Percorso di educazione alimentare rivolto a soggetti affetti da celiachia

Bologna, 05 dicembre 2011

ATTUALITÀ IN TEMA DI CELIACHIA

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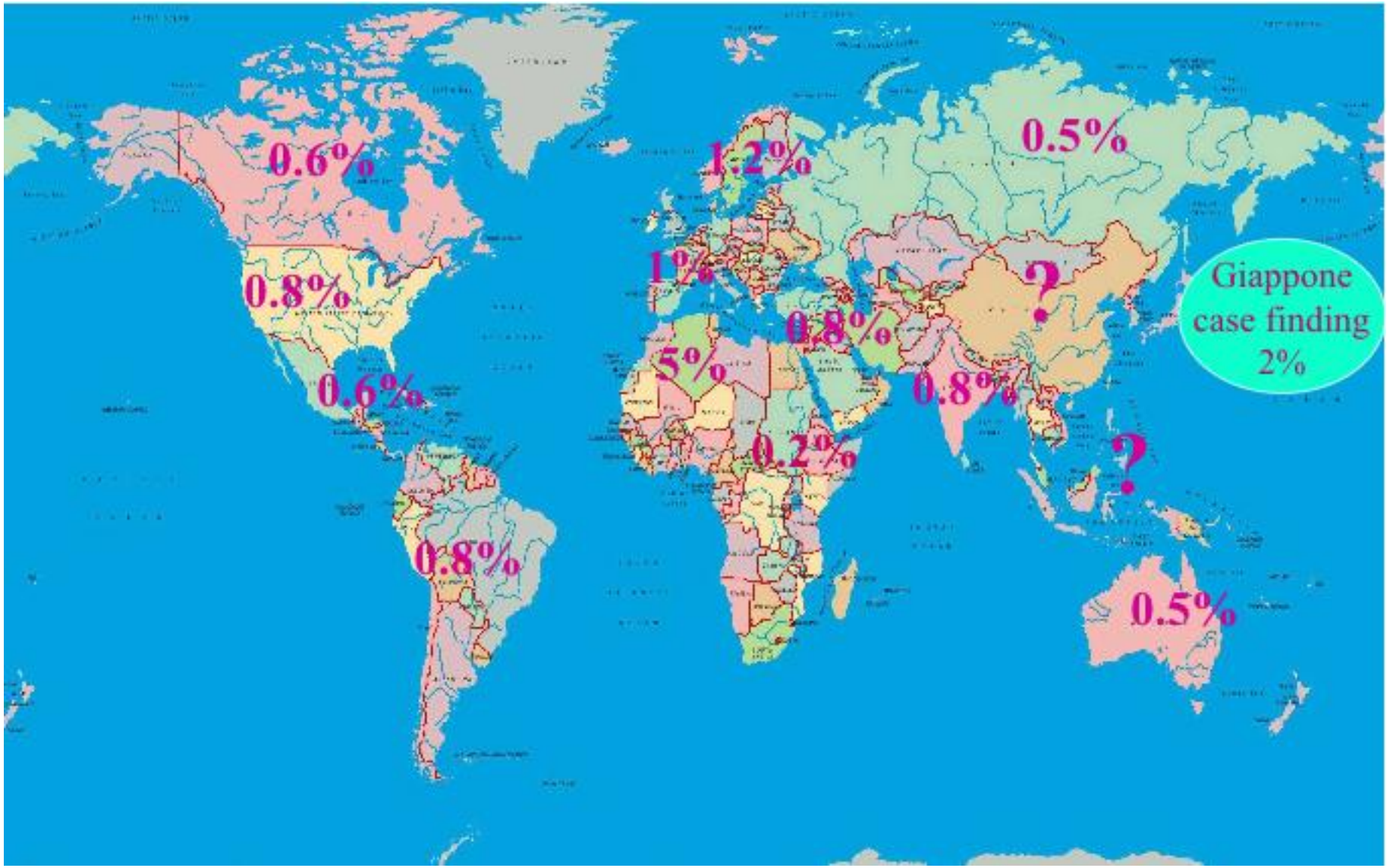
MALATTIA CELIACA

Enteropatia autoimmune permanente scatenata dal glutine - gliadina del grano e alle analoghe proteine alcool-solubili di segale (secalina) ed orzo (ordeina) - in soggetti geneticamente predisposti, portatori degli alleli DQ2/8.

PREVALENZA MC NEL MONDO

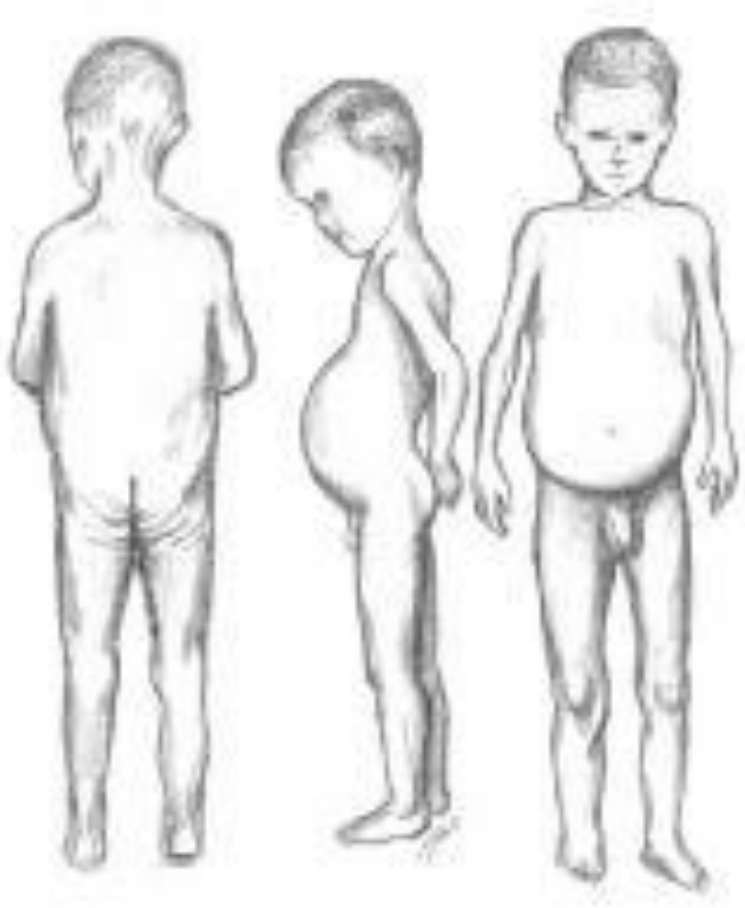


Courtesy of U. Volta

SINTOMATOLOGIA

Forma classica o tipica

- Diarrea cronica
- Scarso accrescimento
- Distensione addominale



SINTOMATOLOGIA

Forme atipiche

SINTOMI ATIPICI SECONDARI A MALASSORBIMENTO

- Anemia sideropenica
- Steatosi epatica
- D.A.R.
- Coliche

SINTOMI ATIPICI INDIPENDENTI DAL MALASSORBIMENTO

- Dermatite erpetiforme
- Ipoplasia smalto dentale
- Alopecia - Psoriasi
- Cirrosi biliare primitiva
- Ipertransaminasemia
- Stomatite aftosa - Atassia
- Miastenia grave
- Pericardite - cardiomiopatie
- Polineuropatia
- Epilessia - Vasculite
- Ipo/Ipertiroidismo

SINTOMATOLOGIA

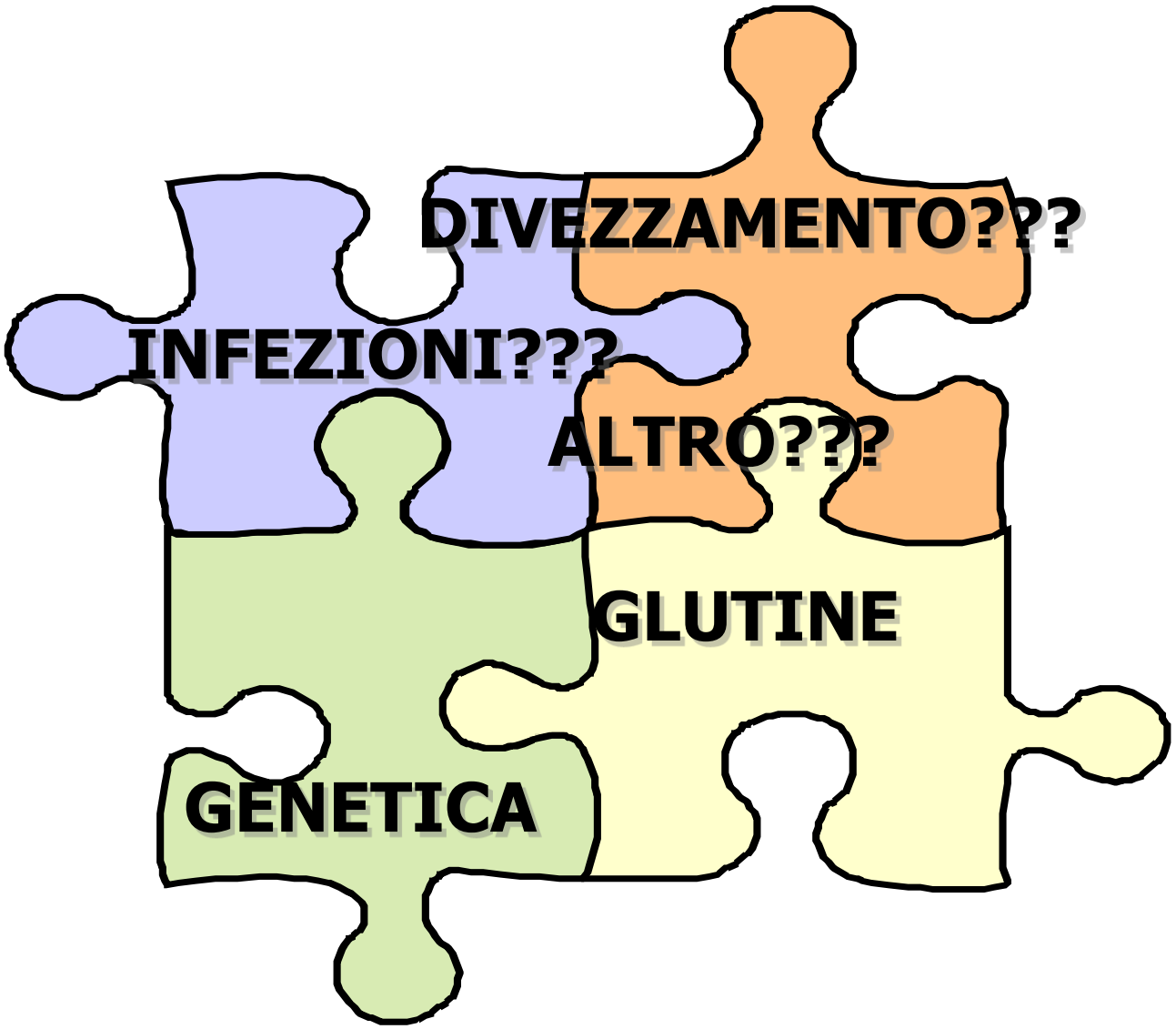
Condizioni associate

MALATTIE ASSOCIATE PROBABILMENTE GLUTINE-DIPENDENTE

- IDDM
- Tiroiditi autoimmune
- Epatiti autoimmuni
- Sindrome di Sjogren
- Morbo di Addison
- Gastrite atrofica autoimmune

MALATTIE ASSOCIATE PROBABILMENTE GLUTINE-INDIPENDENTE

- Sindrome di Down
- Sindrome di Turner
- Cardiopatie congenite
- Sindrome di Sjogren
- Deficit IgA


DIVEZZAMENTO???
INFEZIONI???
ALTRO???
GLUTINE
GENETICA

MALATTIA CELIACA: MODELLO UNICO DI AUTOIMMUNITA'

- **L'unica malattia in cui uno specifico allele HLA è presente nella totalità dei pazienti**
- **L'autoantigene è noto (tTG)**
- **Il trigger ambientale è noto (glutine)**
- **L'eliminazione del trigger ambientale determina la remissione della malattia e la successiva riesposizione provoca la riaccensione della infiammazione**

GLUTINE

Fig. 46. — Séparation du gluten de la farine des céréales au moyen d'un courant d'eau.

ALBUMINE

idrosolubili

GLOBULINE

solubili in sol. salina

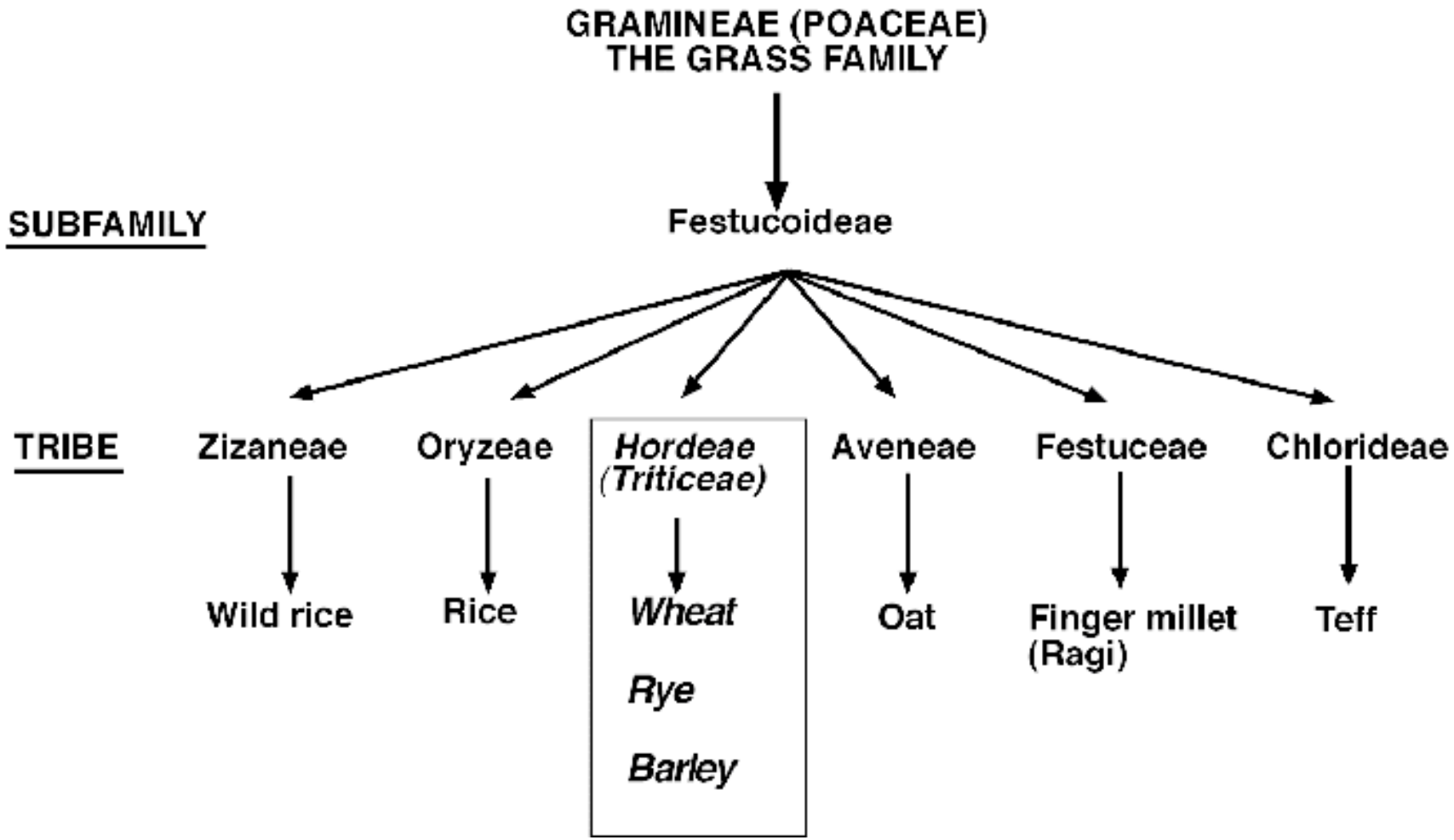
GLIADINA α β γ ω

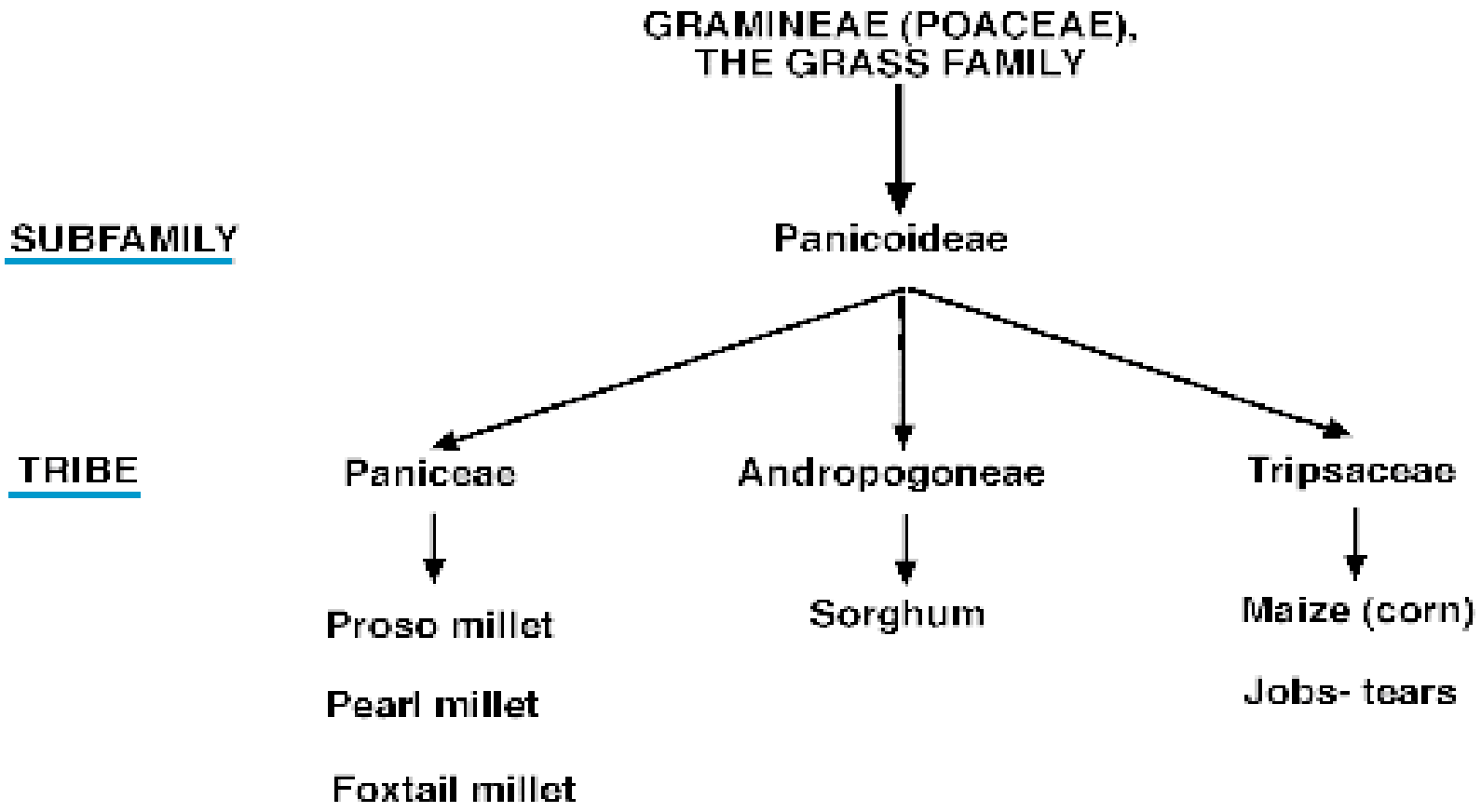
solubili in etanolo

GLUTENINE

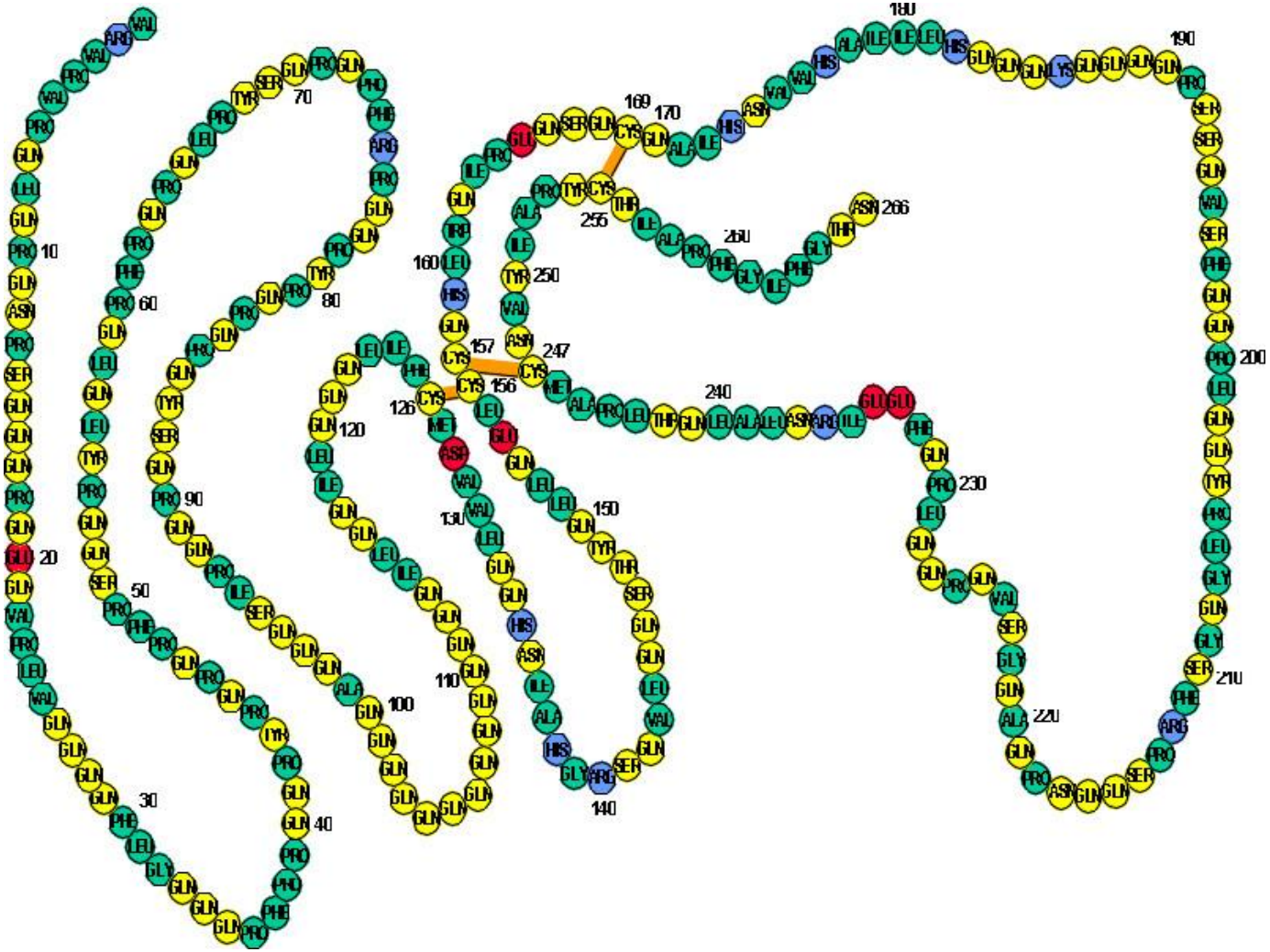
solubili in acido acetico

Attachment I - Kasarda




GRAMINEAE (POACEAE),
THE GRASS FAMILY
SUBFAMILY
Panicoideae
TRIBE
Paniceae
Andropogoneae
Tripsaceae
Proso millet
Pearl millet
Foxtail millet
Sorghum
Maize (corn)
Jobs- tears

GLIADINA



Q = 36 % P = 16 %

Background genetico della MC

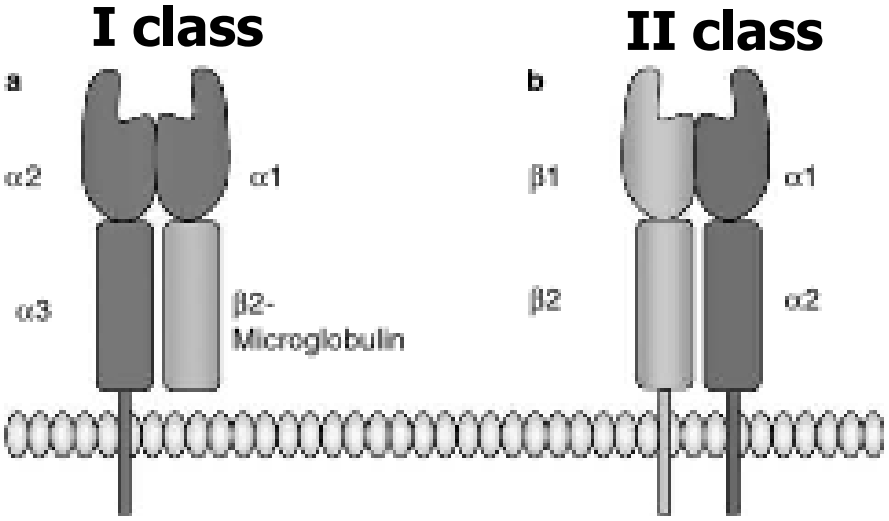
- rischio familiare (5-15%)
- concordanza tra gemelli monozigoti (85%)
- associazione MC con sindromi genetiche (S. di Down, S. di Turner, S. di Williams)

Background genetico della MC

- 90 % DQ2

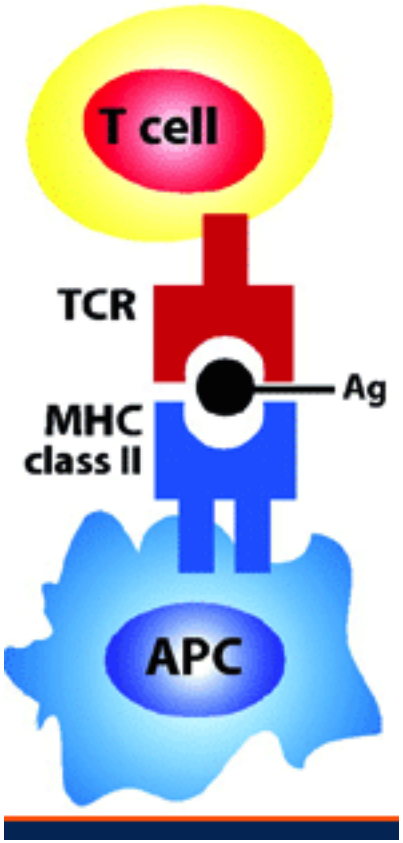
-

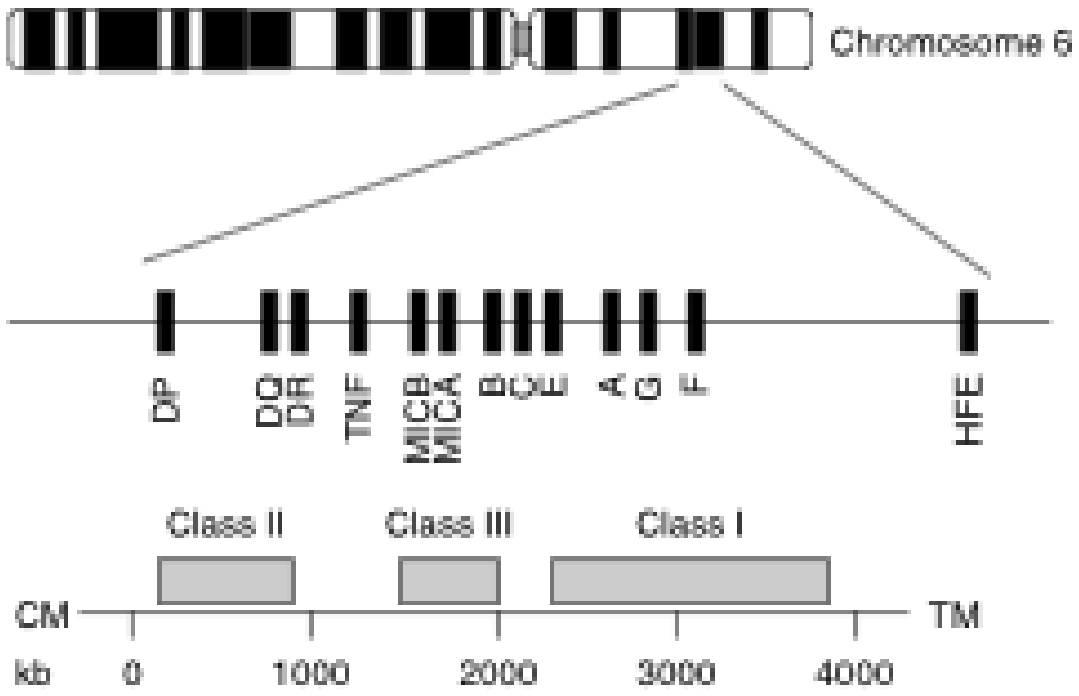
- 8 % DQ8



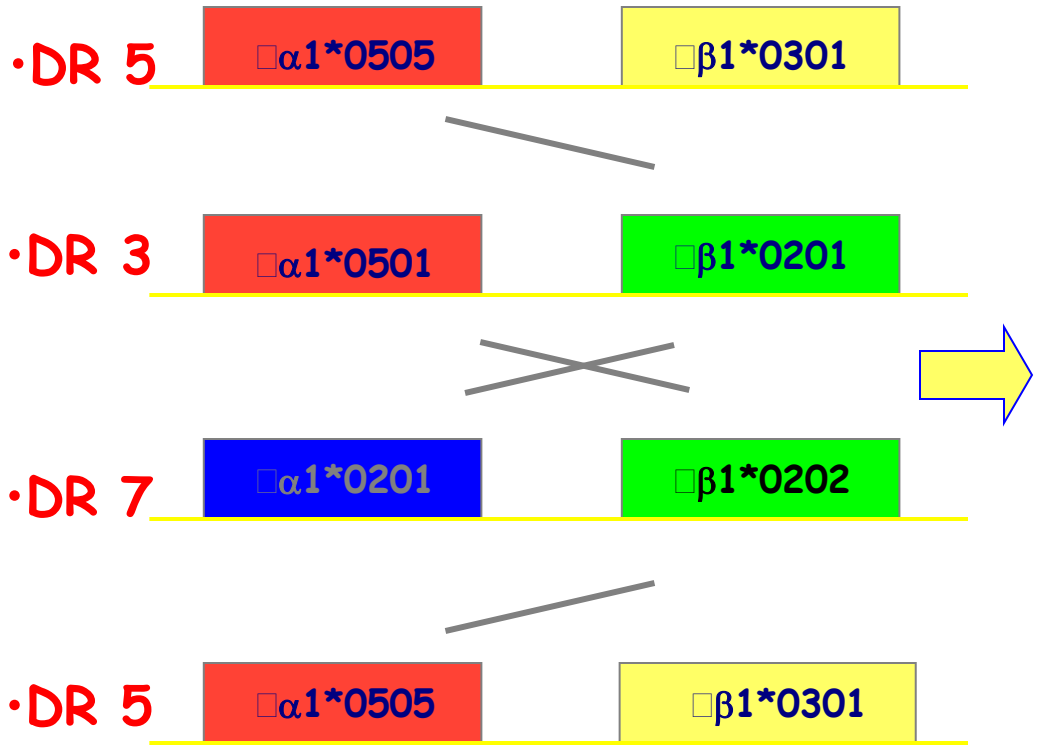
Cassinnotti et al, AJG, 2008

interazione DQ – TCR




Chromosome 6
DP
DQ
DR
TNF
MICB
MICA
B
C
E
A
G
F
HFE
Class II
Class III
Class I
CM
TM
kb
0
1000
2000
3000
4000

·HLA-DQ2



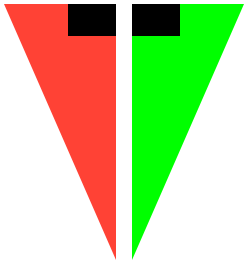
·HLA-DQ2 HETERODIMERS

- □α*0501 - β*0201
- □α*0501 - β*0202
- □α*0505 - β*0201
- □α*0505 - β*0202
- □α*0201 - β*0202

·HLA-DQ2

□α1*0501 □β1*0201

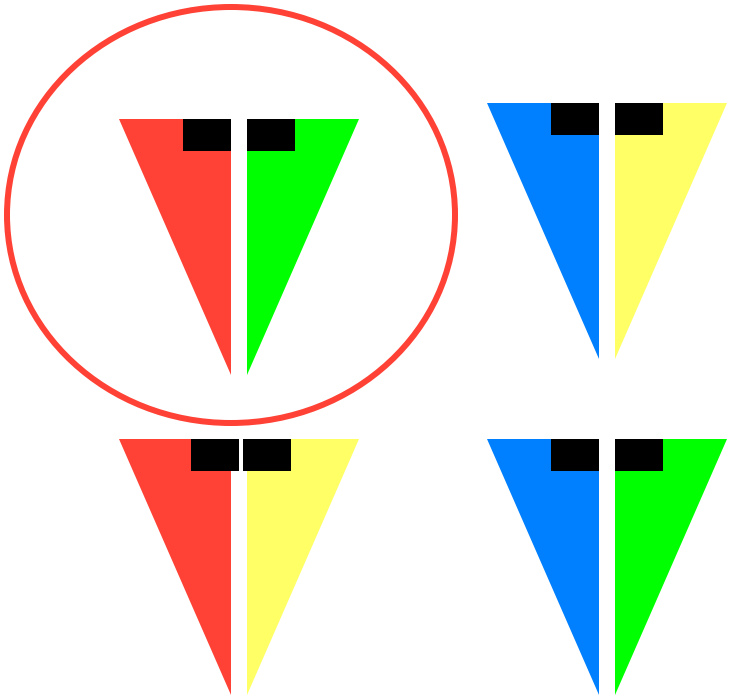
□α1*0501 □β1*0201

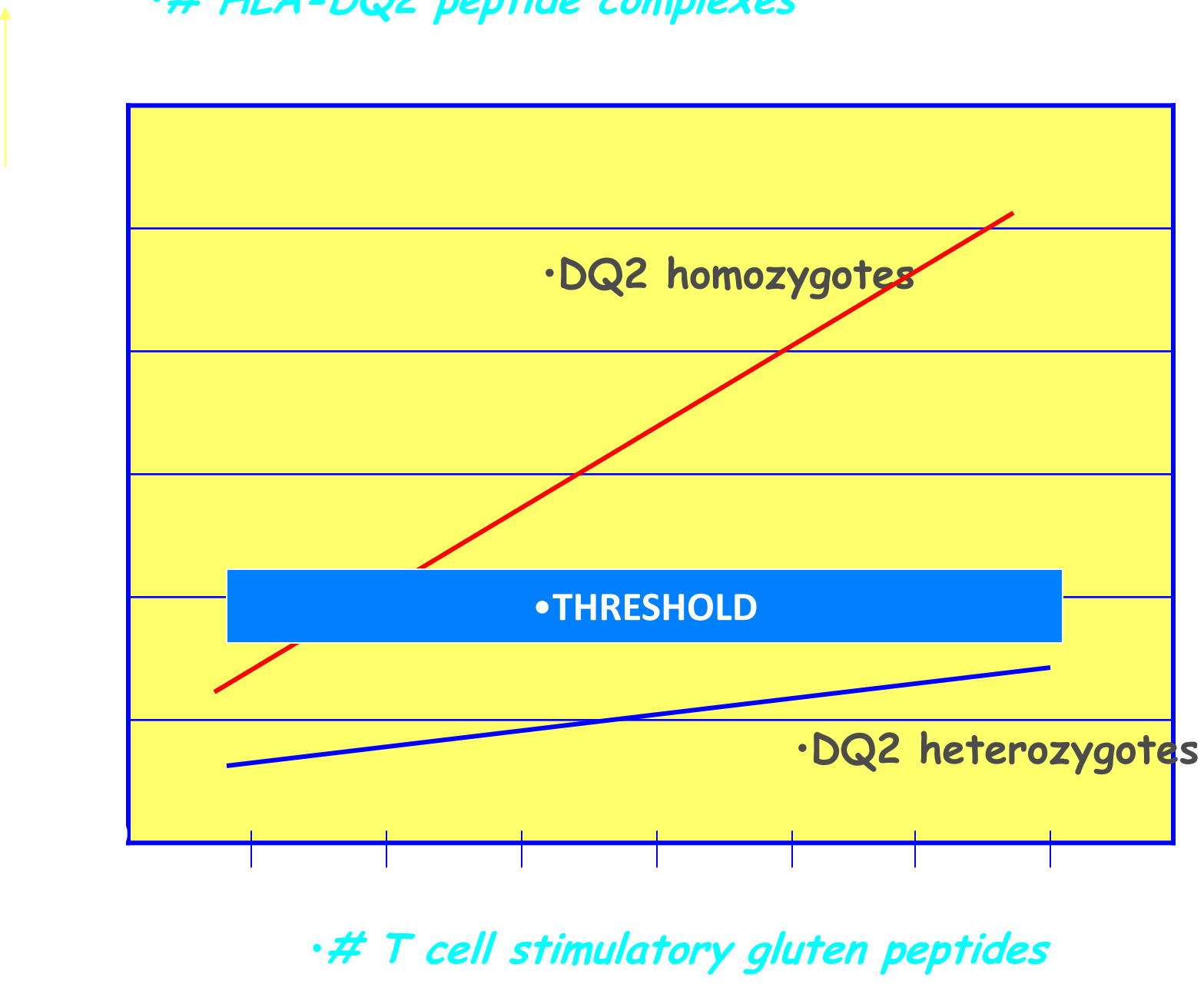


·HLA-DQ2/DQX

□α1*0501 □β1*0201

□α1*0X0X □β1*0X0X




•# HLA-DQ2 peptide complexes
•DQ2 homozygotes
•THRESHOLD
•DQ2 heterozygotes
•# T cell stimulatory gluten peptides

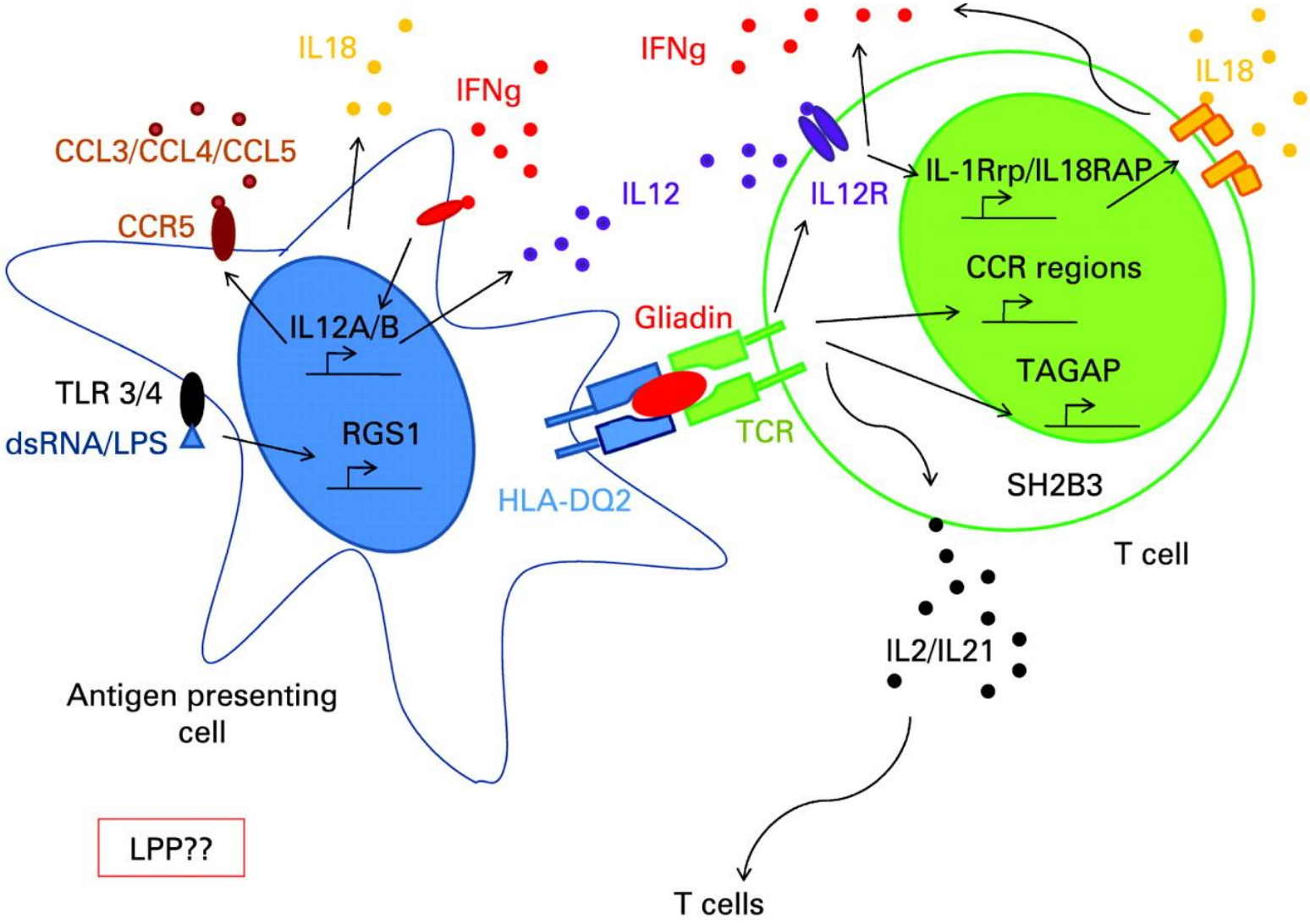
Geni non HLA associati alla MC

Table 1. Non-HLA Loci of Celiac Disease Susceptibility

Loci identified	Type of study used for identification	Origin of the cohort(s)	Candidate genes (function)	Reference
CELIAC 2 5q31-q33	linkage analysis	Italy, Finland, Scandinavia, Europe (meta-analysis)	Unknown	36, 40, 43, 45
CELIAC 3 2q33	Candidate gene approach	France, The Netherlands, Sweden, Norway	CTLA4 (T cell response)	38, 41, 48
CELIAC 4 19p13.1	linkage analysis	Netherland	Myosin IXB (Rho family guanosine triphosphatase)	44
CELIAC 5 15q11-q13	linkage analysis (microsatellite)	Finland	Unknown	49
CELIAC 6 4q27	GWAS (SNPs)	United Kingdom, Netherland, Ireland, Italy, United States, Scandinavia	KIAA1109 TENR (ADAD1) IL2 IL21	31, 33, 35, 39, 47
CELIAC 7 1q31	GWAS (SNPs)	United Kingdom, Netherland, Ireland, Italy, United States	RGS1 (B-cell activation)	31, 33, 39, 47
CELIAC 8 2q11-q12	GWAS (SNPs)	United Kingdom, Netherland, Ireland	IL18RAP IL18R1	31,33, 42
CELIAC 9 3p21	GWAS (SNPs)	United Kingdom, Netherland, Ireland, Spain	CCR1 (chemokines) CCR2 CCRL2 CCR3 CCR5 XCR1	31, 33, 37
CELIAC 10 3q25-q26	GWAS (SNPs)	United Kingdom, Netherland, Ireland, Italy, United States	IL12A	31, 33, 39, 47
CELIAC 11 3q28	GWAS (SNPs)	United Kingdom, Netherland, Ireland, Italy, United States	LPP (zinc binding protein)	31, 33, 39,47
CELIAC 12 6q25.3	GWAS (SNPs)	United Kingdom, Netherland, Ireland, Italy	TAGAP (T cell activation)	31, 33, 47
CELIAC 13 12q24	GWAS (SNPs)	United Kingdom, Netherland, Ireland, Italy, United States	SH2B3 (TLR intracellular adaptor, T-cell activation)	31, 33, 39, 47

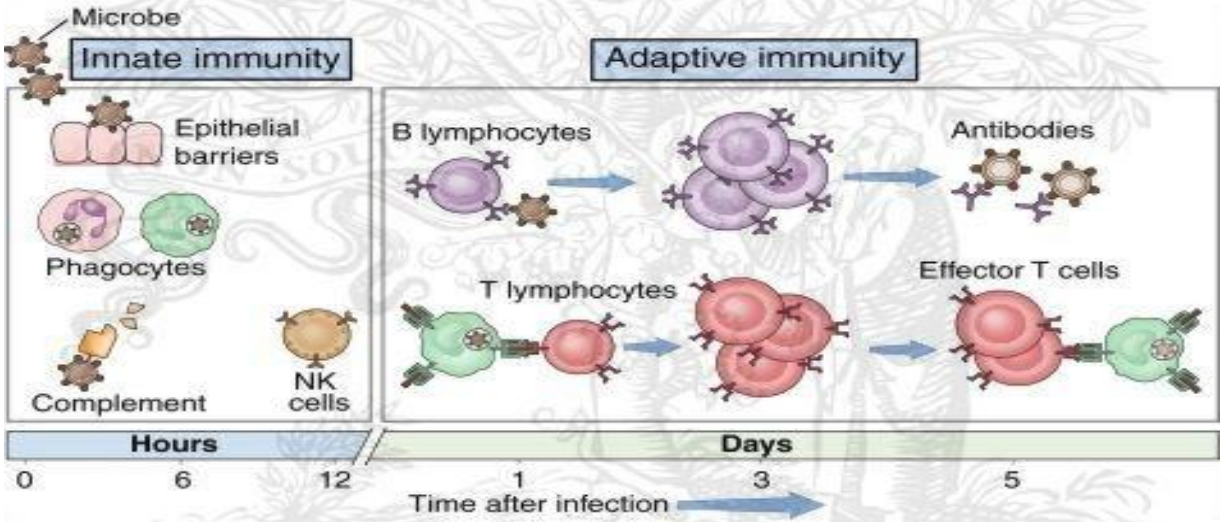
GWAS, genome-wide association study; SNP, single nucleotide polymorphism.

Geni non HLA associati alla MC

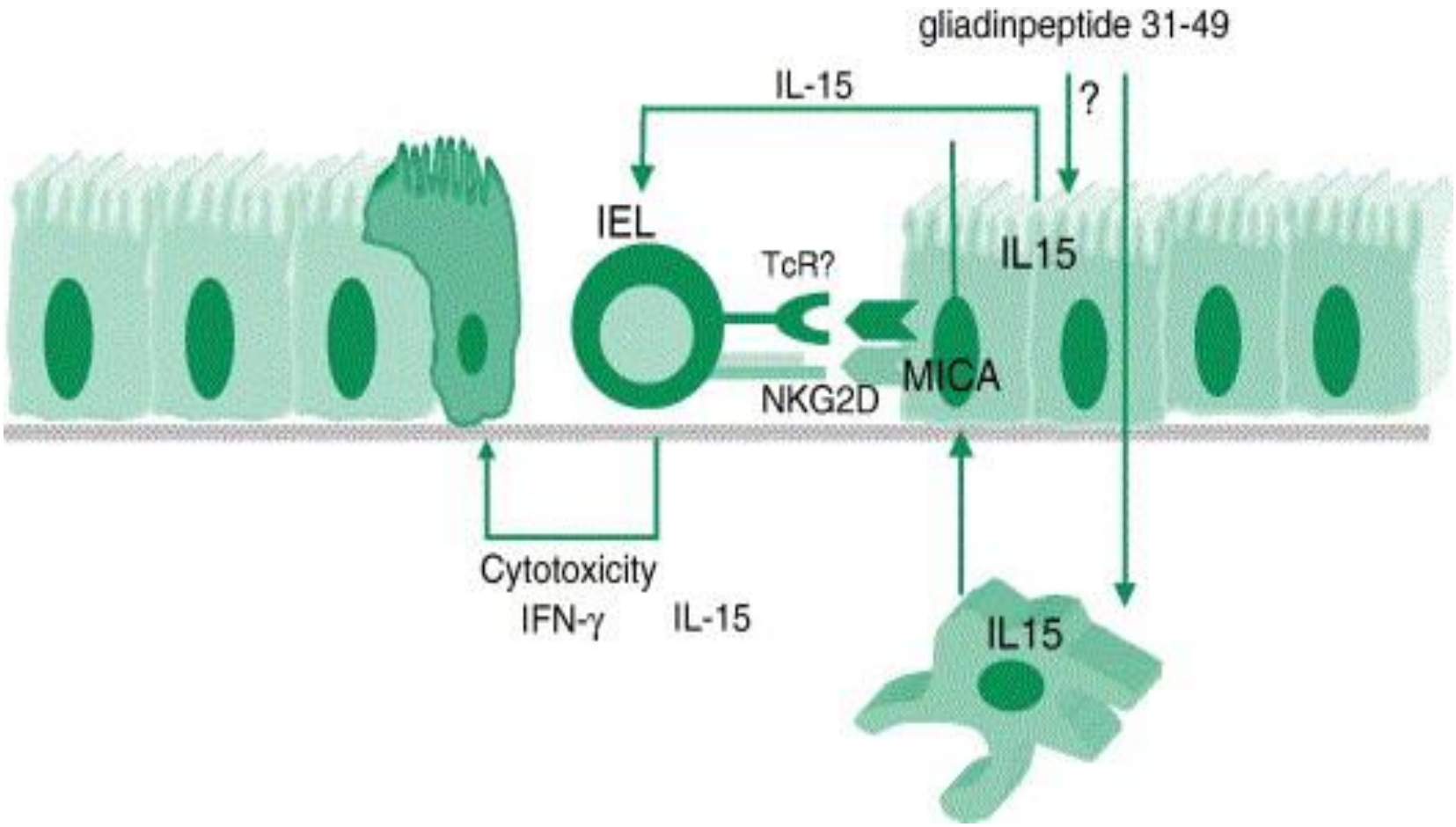


Hunt et al, GUT, 2008

IMMUNITA' INNATA E ADATTATIVA



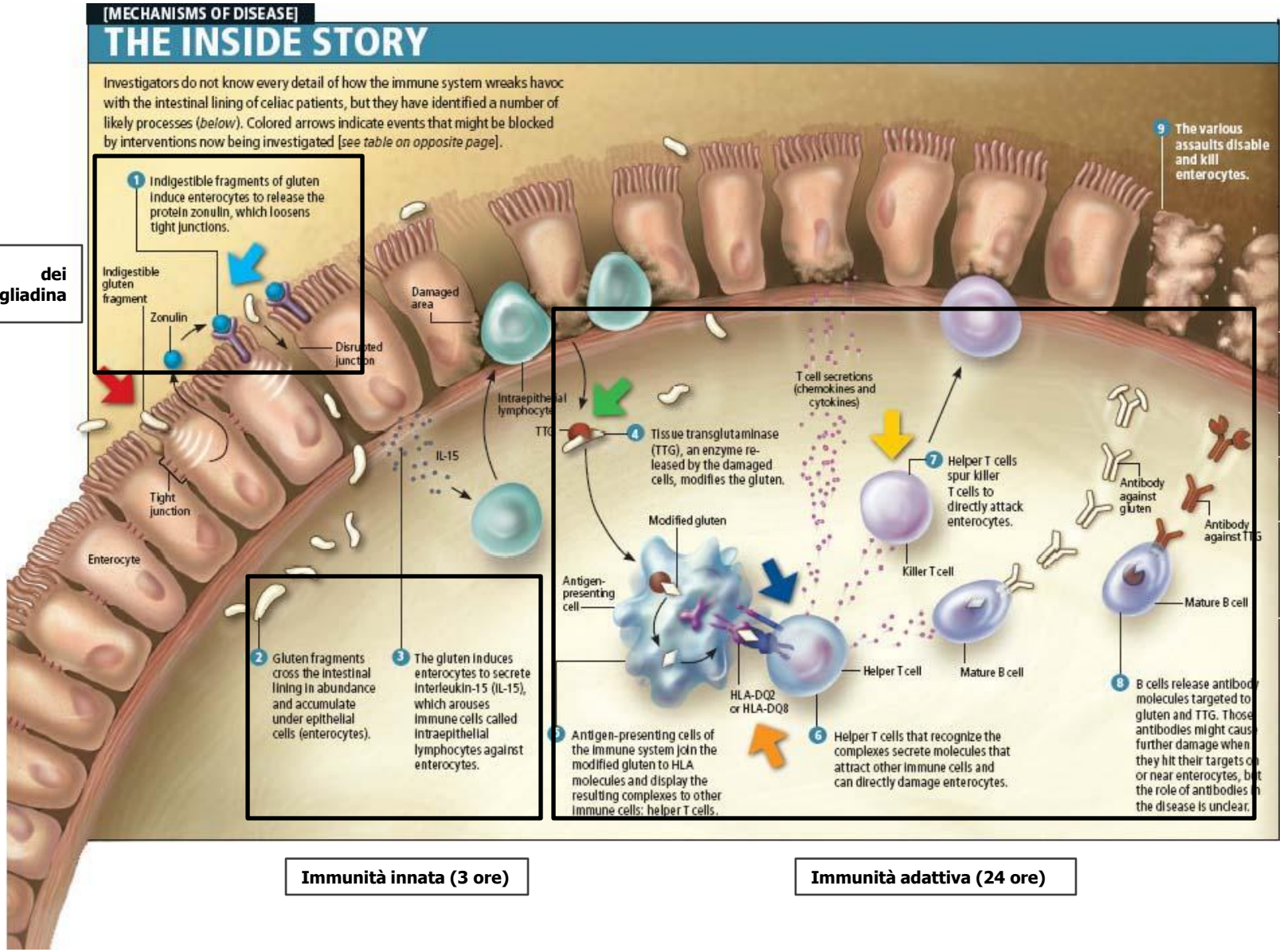
Immunità innata nella MC



Koning F. et al. Best Pract Res Clin Gastr 2005

Patogenesi della MC

Accumulo intralisosomiale dei peptidi della gliadina (minuti)

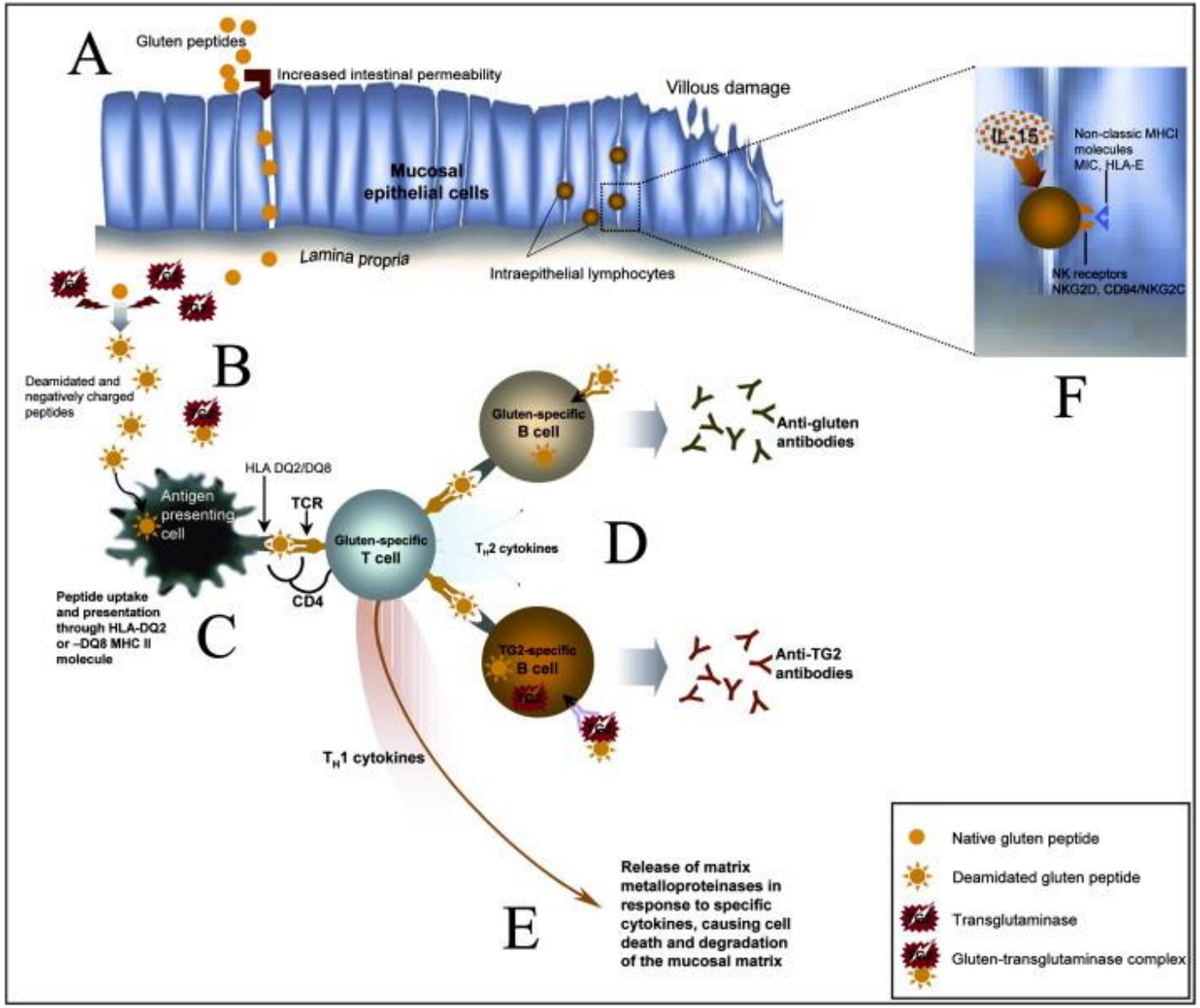


Immunità innata (3 ore)

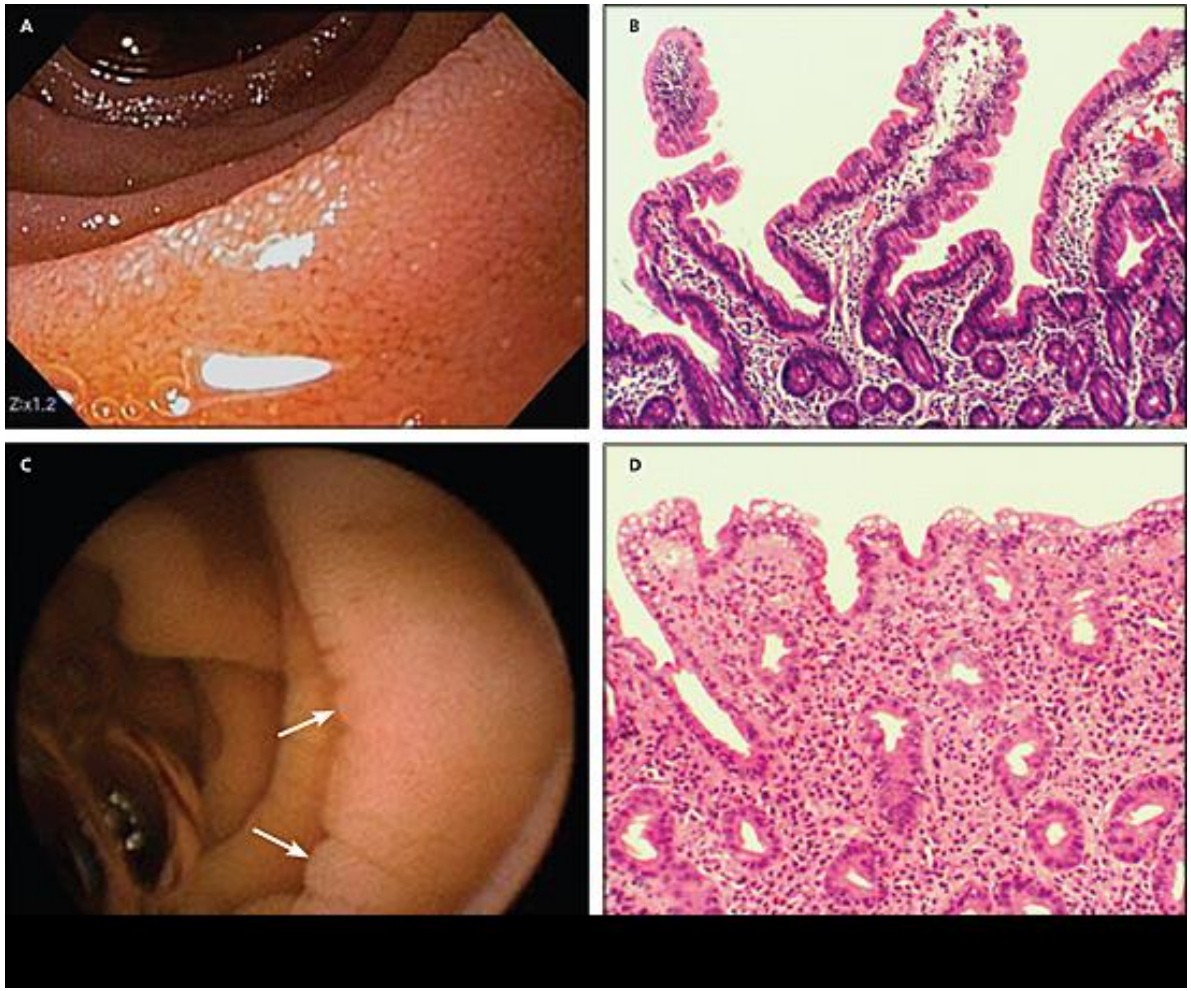
Immunità adattiva (24 ore)

Sollid et al., Mucosal Immunology, 2009

Pathogenesis of celiac disease



Patogenesi della MC



normale

celiaca

MC: un'enteropatia sistemica

Autoanticorpi nella MC

- anticorpi anti gliadina AGA
- anticorpi anti endomisio EMA
- anticorpi anti transglutaminasi tissutale
- anticorpi anti peptidi della gliadina deamidati (anti DGP)

Table 1. Summary of test characteristics of celiac serologies

Test	Sensitivity (reported range) (%)	Specificity (reported range) (%)	Positive predictive value(%),pretest probability of 5%	Negative predictive value (%), pretest probability of 5%
IgA AGA	85 (57–100)	90 (47–94)	18	99
IgG AGA	85 (42–100)	80 (50–94)	31	99
EMA	95 (86–100)	99 (97–100)	83	99
IgA anti-tTG[a]	98 (78–100)	98 (90–100)	72	99
IgG anti-tTG[b]	70 (45–95)	95 (94–100)	42	99
IgA anti-DGP	88 (74–100)	95 (90–99)	44	99
IgG anti-DGP	80 (63–95)	98 (90–99)	68	99
IgA/IgG anti-DGP	97 (75–99)	95 (87–100)	51	99

AGA, anti-gliadin antibody; DGP, deamidated gliadin peptide; EMA, endomysial antibody; tTG, tissue transglutaminase
[a]Anti-human-tTG-based assays only; older tests based on guinea pig antibodies have lower sensitivity and specificity. [b]Sensitivity is significantly higher, about 90–95%, in IgA-deficient populations but lower in the overall celiac population.
Adapted from refs. 5–7, 18, 24, 26, 29, 31, 34, 36, and 37.

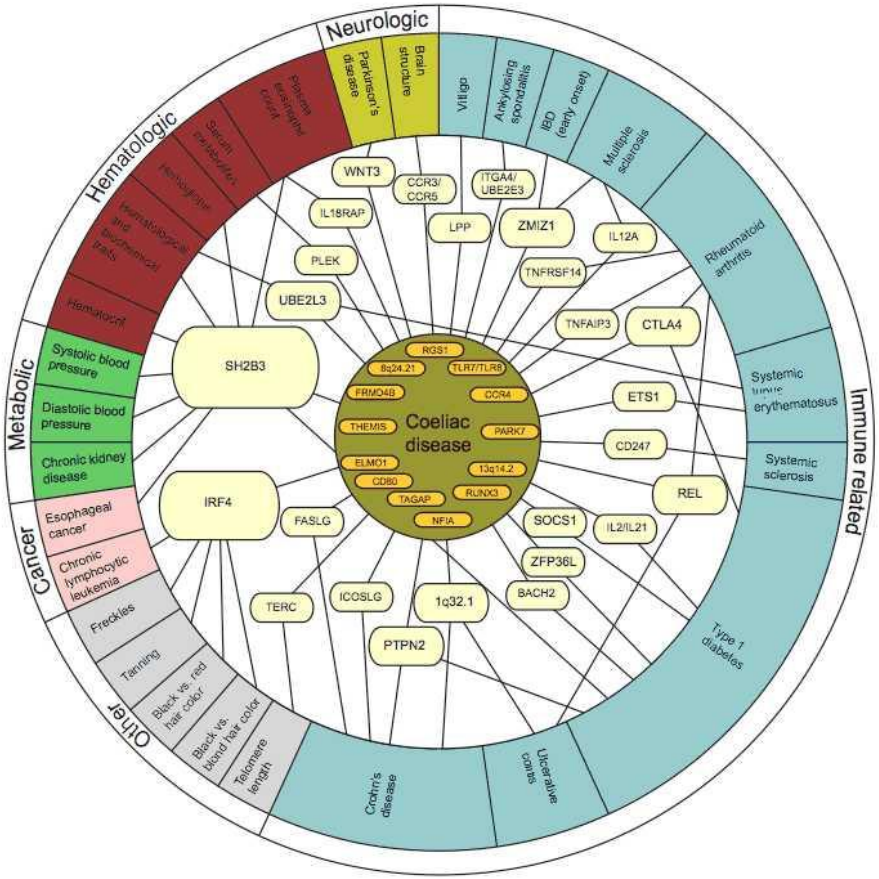
AJG THE RED SECTION

nature publishing group

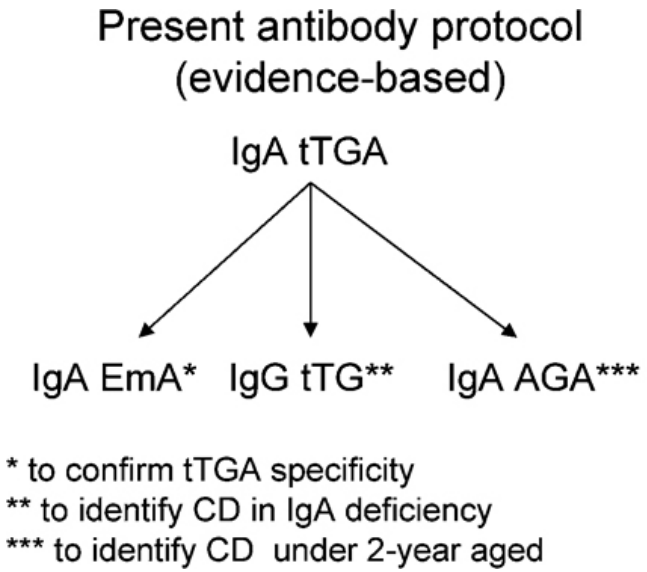
Update on Serologic Testing in Celiac Disease

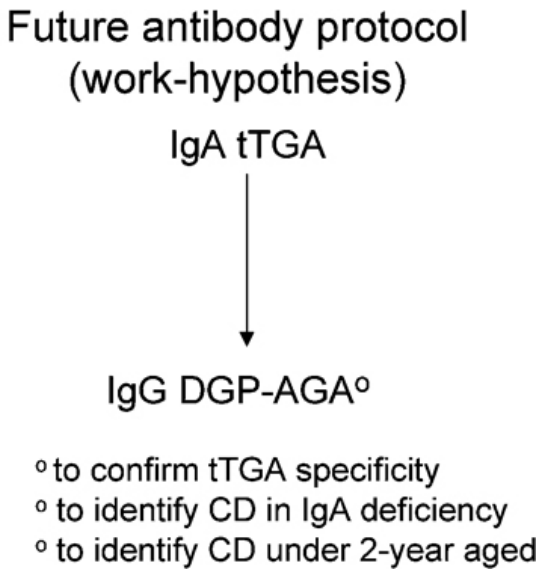
Daniel A. Leffler, MS, MD[1] and Detlef Schuppan, MD, PhD[1]

Condizioni extra intestinali associate alla MC



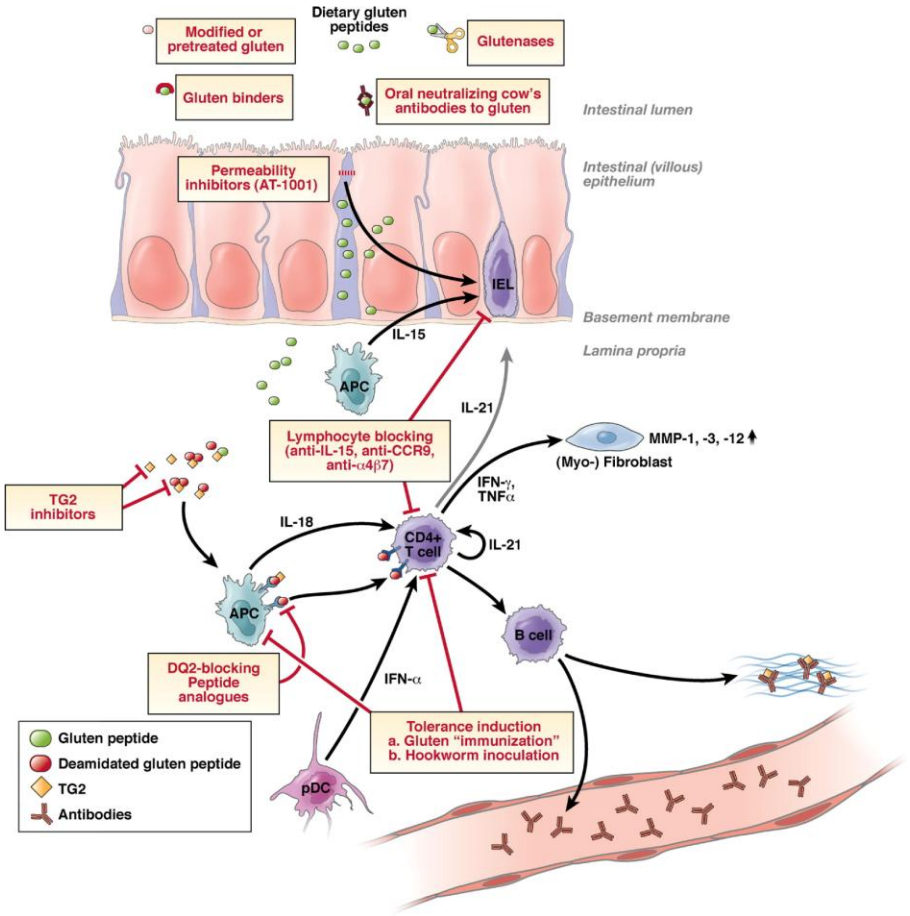
Dalla teoria alla pratica: workflow per la diagnosi di MC





Volta et al., CMI, 2008

Prospettive terapeutiche alternative alla GFD



Schuppan et al., Gastroneterology, 2010; 137:1912

Prospettive terapeutiche alternative alla GFD

Table 2. Novel Therapies for Celiac Disease

Target	Drug/modification	State of development	Reference
Intraluminal therapies			
Wheat varieties	(Ancient) wheat variants with low immunogenicity	Preclinical, tested biopsy specimens and gliadin-reactive T-cell lines	191, 193–197 198
	Genetically modified wheat variants or deletion lines of common wheat with lower immunogenecity		
Flour/dough	Pretreatment with lactobacilli	Clinical trial on 17 patients	207
	Transamidation of gliadin	Preclinical, tested on gliadin-reactive T-cell lines	209
Ingested gliadin peptides	Prolyl endopeptidases from Aspergillus niger	Phase 1 clinical trial (NCT00810654)	219, 220
	Sphingomonas capsulate in combination with (EP)-B2 from germinating barley	Phase 1 clinical trial (NCT00626184)	226, 227
	Intraluminal gliadin binding by polymers	Preclinical	228
	Gluten neutralizing cow's milk antibodies	Preclinical	
Transepithelial uptake			
Epithelial tight junctions	ZOT receptor antagonist AT1001	Phase 2b clinical trial (NCT00889473)	171
Dampening of the adaptive immune response			
TG2	Transglutaminase inhibitors	Preclinical, tested ex vivo on biopsy specimens	240, 241
	"Inhibitory" innate gluten peptides	Preclinical, tested on biopsy specimens and gliadin-reactive T-cell lines	242–249
HLA-DQ2	Blocking DQ2 analogues	Preclinical, tested on gliadin-reactive T-cell lines	251, 252, 256, 257
Immune modulators			
	Hookworm infection	Phase 2 clinical trial (NCT00671138)	264–266
	Gluten "vaccination" (Nexvax2)	Phase 1–2 clinical trial (NCT00879749)	262
Biologicals (systemic T-cell or cytokine blockers)			
Small intestine homing T cells	CCR9 antagonists (Ccx282-B, CCX025)	Phase 2 clinical trial planned (NCT00540657)	273
Gut homing T cells	Anti-integrin α4β7 (LDP-02)	Phase 2 clinical trial for Crohn's disease (NCT00655135)	
Clonal IELs	Anti-IL-15 (AMG 714),	Phase 2 clinical trial for rheumatoid arthritis (NCT00433875)	277
	Anti-JakS (CP-690-550)	Phase 2 clinical trial for rheumatoid arthritis, transplant rejection (NCT00550446, NCT00658359)	278
Clonal intestinal T cells	Autologous bone marrow transplantation	Clinical trial on patients with EATL	132
	Mesenchymal stem cell transplantation (prochymal)	Phase 2 clinical trial for Crohn's disease (NCT00294112)	280
Mucosal destruction in refractory celiac disease	Anti–tumor necrosis factor α, anti–IFN-γ (HuZAF)	Case reports in celiac disease	285, 286
	Anti-CD52 (Alemtuzumab)	Phase 2 clinical trial for Crohn's disease (NCT00072943)	287
		Case reports in celiac disease	

GRAZIE PER L'ATTENZIONE