pernicious anemia, *T1D* type 1 diabetes, *TIN* tubulo-interstitial nephritis, *VIT* vitiligo

Spectre mutationnel

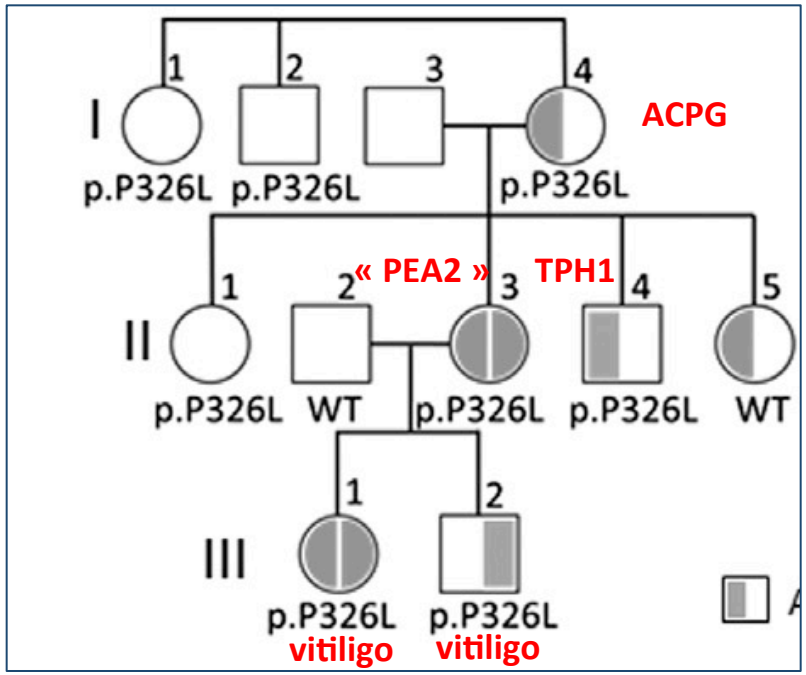
Pas de corrélation génotype- phénotype (sf Y85C)

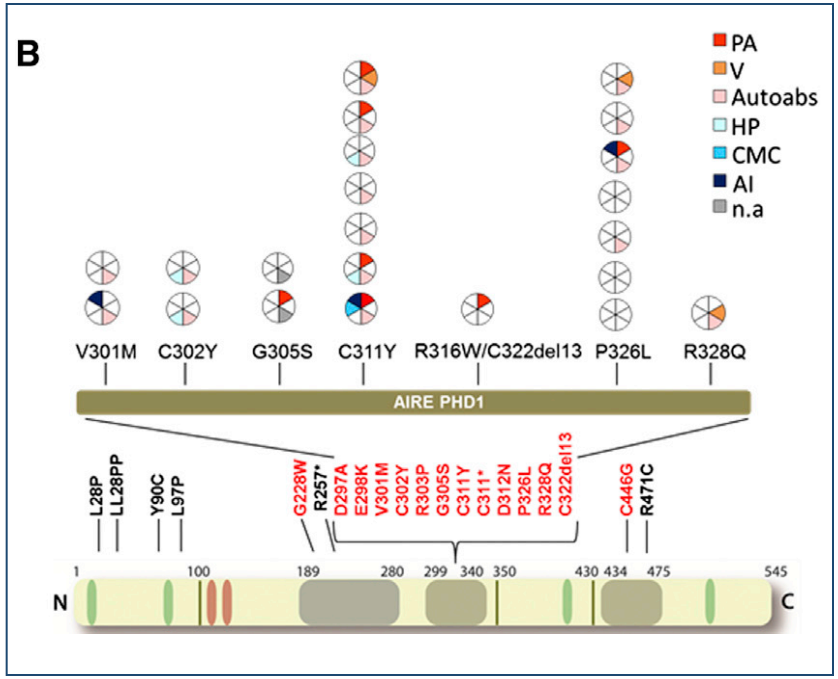


Mutations perte de fonction; Mutations à effet dominant négatif

Bruserud, Curr Opin Immunol 2016

Autoimmunité associée à AIRE

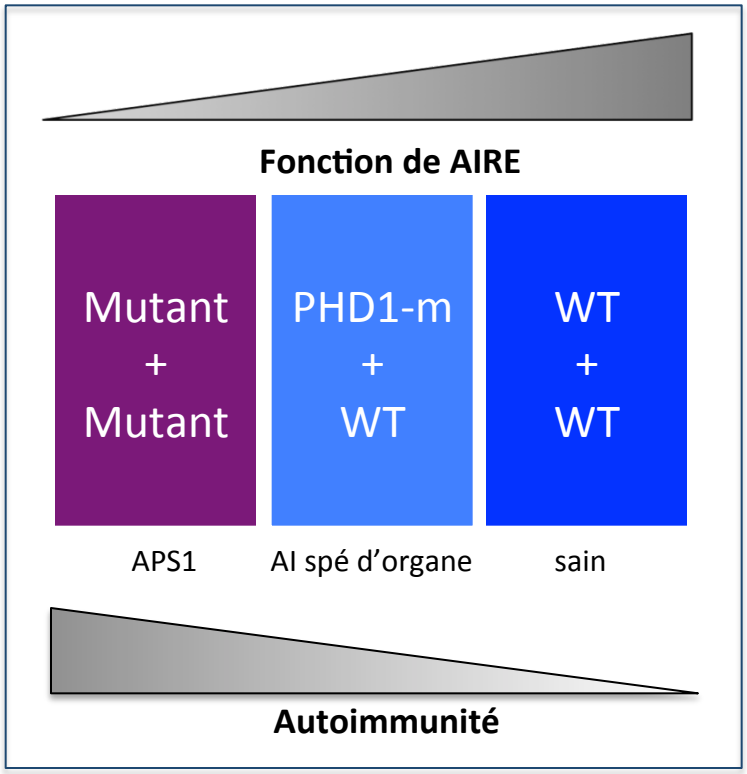


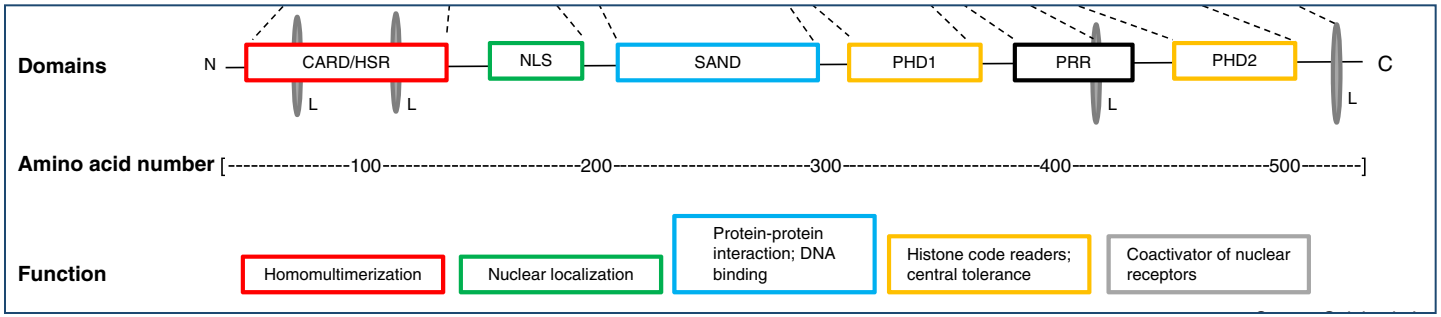


Mutations avec effet dominant négatif du domaine PHD1→ AI familiale

Oftedal, Immunity 2016

Autoimmunité associée à AIRE





Oftedal, Immunity 2016

Syndrome IPEX

Immunodeficiency, polyendocrinopathy , enteropathy X-linked

très rare: 150 cas

lié à l'X

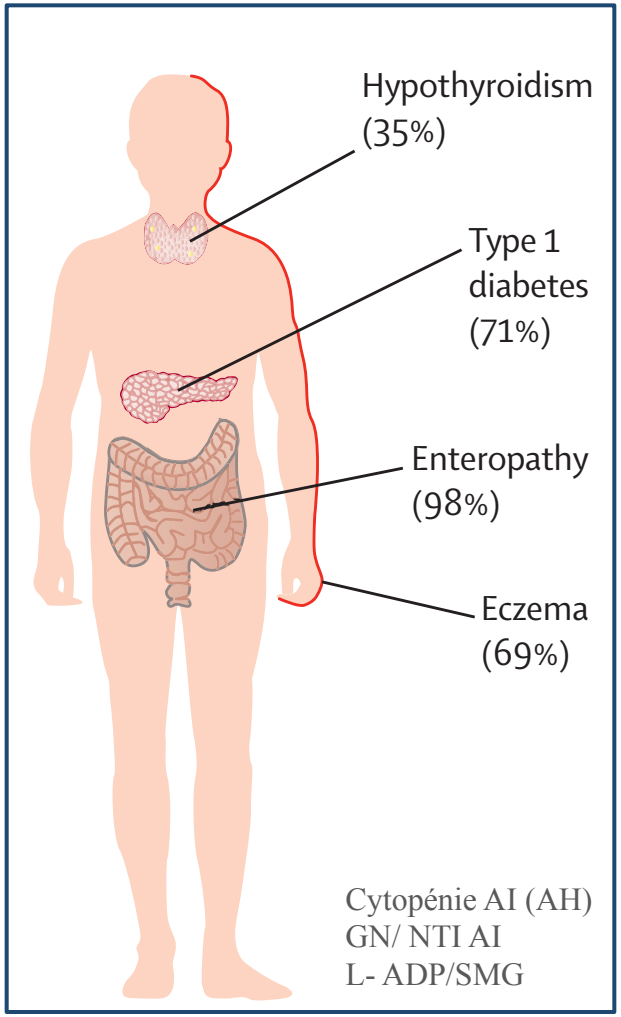
mutations du gène FOXP3 (70)

manifestations cliniques NN

pronostic sévère

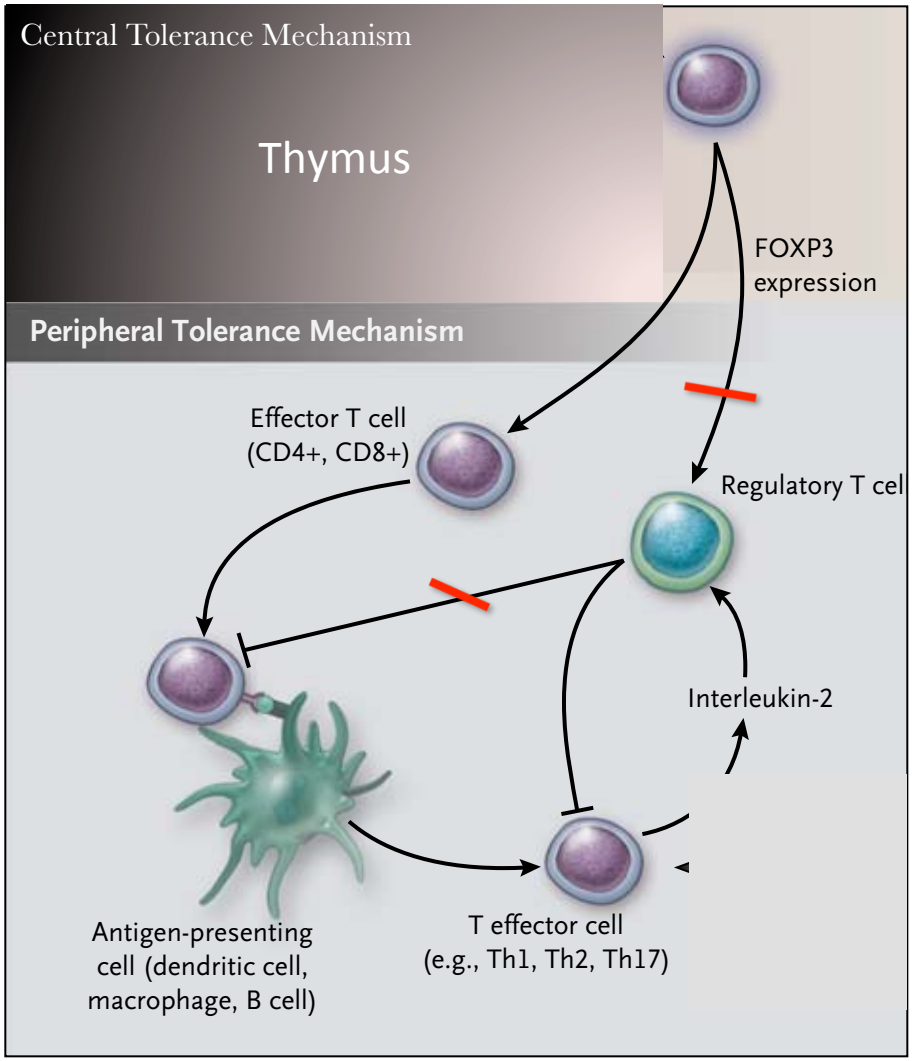
→ **entéropathie + DT1 précoce**

IPEX-like: mutation IL2-RA

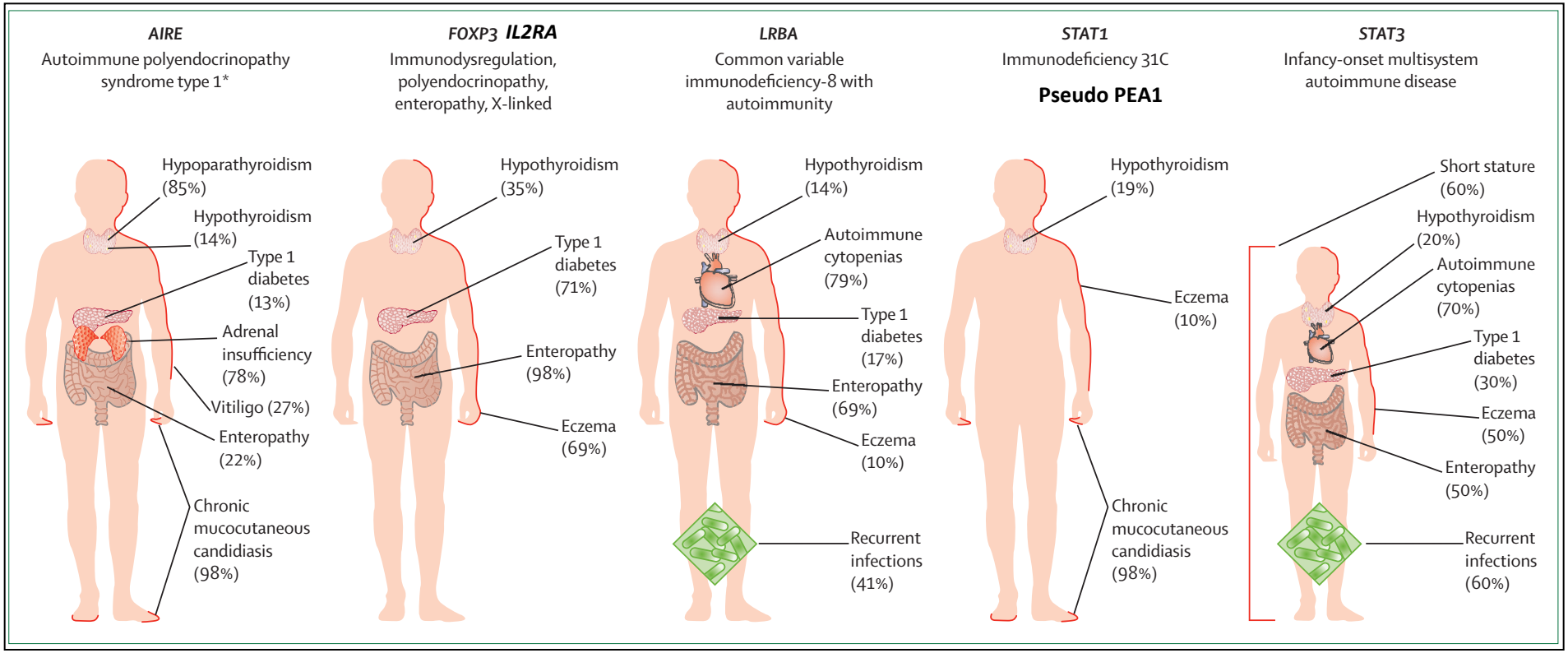


Anomalie des cellules régulatrices

FOXP3: maturation des T reg



Polyendocrinopathies autoimmunes monogéniques



anomalie tolérance centrale	anomalie cellules régulatrices	pas d'expression CTLA4 L prolifération / AI	mut gain de fct, autos dom hyperac IFNα	mut gain de fct, autos dom hyper TH17

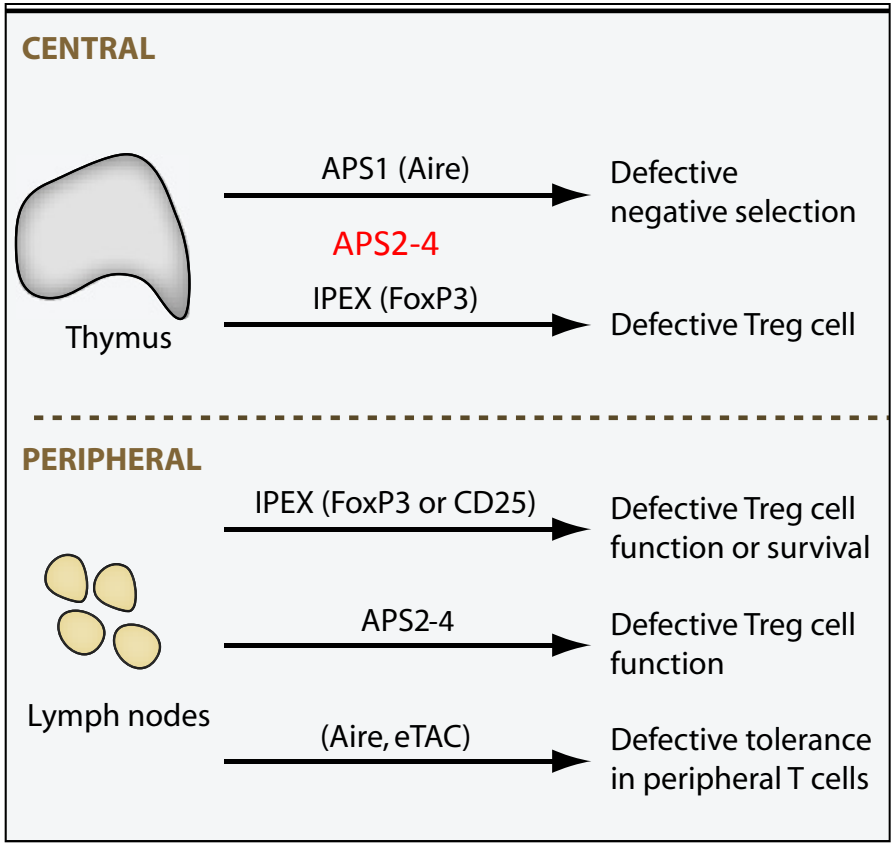
MB Johnson , Lancet Diabetes Endocrinol 2016

Polyendocrinopathie AI de type 2 à 4

PEA 2: Addison + autre
PEA 3: Thyroïde + DT1 sans Addison
PEA 4: 2 MAI mais autres que PEA 2-3

4-5/100 000 (150/100 00?)
Polygénique, autos dominante
Prédominance féminine (3/1)
Survenue « tardive » (30-40 ans)
DT1: 50- 60%

Anomalies conjuguées
de tolérance centrale et périphérique



Autoimmunité des PEA 2-4

Table 1. *Prevalence of organ-specified autoantibodies and autoimmune diseases*

Disease or AB	General population		Type 1 diabetes mellitus	Coeliac disease	Addison's		Hypothyroidism
Type 1 diabetes mellitus	2-3%				12-14%	X 4	4%
anti-islet AB	1-3%		85-90%				
Coeliac	0.5%	X 10	1-8%		5%		4%
transglutaminase AB	0.5-1%		8-12%	99%			
Addison's	0.005%	X 10	0.5%				
21-hydroxylase AB	0-0.6%		0.7-3%		83-90%		
Hypothyroidism	5-9%	X 3	30%	3-12%	14-21%	X 3	
aTPO	2-10% in adults 1-4% in children		15-30% in adults 5-22% in children	18%	23-40%		47-83%
Graves'	0.1-2%		6-10%		10-20%		
TSH receptor AB	?		?				
Pernicious anaemia/	2% for AIG	X 4	5-10% for AIG				
autoimmune gastritis	0.15-1% for PCA		2-4% for PCA				
PCA	2.5 - 12%		15-25% in adults 10-15% in children		6%	X 3	2%

AB = antibody; AIG = autoimmune gastritis; PCA = parietal cell antibodies; T1DM = type 1 diabetes mellitus.

Van den Driessche, Ned J Med 2009

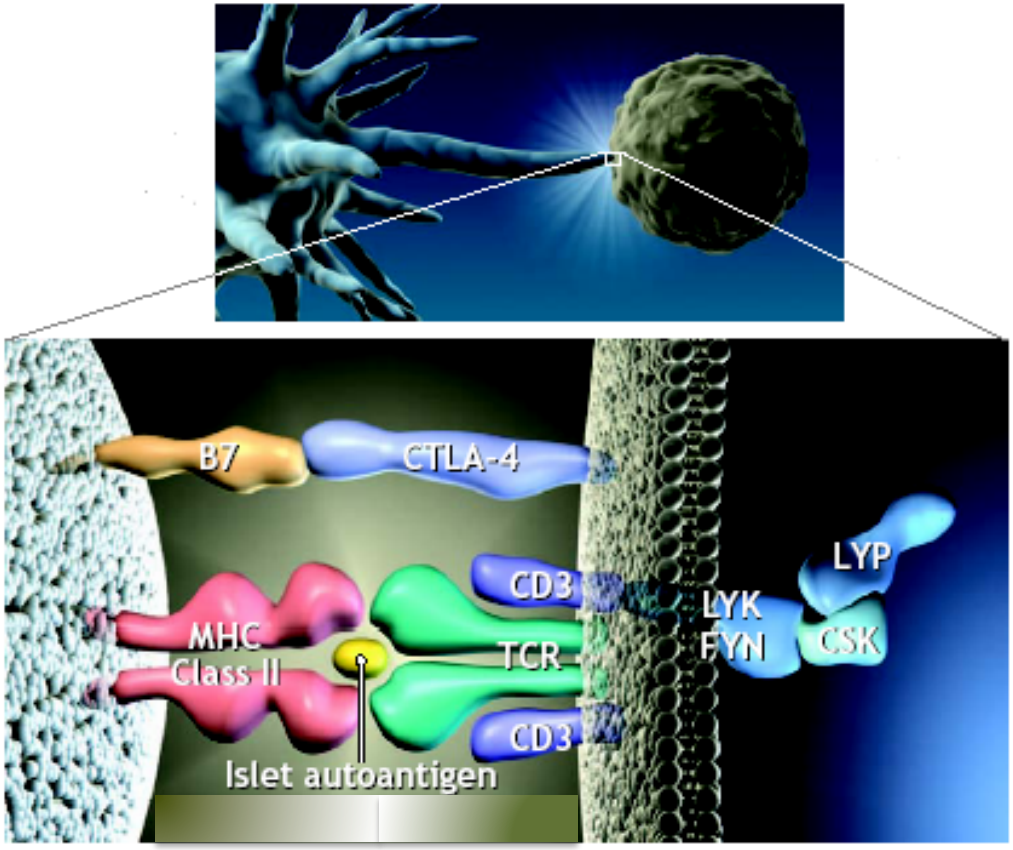
Une susceptibilité génétique partagée …

OR pour les gènes de susceptibilité aux différentes MAI

	T1D	HT	GD	AD
HLA-DR3	3.5	3.7	2-4	5
MICA	1.6	2.5	2	7
PTPN22	1.8	1.6	1.6	1.5
CTLA-4	1.5	5	1.5	1.8

Association DT1-MAIT: *DPB1*0201; GPR103*

… pour des gènes de l'activation lymphocytaire



HLA: présentation de l'Ag aux LT
CTLA-4: co-activation LT/APC
PTPN22: co-activation LT/APC
MIC-A: co-activation LT/cible

Présentation clinique

Maladies auto-immunes de la thyroïde
Diabète de type 1 auto-immun
Insuffisance surrénalienne
Gastrite auto-immune
Maladie coeliaque
Vitiligo
Ovarite auto-immune
Alopécie
Hépatite autoimmune
Myasthénie
Hypophysite auto-immune

Présentation clinique

Maladies auto-immunes de la thyroïde
Diabète de type 1 auto-immun
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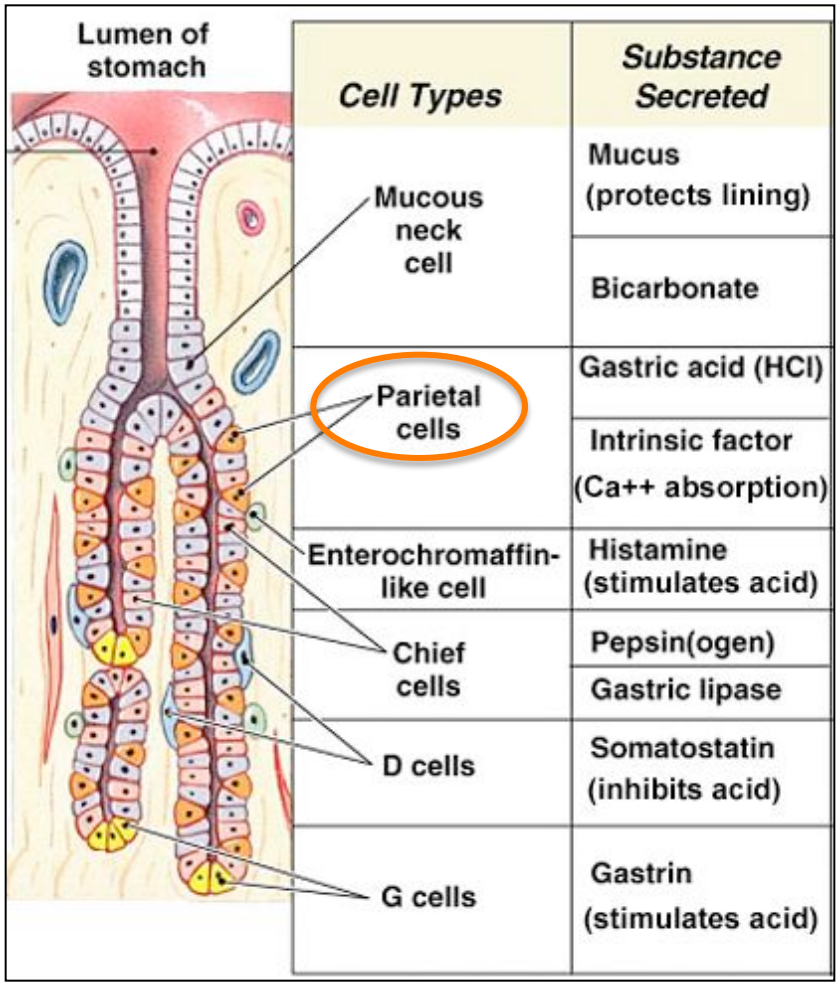
Myasthénie
Hypophysite auto-immune

Gastrites autoimmune (GAI)

Gastrite atrophique (GA), Anémie de Biermer (AB)



Cell Types	Substance Secreted
Mucous neck cell	Mucus (protects lining)
	Bicarbonate
Parietal cells	Gastric acid (HCl)
	Intrinsic factor (Ca++ absorption)
Enterochromaffin-like cell	Histamine (stimulates acid)
Chief cells	Pepsin(ogen)
	Gastric lipase
D cells	Somatostatin (inhibits acid)
G cells	Gastrin (stimulates acid)

Antigène: H+/K+ ATPase des CPG

➔Atrophie **fundique**

Rôle favorisant de helicobacter Pylori?

GA: 2% pop g^{ale} / 5-10% DT1

AB: 1% pop g^{ale} / 2.5-4% DT1

ACPG +: 2-10% pop g^{ale} /15-25% des DT1

FDR: sexe et âge

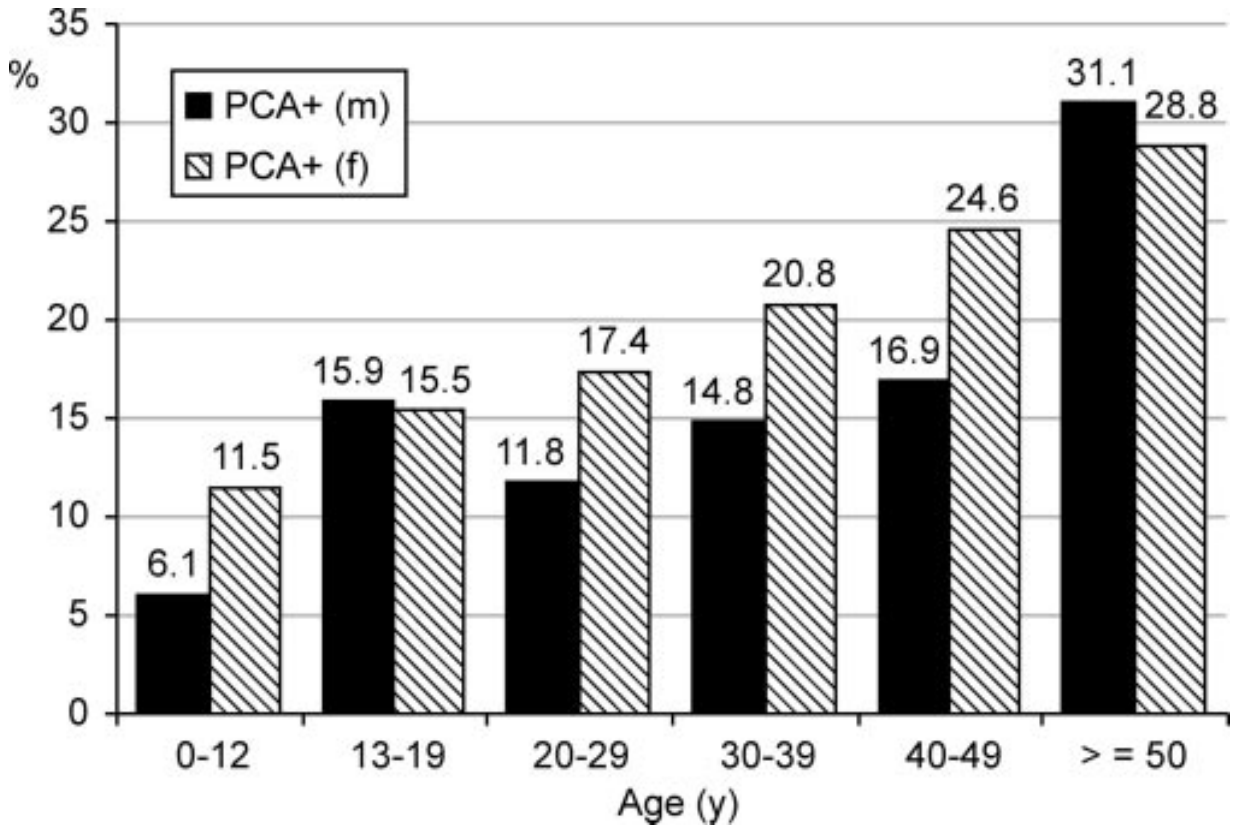


FIG. 2. Prevalence of PCA in type 1 diabetes. +, Positive; f, female; m, male.

De Block et al, Diabetes 2008

FDR: autoimmunité associée

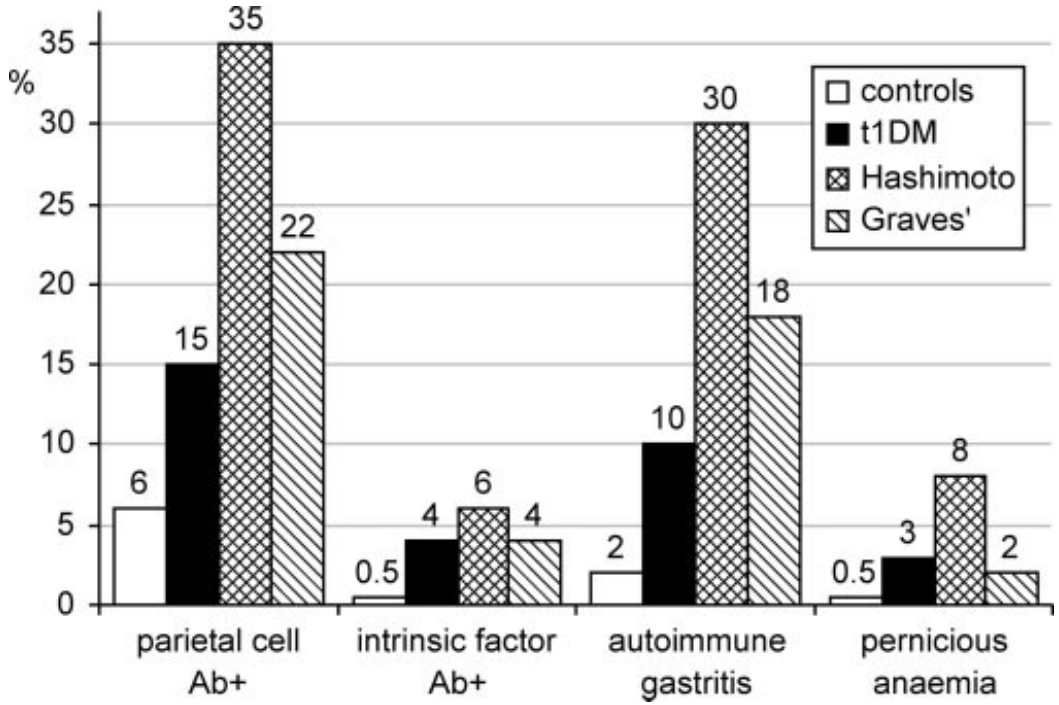


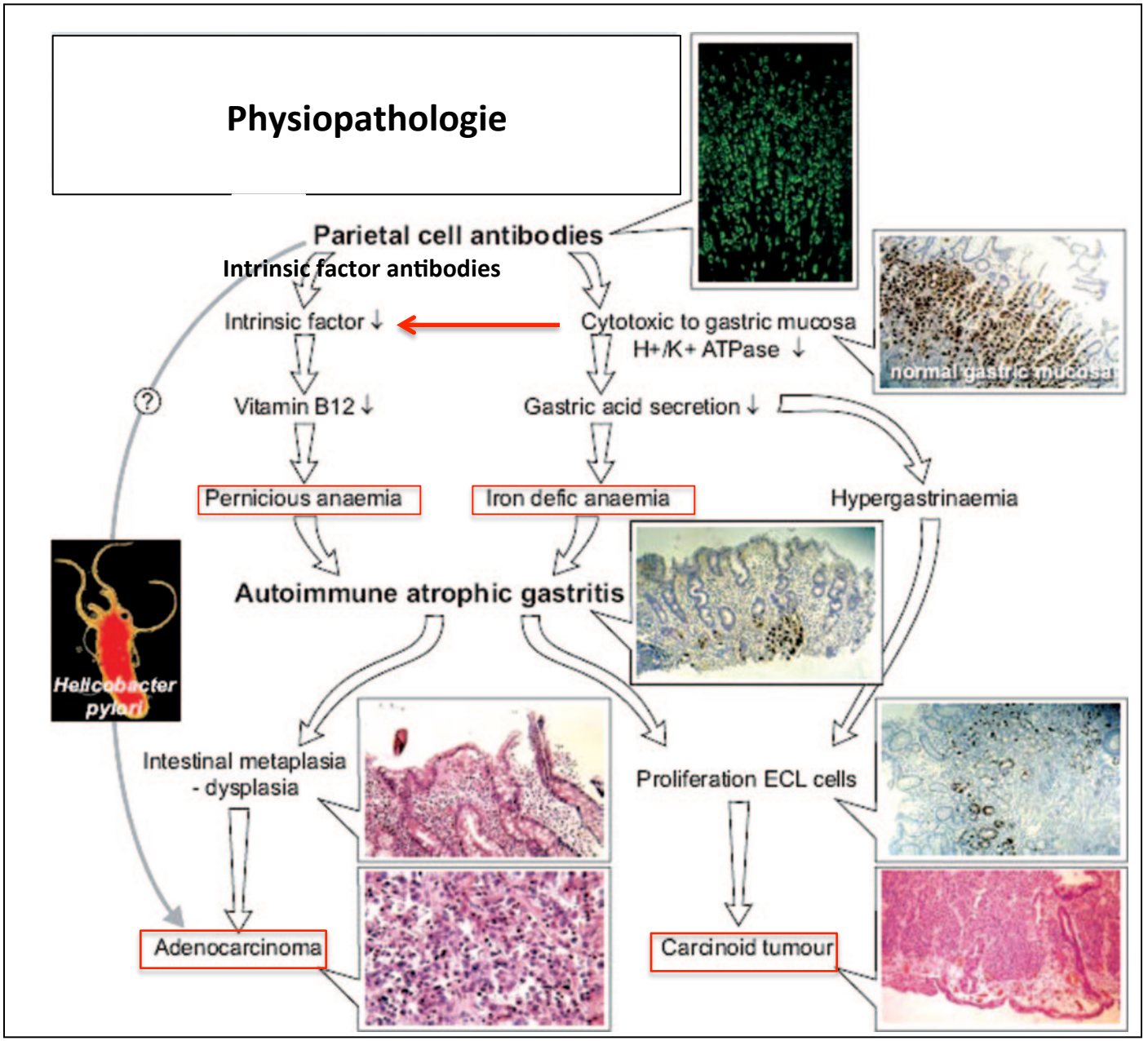
Fig. 3. Prevalence of PCA, AIF, autoimmune gastritis, and pernicious anemia in the general population and endocrine diseases. +, Positive; Ab, ; t1DM, type 1 diabetes mellitus.

La GAI est associée à:

- DT1 4%
  - GADA+
  - ATPO+
- MAIT 12%
  - 50% GAI sont ATPO+
- Addison 6%
- Vitiligo 8%

De Block et al, Diabetes 2008

Physiopathologie



De Block, JCEM 2008

Manifestations cliniques

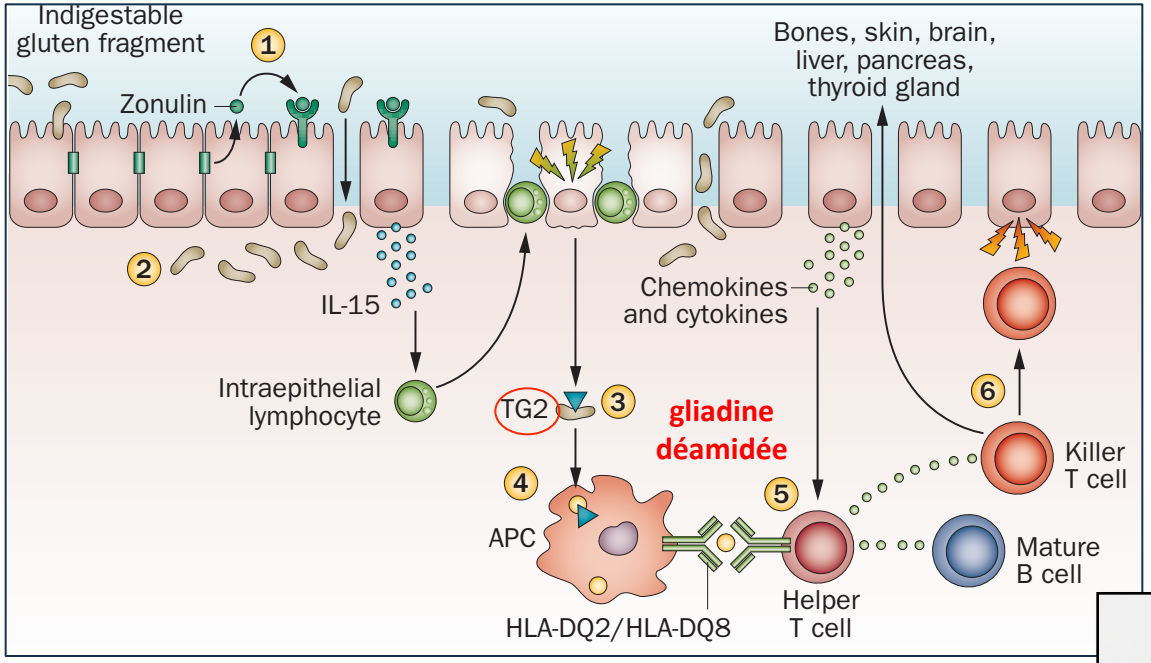
- ***Carence martiale***
  - 20 - 40% des patients GAI
  - 20 - 30% des carences martiales sont secondaires à une GAI

- ***Carence en vitamine B12***
  - 25% des patients GAI
  - Conséquences:
    - Neuropathie périphérique, démence
    - Glossite

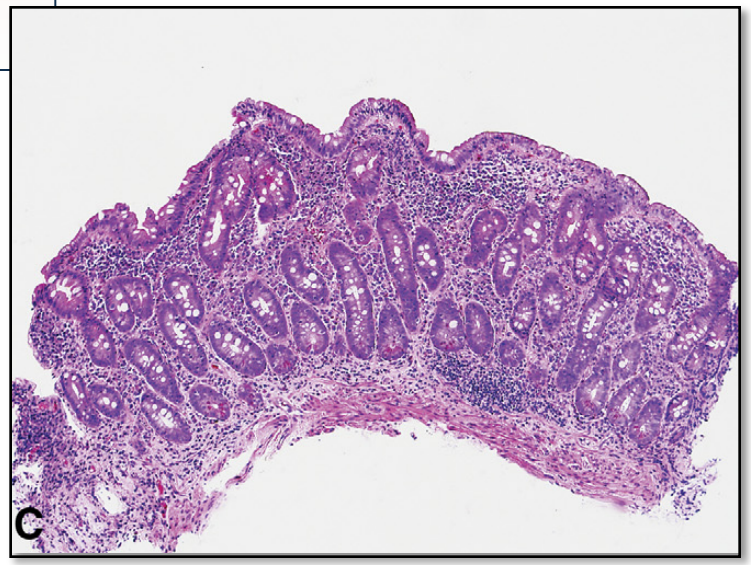
- ***Cancer gastrique***
  - T carcinoïde: 4-10% (X 13): Hypergastrinémie / Chromogranine A
  - Adénocarcinome: 1-9% (X 6)

→ NFS, bilan Fer, B12, FOGD (recherche HP), K

Maladie coeliaque



Ag : transglutaminase



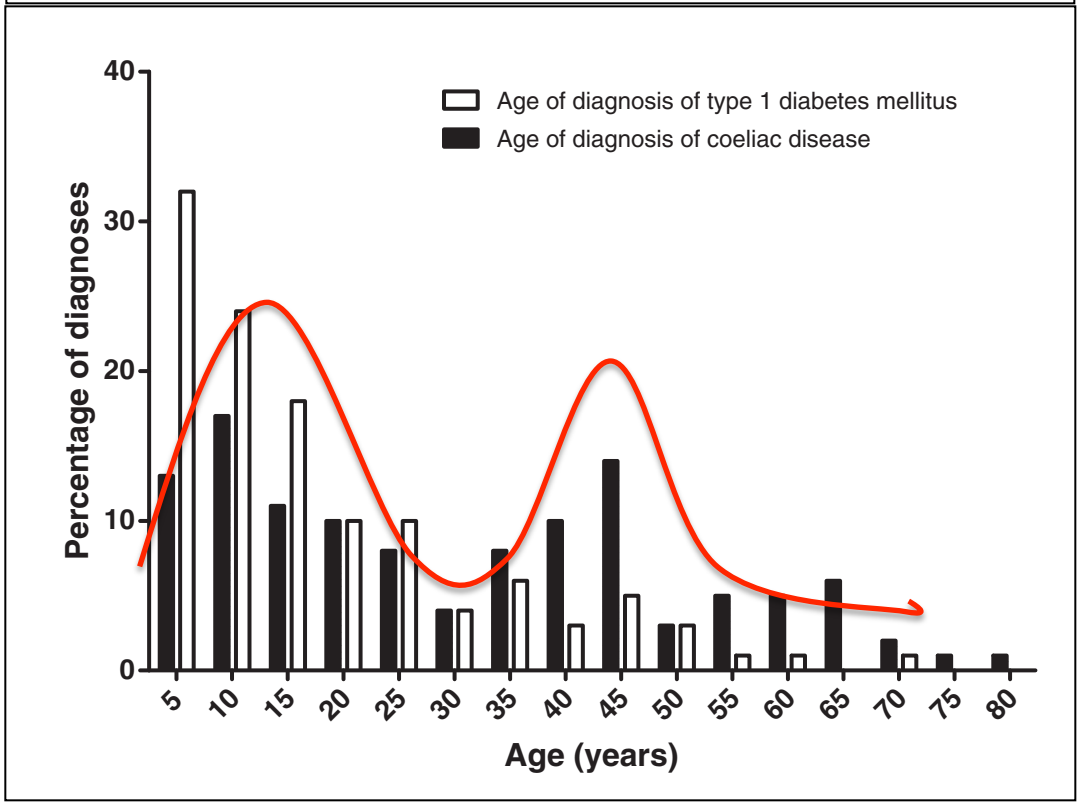
Epidémiologie

10% DT1 vs 1% de la pop g^{ale}, prédominance féminine (3/1)

pourtour méditerranéen et pays nordiques

118 sujets DT1 + MC

âge DT1: 11(5-22); âge MC : 26 (10-43)



- MC après DT1: 90% cas dans les 2 ans chez l'enfant
- **MC à tout âge**

pics de fréquence 10 et 45 ans

- Délai avant dgc:

< 18 ans au DT1: 60% < 6 mois

> 18 ans au DT1: 50% > 5ans

→ Bilan martial, BH, vitamine D, FOGD

Bakker et al, Eur J Intern Med 2013

Manifestations cliniques

asymptomatique (50-80%) ou présentation incomplète

- Manifestations révélatrices:
  - Diarrhée chronique (40%), douleurs abdominales
  - Anémie (20%):
    - carence Fe, B9, B12, inflammation chronique
    - marqueur de sévérité
    - résistance à la supplémentation en fer
    - 3-10% des carences martiales <--> MC
  - Hépatite
    - cytolyse
    - 10% des hépatites cytolytiques <--> MC
    - évolution cirrhogène

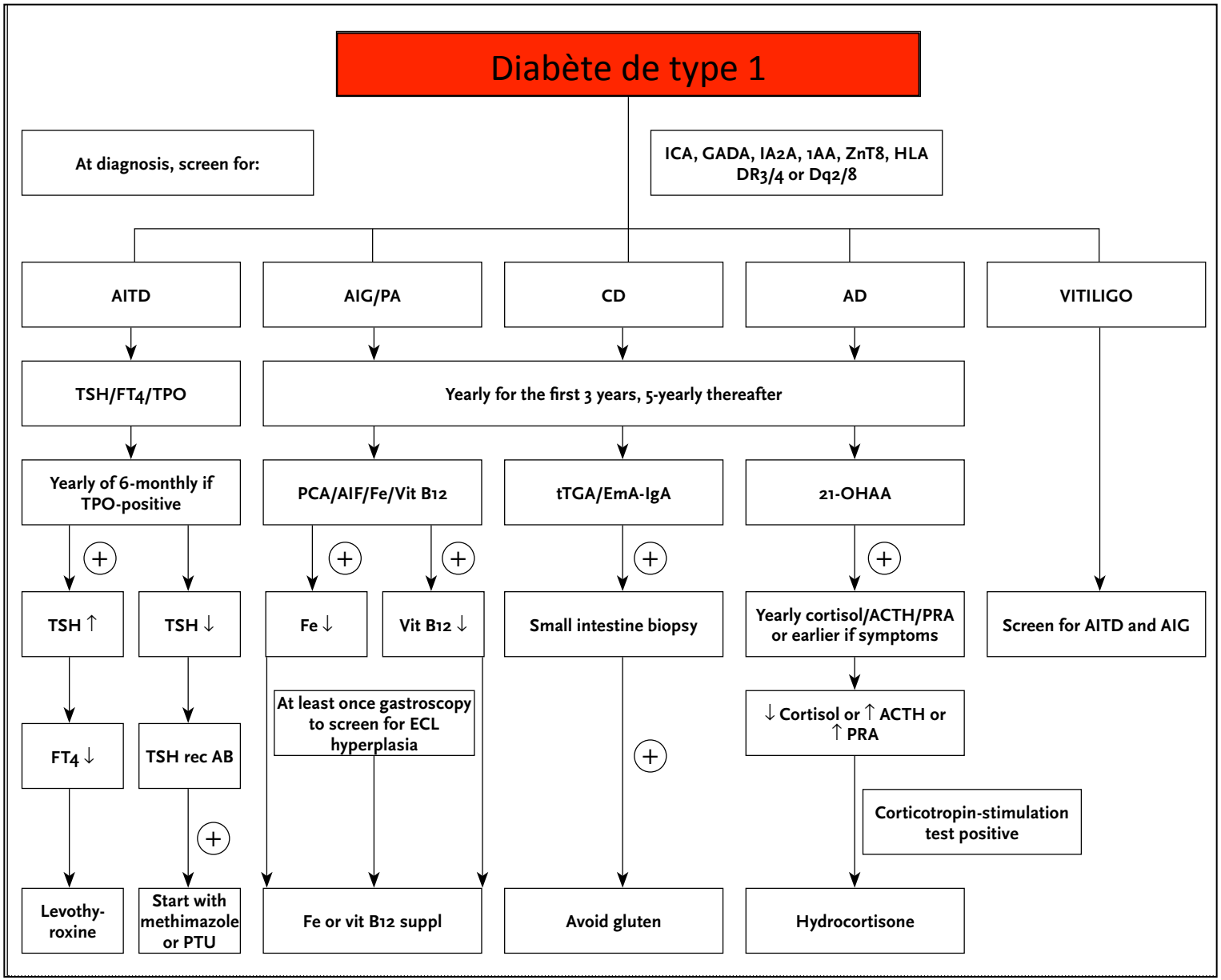
- Manifestations digestives/malabsorption

  Pancréatites récurrentes, neuropathie périphérique

- Manifestations systémiques:
  - Arthrite, sacro-iléite
  - Dermatite herpétiforme (fixation Ac à la TG3)
  - Ataxie au gluten
    - Autoimmune: cross-réactivité cellules de Purkinje
    - Atrophie cérébelleuse
  - Schizophrénie
  - Déficit en IgA (1/40)

→ Bilan martial, BH, vitamine D, FOGD

Dépistage des MAI / PEA 2-4



Van den Driessche, Ned J Med 2009