



Università degli Studi di Messina

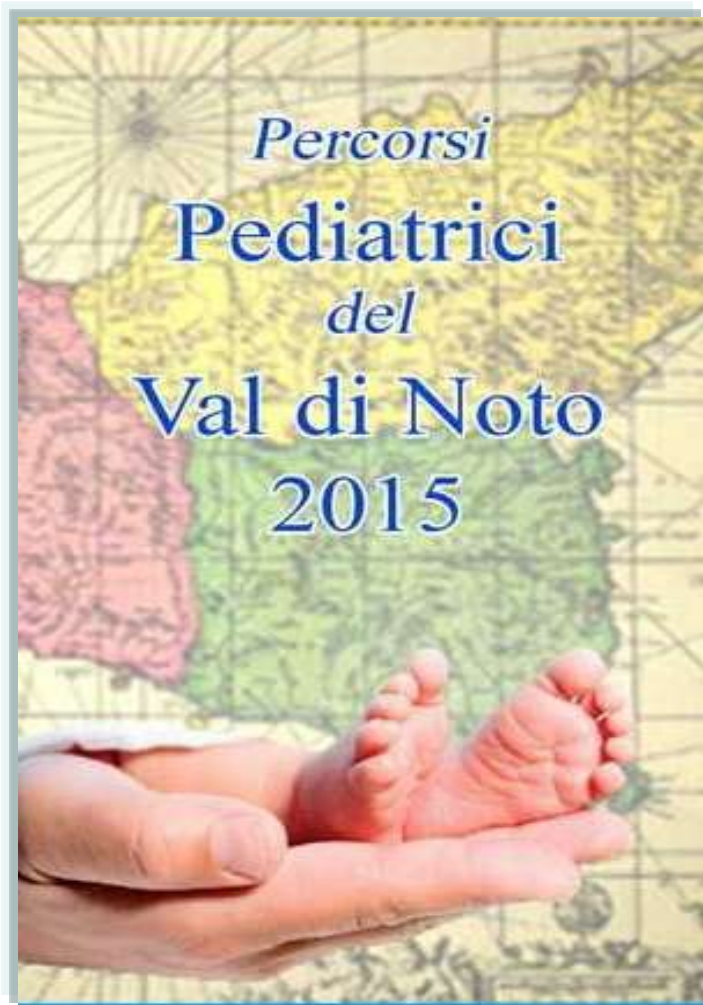
Dipartimento di Scienze Pediatriche, Ginecologiche, Microbiologiche e Biomediche

Scuole di Specializzazione in Pediatria e Genetica Medica

Centro di Riferimento Regionale per la Prevenzione, Diagnosi e Cura delle Malattie Genetiche

U. O. C. di Genetica e Immunologia Pediatrica

Direttore: Prof. Carmelo Salpietro

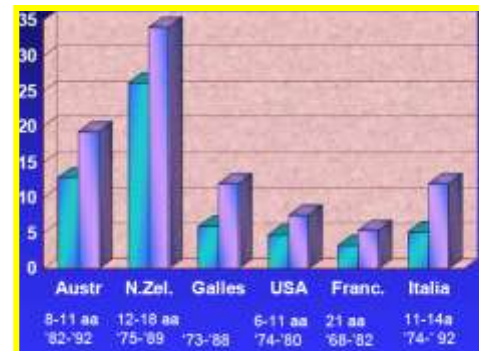


GENETICA DELLE MALATTIE ALLERGICHE

MALATTIE ALLERGICHE: EPIDEMIOLOGIA



NEGLI ULTIMI 20 ANNI LA PREVALENZA DELLE MALATTIE ATOPICHE È AUMENTATA CONSIDERevolmente IN MOLTI PAESI, SOPRATTUTTO NEI BAMBINI



1/4

19-20%
9 milioni



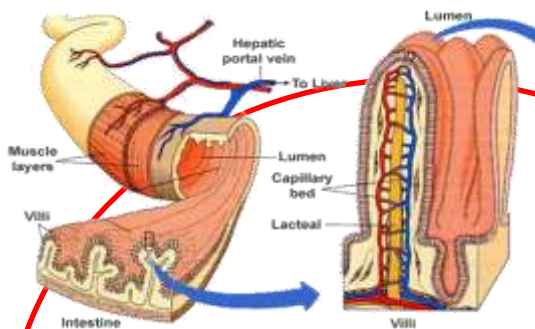
30% DEI BAMBINI SOFFRE MALATTIE ATOPICHE

- 35% ASMA
- 15% RINITE
- 10% CONGIUNTIVITE
- 20% DERMATITE
- 12% ORTICARIA/ANGIOEDEMA
- 8% ALLERGIA ALIMENTARE

FENOTIPI ALLERGICI



8% ALLERGIA ALIMENTARE



20% DERMATITE



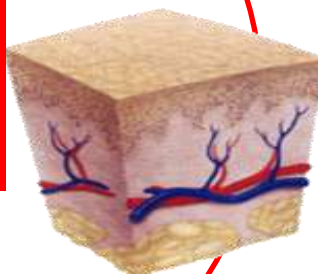
ORTICARIA



12% ANGIOEDEMA

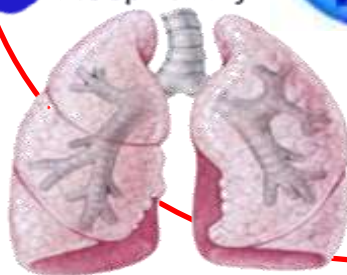


Allergia = malattia sistemica



Skin

Respiratory



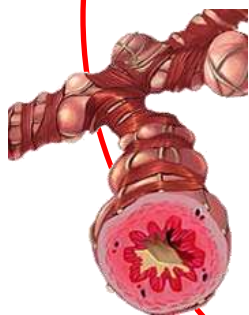
15% RINITE



10% CONGIUNTIVITE



30% ASMA





ASMA



DERMATITE



ORTICARIA



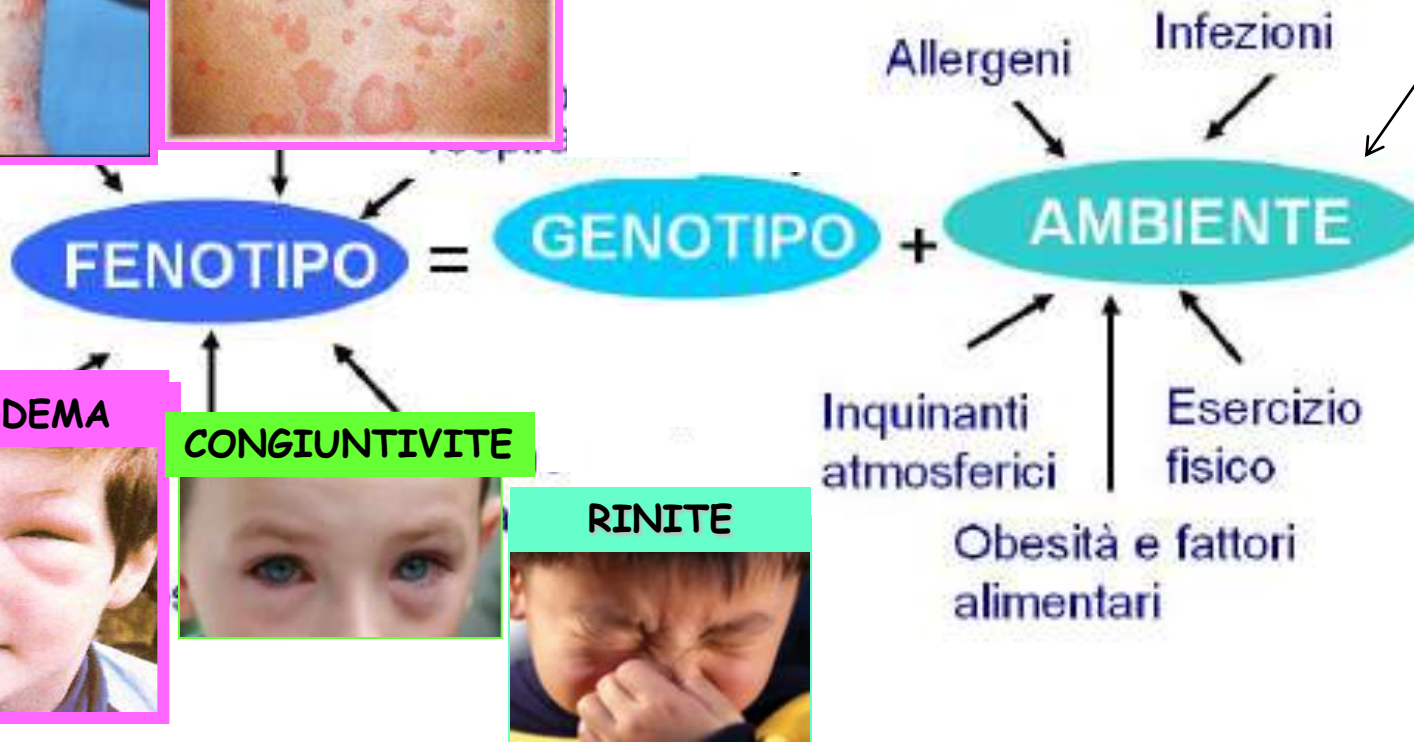
ANGIOEDEMA



CONGIUNTIVITE



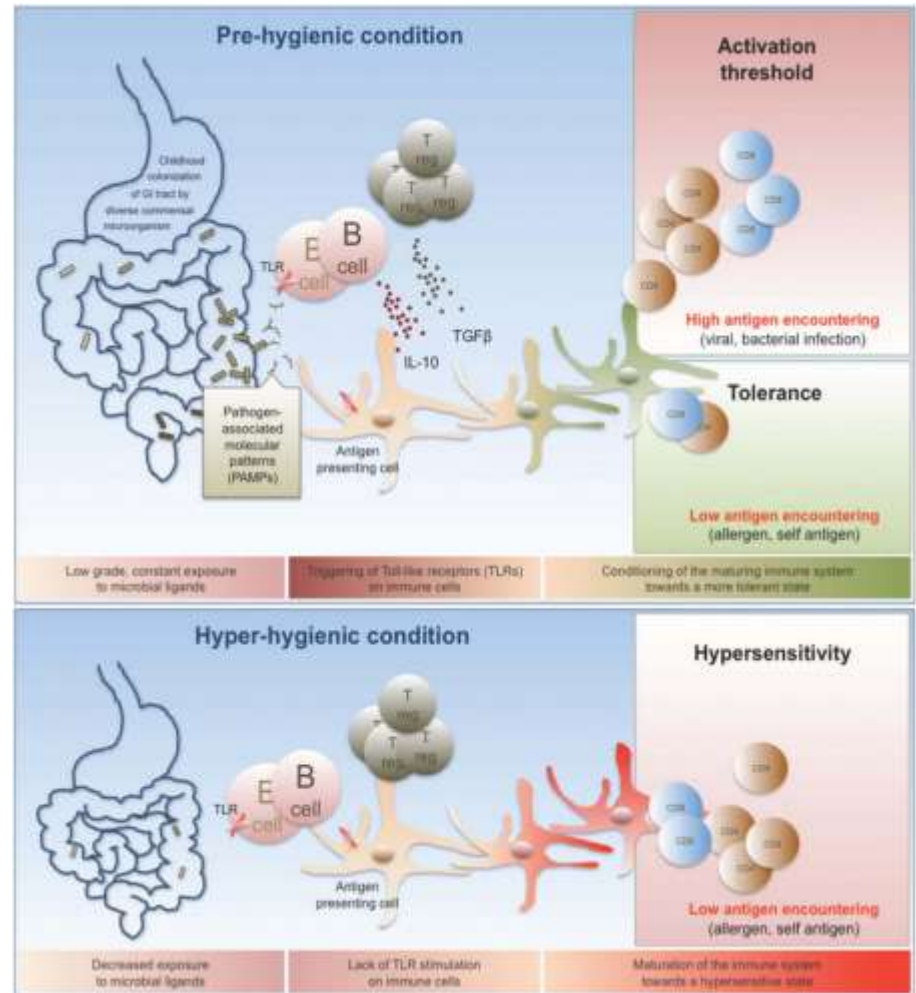
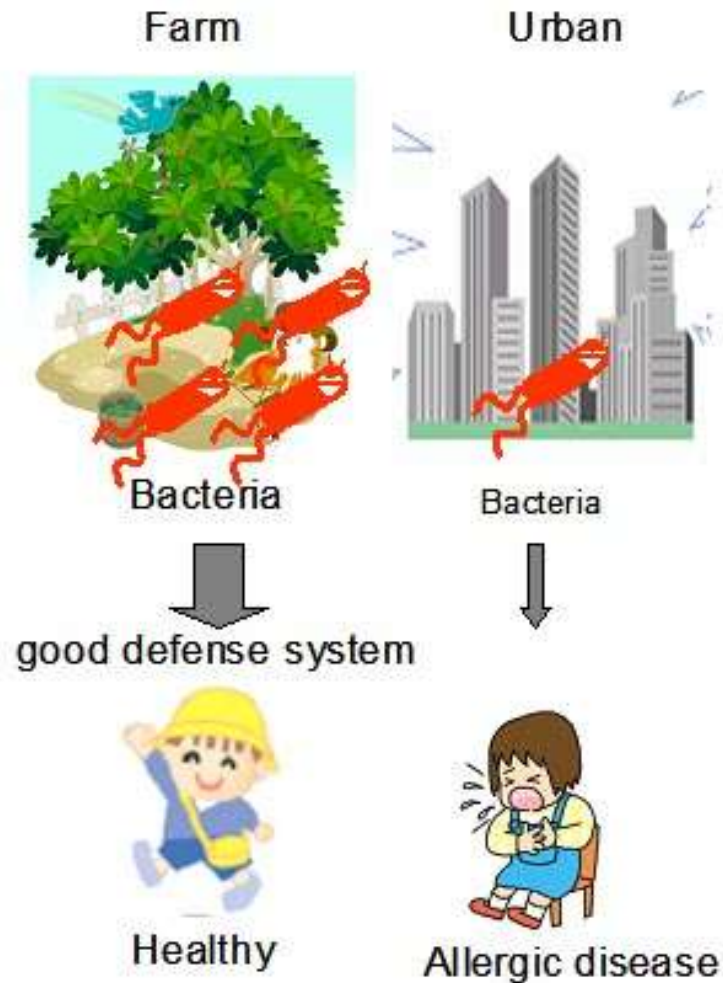
RINITE



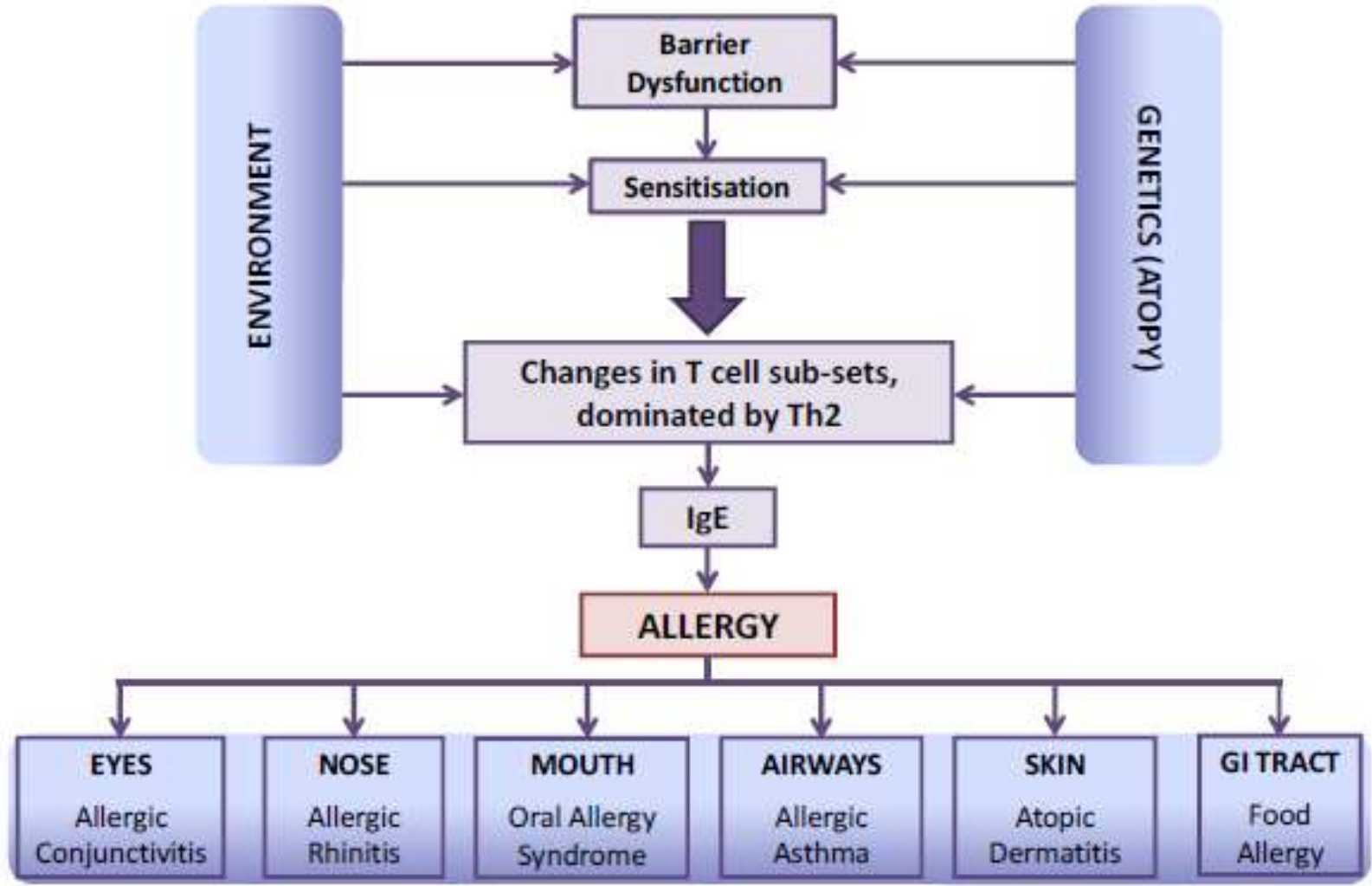
HYGIENE HYPOTHESIS



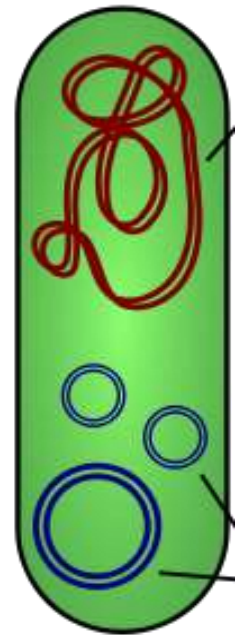
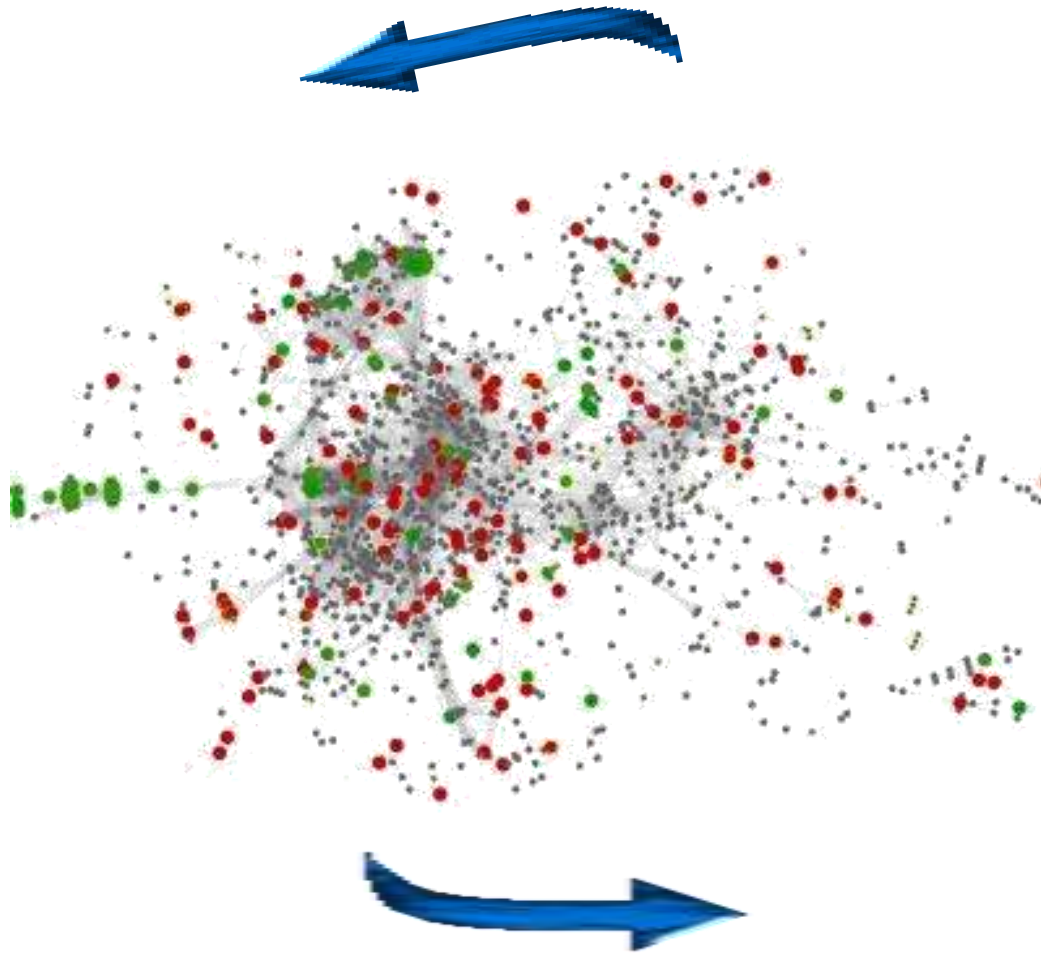
HYGIENE HYPOTHESIS



MALATTIE ALLERGICHE: DINAMICA EVOLUTIVA/OMEOSTASI

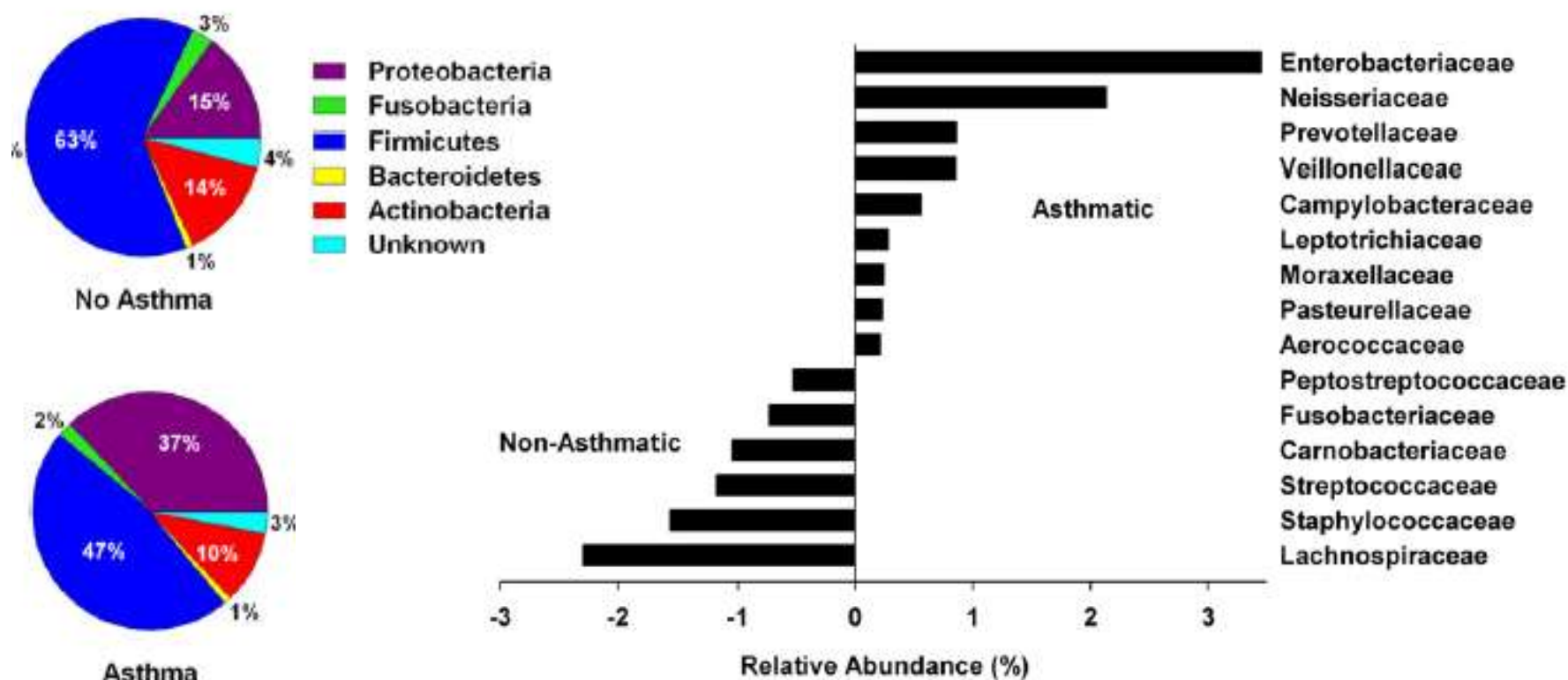


NETWORK GENOMA UMANO/GENOMA MICROORGANISMI

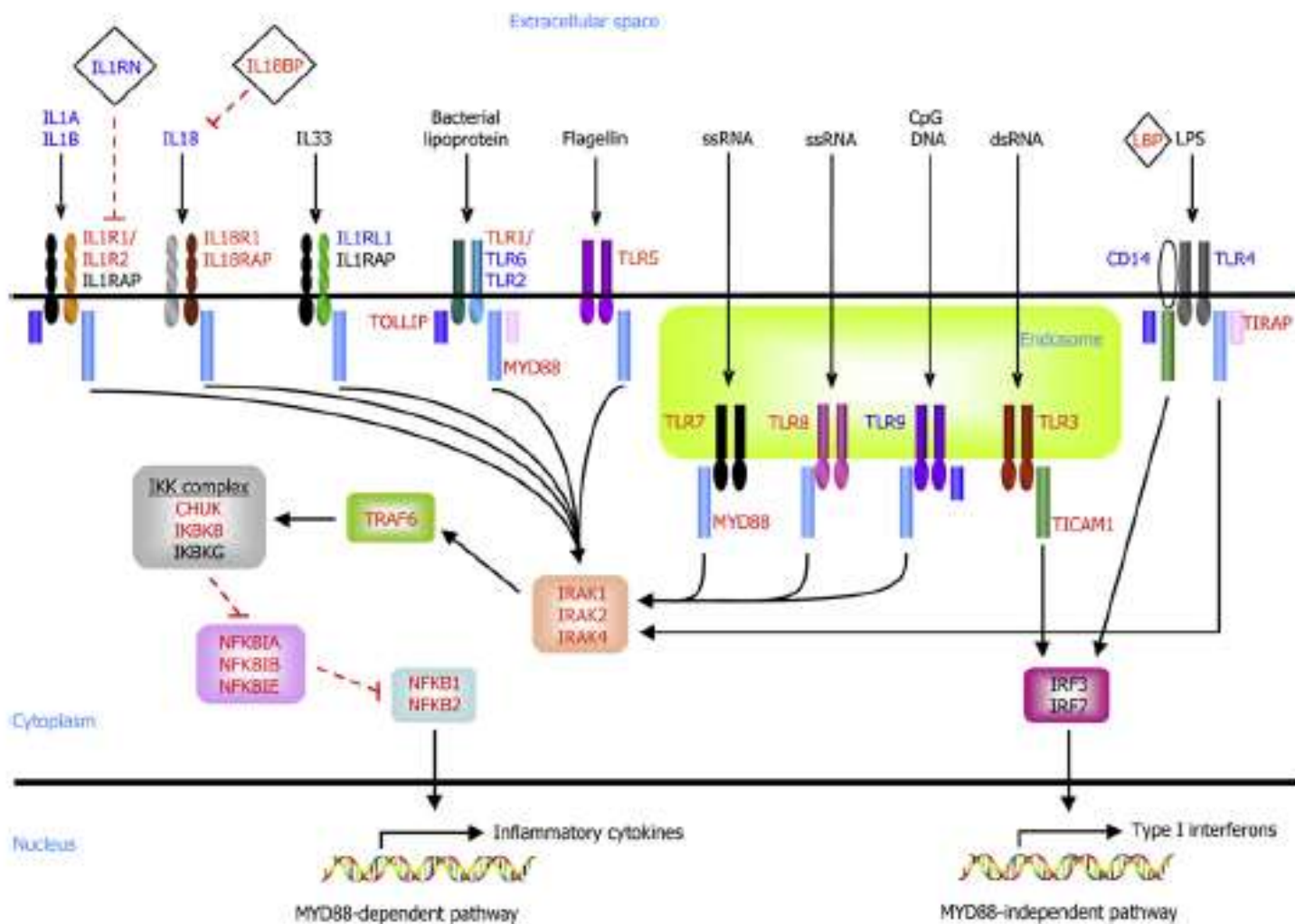


Asthma-associated differences in microbial composition of induced sputum

Pradeep Reddy Marri, PhD,^a Debra A. Stern, MS,^b Anne L. Wright, PhD,^b Dean Billheimer, PhD,^{a,c} and Fernando D. Martinez, MD^{a,b} Tucson, Ariz



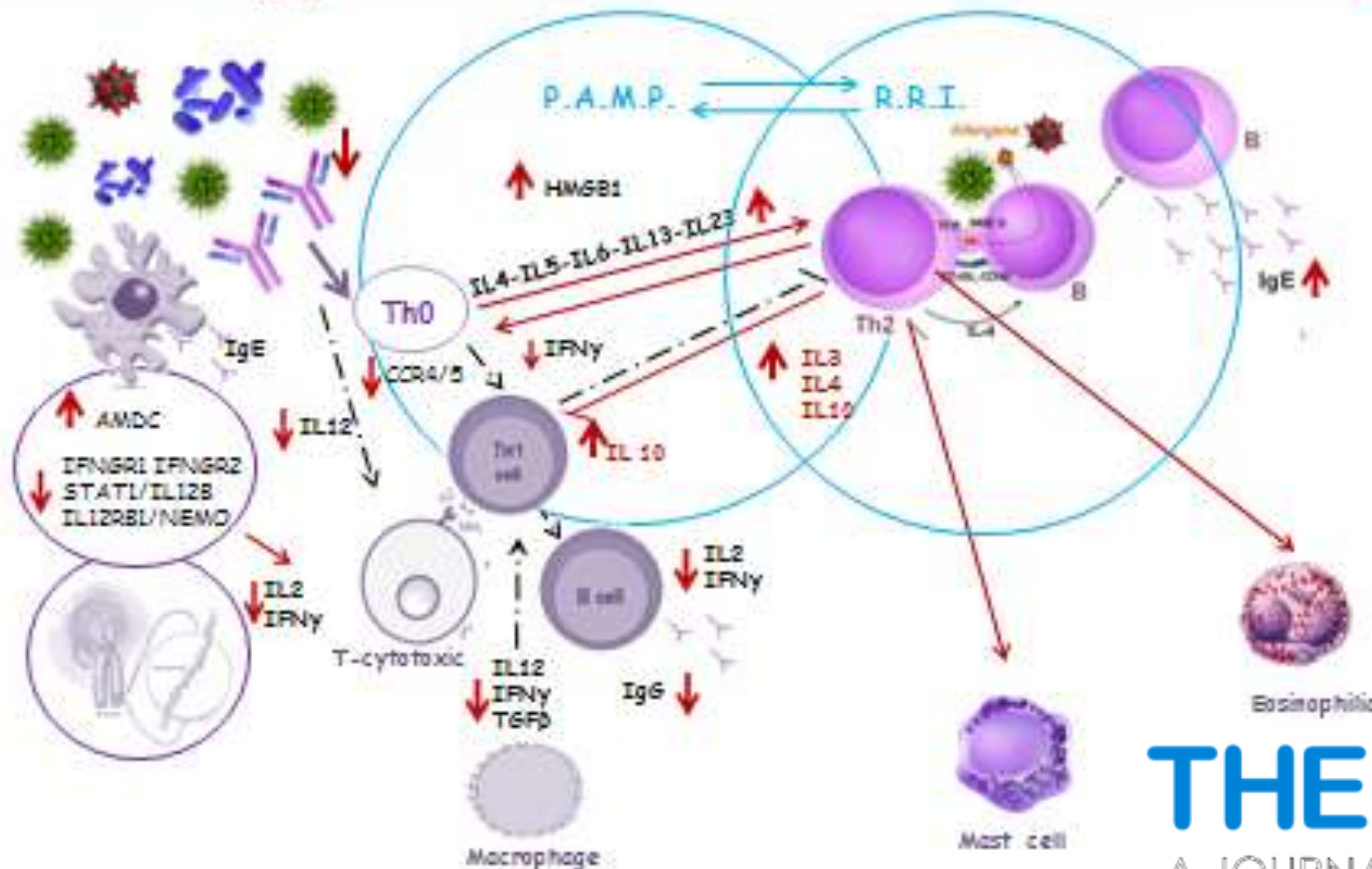
Associations and interactions of genetic polymorphisms in innate immunity genes with early viral infections and susceptibility to asthma and asthma-related phenotypes



The TLR1 variant (rs4543123) was associated with both multiple viruses (respiratory syncytial virus and parainfluenza virus) and multiple phenotypes.

A New Hypothesis: correlation between Phlogosis Allergic Minimum Persistent (P.A.M.P.) and Recurrent Respiratory Infections (R.R.I.)

Cuppari C, Manti S, Salpietro A, Colavita L, Valenti S, De Vivo D, Arrigo T, Salpietro C



3121 b.ni
con IRR



41%
ATOPIA



ASMA



DERMATITE



ORTICARIA



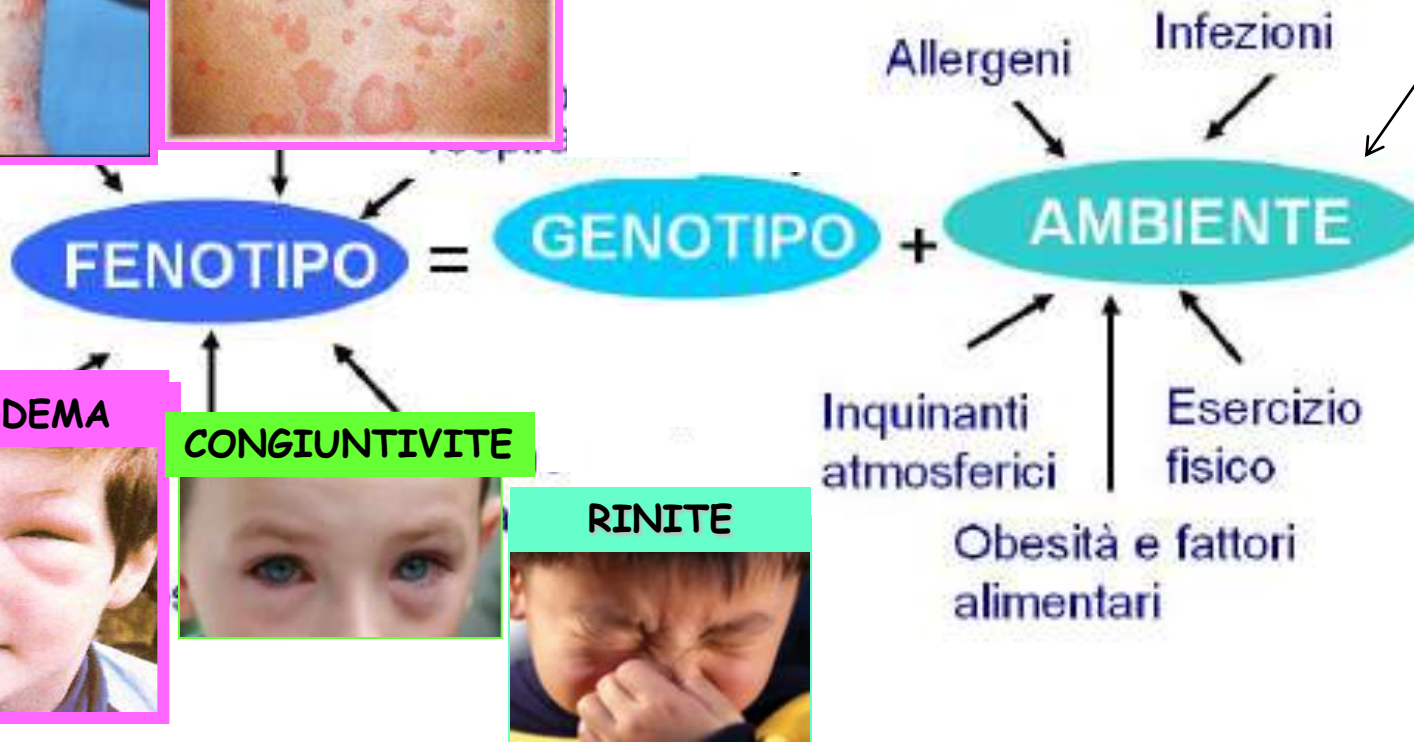
ANGIOEDEMA



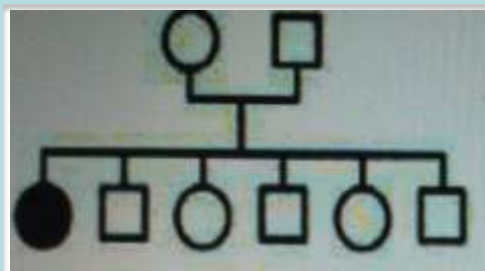
CONGIUNTIVITE



RINITE



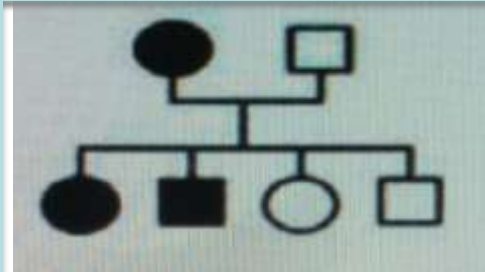
ALLERGOPATIE: ALLERGOPATIE



Genitori non atopici



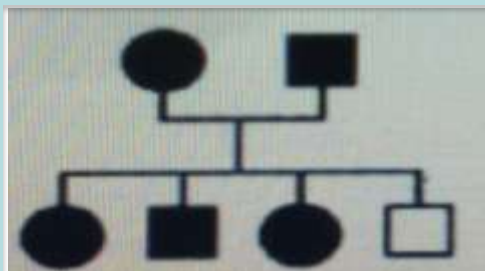
15% dei figli con la malattia



Un genitore atopico



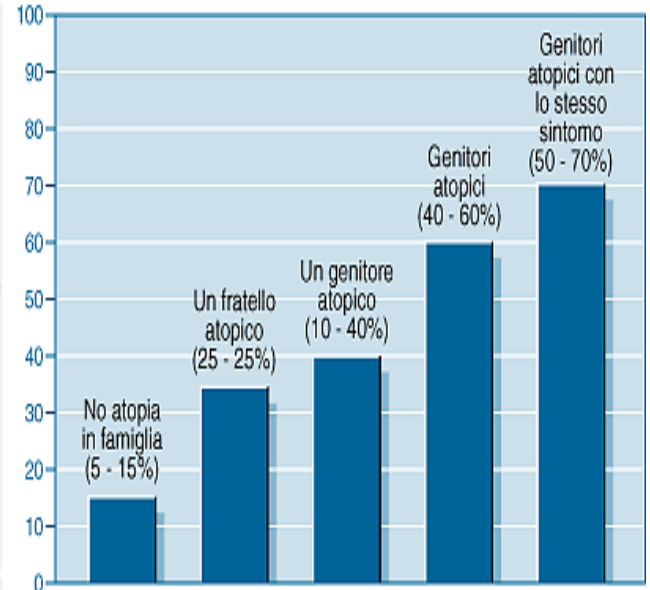
40-50% dei figli con la malattia



Entrambi i genitori atopici

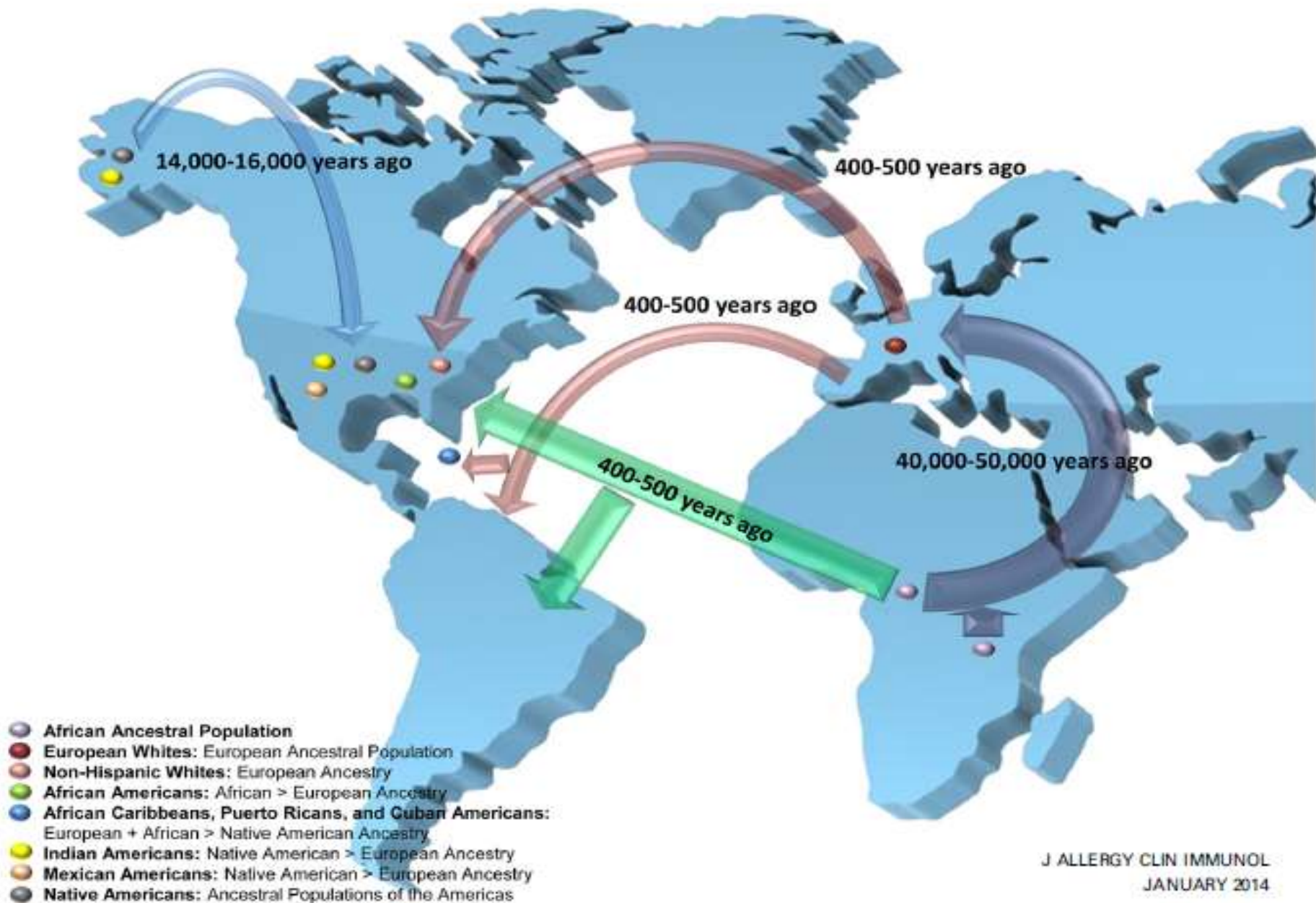


75% dei figli con la malattia

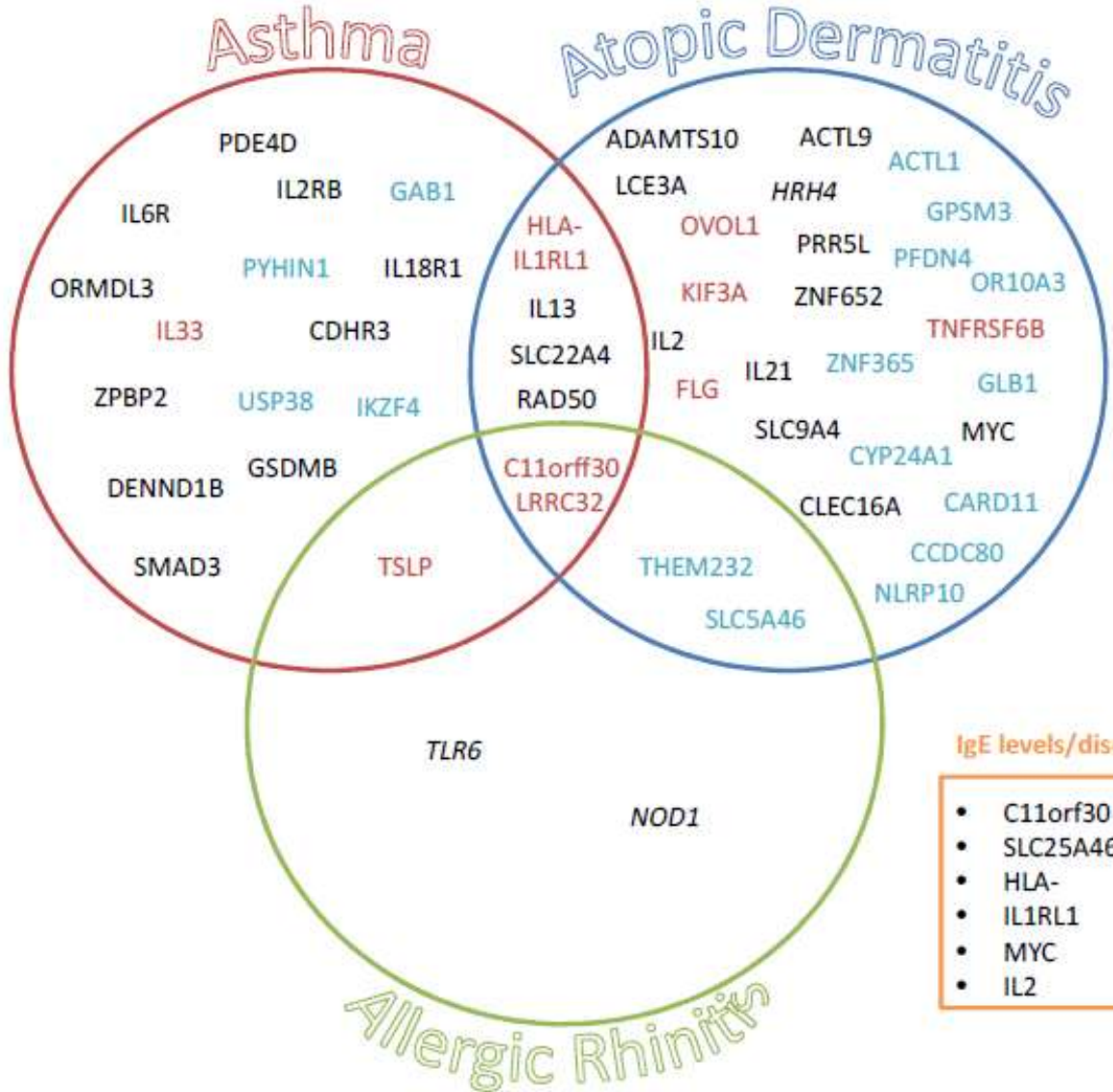


Kjellman et al. 1977

GRUPPI ETNICI E VARIABILITA' GENETICA

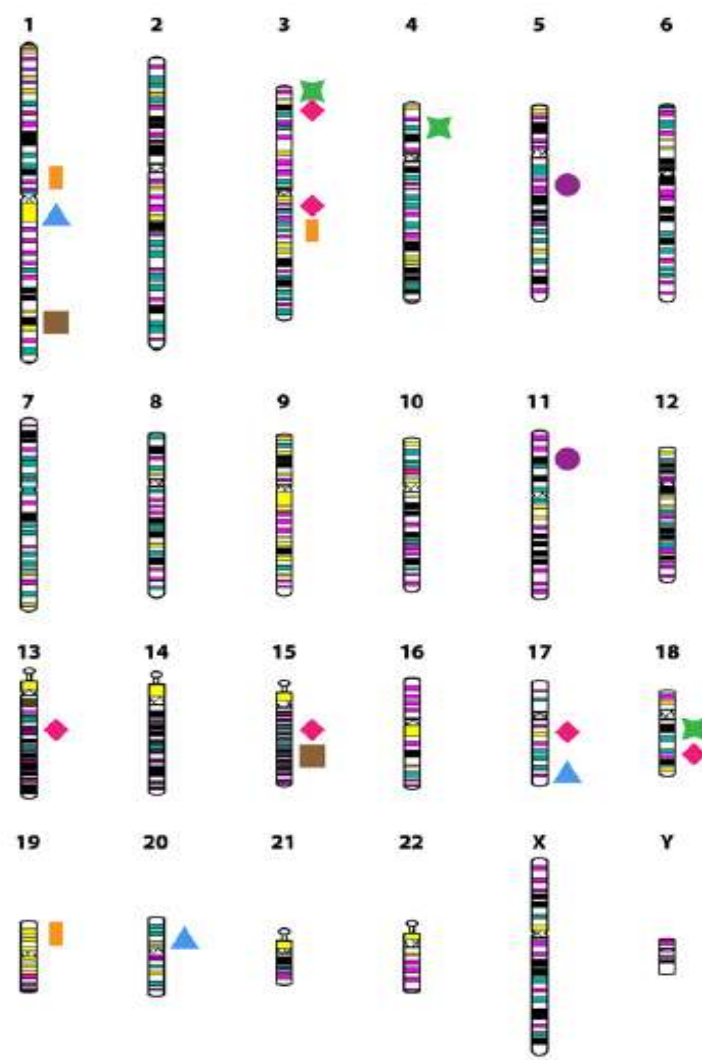


Genetic risk factors for the development of allergic disease identified by genome wide association



- IgE levels/disease loci overlap**
- C11orf30
 - SLC25A46
 - HLA-IL1RL1
 - MYC
 - IL2

DA: GENI CANDIDATI



- Lee et al. 2000 (German/Scandinavian)
- ▲ Cookson et al. 2001 (British)
- ◆ Bradley et al. 2002 (Swedish)
- ★ Haagerup et al. 2004 (Danish)
- Guilloud-Bataille et al. 2007 (French)
- Enomoto et al. 2008 (Japanese)

Table 1 Candidate Genes for Atopic Dermatitis

Gene Symbol	Gene Name	Locus
Pattern Recognition Receptors		
CARD4 (NOD1)	caspase recruitment domain-containing protein 4	7p15-p14
CARD15 (NOD2)	caspase recruitment domain-containing protein 15	16q21
CD14	monocyte differentiation antigen CD14	5q31.1
MBL2	lectin, mannose-binding, soluble, 2	10q11.2-q21
TLR2	Toll-like receptor 2	4q32
TLR4	Toll-like receptor 4	9q32-q33
TLR6	Toll-like receptor 6	4p14
Chemokines and Associated Molecules		
CCL2 (MCP-1)	chemokine (C-C motif) ligand 2	17q11.2-q12
CCL5 (RANTES)	chemokine (C-C motif) ligand 5	17q11.2-q12
CCL11 (Eotaxin)	chemokine (C-C motif) ligand 11	17q21.1-q21.2
CCL17 (TARC)	chemokine (C-C motif) ligand 17	16q13
CCR3	chemokine (C-C motif) receptor 3	3p21.3
CCR4	chemokine (C-C motif) receptor 4	3p24
CMA1	chymase 1	14q11.2
Cytokines and Associated Molecules		
IL1RN	interleukin 1 receptor antagonist	2q14.2
IL1RL1 (ST2)	interleukin 1 receptor-like 1	2q11.2
IL1A	interleukin 1, alpha	2q14
IL1B	interleukin 1, beta	2q14
IL4	interleukin 4	5q31.1
IL4R	interleukin 4 receptor	16p12.1-p11.2
IL5	interleukin 5	5q31.1
IL6	interleukin 6	7q21
IL10	interleukin 10	1q31-q32
IL12B	interleukin 12, beta	5q31.1-q33.1
IL12RB1	interleukin 12 receptor, beta-1	19p13.1
IL13	interleukin 13	5q31
IL18	interleukin 18	11q22.2-q22.3
TGFβ1	transforming growth factor, beta-1	19q13.1
TNFα	tumor necrosis factor, alpha	6p21.3
GM-CSF (CSF2)	granulocyte-macrophage colony-stimulating factor 2	5q31.1
STAT6	signal transducer and activator of transcription 6	12q13
IFNγ	interferon, gamma	12q14
Antigen Presentation Molecules		
HLA-A	major histocompatibility complex, class I, A	6p21.3
HLA-B	major histocompatibility complex, class I, B	6p21.3
HLA-DMA	major histocompatibility complex, class II, DM alpha	6p21.3
HLA-DMB	major histocompatibility complex, class II, DM beta	6p21.3
PSMB8 (LMP7)	proteasome subunit, beta-type, 8	6p21.3
PSMB9 (LMP2)	proteasome subunit, beta-type, 9	6p21.3
TAP1	transporter, ATP-binding cassette, major histocompatibility complex, 1	6p21.3
TAP2	transporter, ATP-binding cassette, major histocompatibility complex, 2	6p21.3
Others		
CTLA4	cytotoxic T lymphocyte-associated 4	2q33
KLK7 (SCCE)	kallikrein 7	19q13.33
RUNX1 binding site between SLC9A3R1- NAT9	runt-related transcription factor1 binding site between solute carrier family 9, isoform 3 regulatory factor 1 and N-acetyltransferase 9	17q25
SPINK5	serine protease inhibitor, Kazal-type, 5	5q32
Drug-Metabolizing Enzymes		
GSTP1	glutathione s-transferase, pi	11q13
GSTM1	glutathione s-transferase, mu-1	-13.3
GSTT1	glutathione s-transferase, theta-1	11.2
NAT2	N-acetyltransferase 2	23.1-p21.3

Table 2 Polymorphisms of Candidate Genes for Atopic Dermatitis

Gene symbol	SNP	Ref.
Pattern-Recognition Receptors		
CARD4 (NOD1)	haplotype (rs2736726 (A>G), rs2075817 (A>G), rs2975632 (C>T), rs3030207 (A>G), rs2075818 (C>G), rs2235099 (C>T), rs2075821 (A>G), rs2075822 (C>T), rs2907749 (A>G), rs2907718 (C>T), rs5743368 (A>G))	<u>24</u>
CARD15 (NOD2)	- 60A > G, 534G > C, 802T > C, 2104C > T, <u>2722G > C</u> , rs1077861 (intron10A > T), 2863G > A, 4278A > G, 3020C	25, <u>26</u>
CD14	- 1145G > A, - 1359G > T, - 550C > T, - <u>159C > T</u>	<u>27</u> , 28, 29
MBL2	Gly54Asp	30
TLR2	<u>rs5743708 (A > G)</u> , rs4696480 (T > A), rs3804099 (T > C), rs3804100 (T > C)	<u>31</u> , 32
TLR4	rs4986790 (A > G), rs4986791 (C > T), rs2770150 (T > C), rs6478317 (A > G), rs1927911 (C > T), rs2149356 (C > T), rs7873784 (G > C), rs1927906 (A > G)	31, 32
TLR6	rs5743810 (T > C)	33
Chemokines and Associated Molecules		
CCL2 (MCP-1)	- 2518A > G	63
CCL5 (RANTES)	- 403G > A, - <u>401G > A</u> , - 28C > G	63, <u>64</u>
CCL11 (Eotaxin)	- 426C > T, - 384A > G, 67G > A	67
CCL17 (TARC)	- 431C > T	71
CCR3	51T > C	75
CCR4	1014C > T	76
CMA1	- <u>1903A > G</u>	<u>77</u> , 78, 79, 80, <u>81</u> , <u>82</u>
Cytokines and Associated Molecules		
IL1RN	penta-allelic 86-bp tandem repeat in intron 2	100
IL1RL1 (ST2)	- <u>26999G > A</u> , - <u>27639A > G</u> , 744C > A, 11147C > T, 2992C > T, 5283G > A, 5860C > A	<u>101</u>
IL1A	- 899T > C	102
IL1B	- 1418T > C, - 511T > C, 315T > C, 3953T > C	100, 102, 103
IL4	- <u>590T > C</u> , - <u>589C > T</u> , 33T > C	<u>104</u> , <u>105</u> , 106
IL4R	- 3112C > T, - 1803T > C, - 327C > A, - 326A > C, - 186G > A, 223C > G > T > A, 1199C > A, 1291C > T, 1242T > G, 1307T > C, 1507C > T, <u>1727G > A</u> , 2356C > T	106, 107, <u>108</u> , <u>109</u>
IL5	- 703C > T	110
IL6	- 922A > G, - 174C > G	100, 102
IL10	- 1117G > A, - 1082G > A, - 854C > T, - 819T > C, - 592A > C, - 571C > A	100, 102, 106
IL12B	<u>1188A > C</u> , 4237G > A, 4496A > G, 4510G > A	106, <u>111</u>
IL12RB1	- 111A > T, - 2C > T, 4443C > T, 5970G > C, 17183T > C, 17369C > T, 25748T > C, <u>27637A > T</u>	<u>112</u>
IL13	- 1111C > T, - <u>1024C > T</u> , 704A > C, 1103C > T, <u>Arg144Gln</u> , 1293C > T	102, <u>105</u> , 106, <u>113</u> , <u>114</u> , <u>115</u>
IL18	- <u>137G > C</u> , - 133C > G, - 132A > G, 113T > G, 127C > T	116
TGFβ1	- 590C > T, 869C > T, <u>915G > C</u>	102, <u>117</u>
TNFα	- 1031T > C, - 863C > A, - 857C > T, - 308G > A, - 238G > A	100, 102, 103, 106
GM-CSF (CSF2)	- <u>1916T > C</u> , - <u>677C > A</u> , 3606T > C, 3928C > T	<u>103</u> , 119
STAT6	2964G > A, <u>13/14/15/16 GT repeat in exon 1</u> , short tandem repeat in exon 1	106, <u>120</u>
IFNγ	short tandem repeat in intron 1	106

POLIMORFISMI DEI GENI CANDIDATI

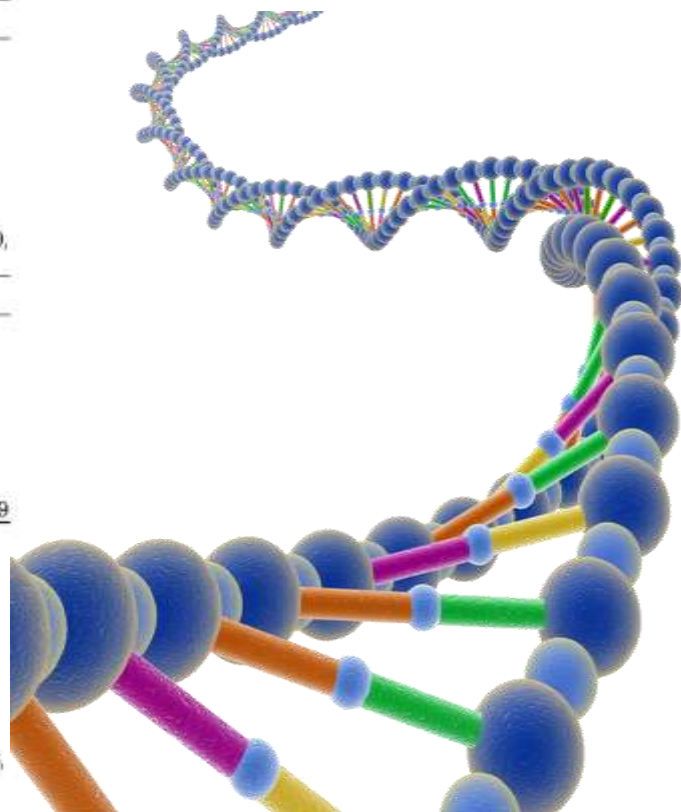
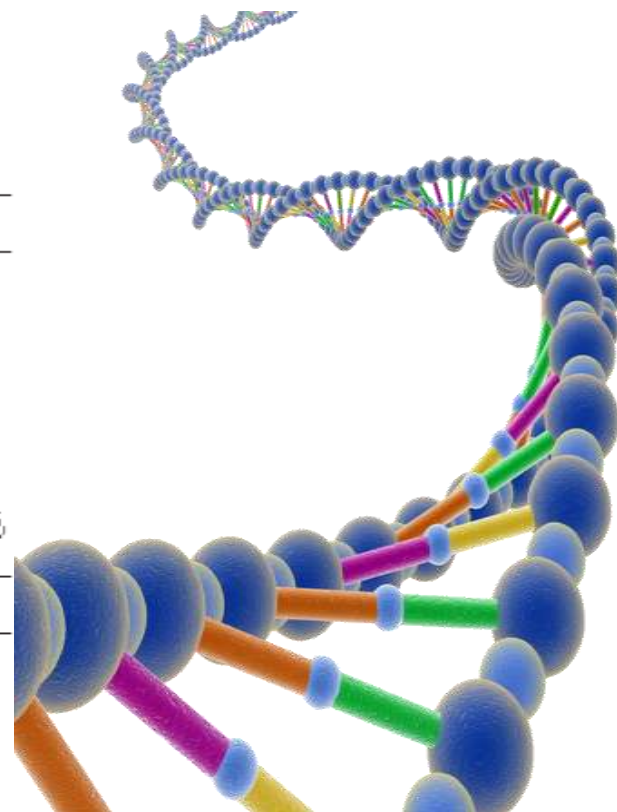


Table 2 (Continued)

Gene symbol	SNP	Ref.
Antigen-Presentation Molecules		
HLA-A	1, 2, 3, 11, <u>24</u> , 26, 29, 30, 31, 33, 66	<u>130</u>
HLA-B	7, 8, 13, 14, 16, 27, 35, 37, 38, 39, 46, 48, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 67, 71, 75	130
HLA-DMA	Val140Ile, Gly155Ala, Ile179Thr, 184Arg-His-Cys	131
HLA-DMB	144Ala-Glu-Val	131
PSMB8 (LMP7)	3911G > T, 3912C > T, 4069C > T	130
PSMB9 (LMP2)	Arg60His	130
TAP1	Val333Ile, <u>Gly637Asp</u>	130, <u>136</u>
TAP2	Ile379Val, <u>Thr565Ala</u> , <u>Ala665Thr</u> , Gln687Stop	<u>130</u>
Others		
CTLA4	49A > G	159
KLK7 (SCCE)	<u>AACC insertion</u>	<u>170</u>
RUNX1 binding site between SLC9A3R1- NAT9	rs734232 (G > A)	171
SPINK5	<u>IVS12 - 26C > T</u> , <u>IVS12 - 10A > G</u> , <u>IVS14 + 19G > A</u> , <u>IVS13 - 50G > A</u> , <u>1103A > G</u> , <u>1156G > A</u> , <u>1188T > C</u> , <u>1258G > A</u> , Asp106Asn, Gly463Gly, Val553Val, Leu756Leu, Gly804Gly	<u>173</u> , <u>174</u> , <u>175</u> (<u>175</u>), <u>176</u> , <u>177</u>
Drug-Metabolizing Enzymes		
GSTP1	1404A > G, 2294C > T	189
GSTM1	Deletion polymorphism (non-null or null genotype)	189
GSTT1	Deletion polymorphism (non-null or null genotype)	189
NAT2	481C > T, 590G > A, 857G > A	195, 196

POLIMORFISMI DEI GENI CANDIDATI



Disease susceptible SNPs found to be significant in one study and the corresponding references are single-underlined.

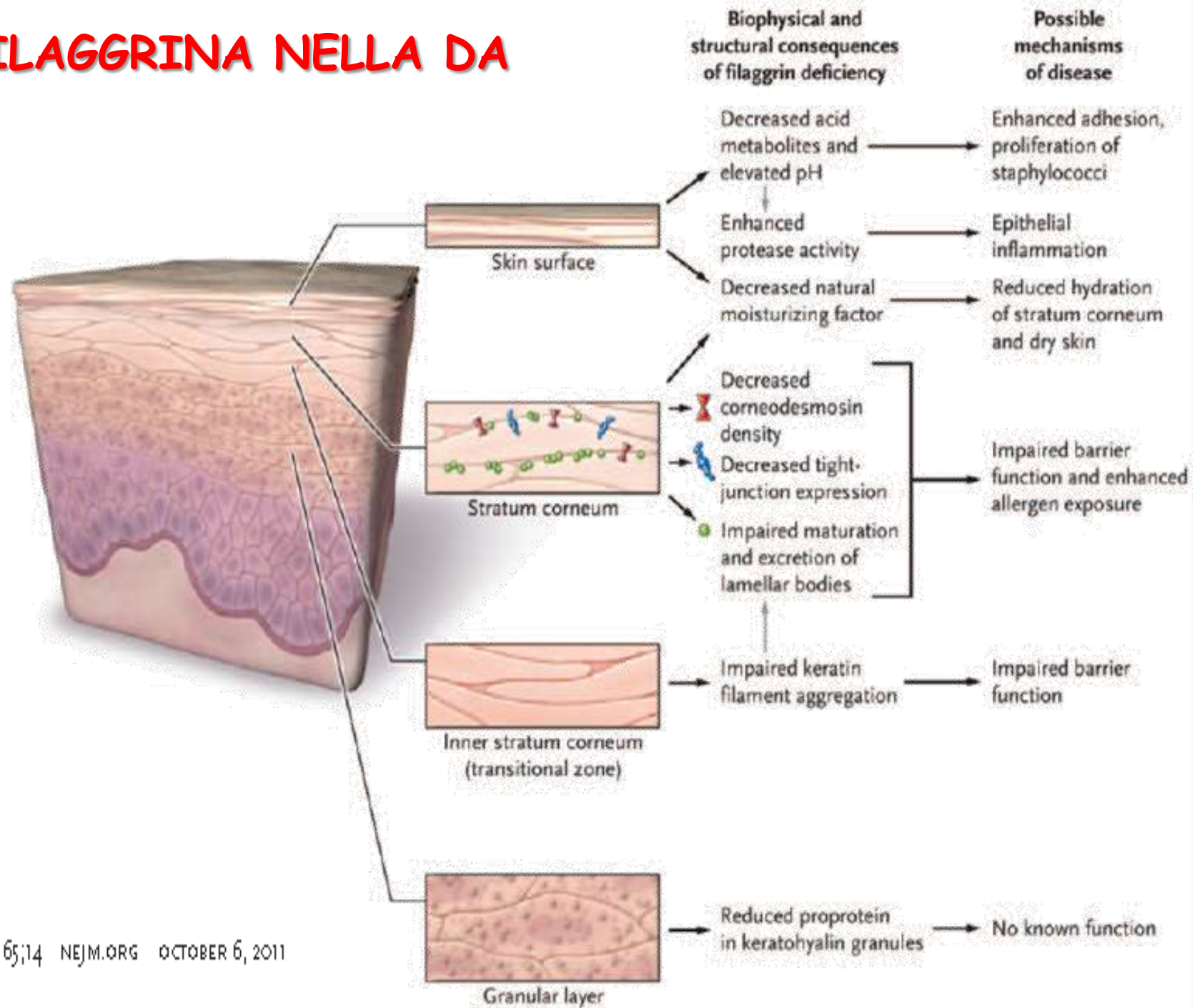
Disease susceptible SNPs found to be significant at least in two independent studies and the corresponding references are double-underlined.

Table 1 Susceptibility loci of atopic dermatitis identified by GWAS

Populations	Ref.	Chromosome	Genes
European	ref. 46	11q13.5	C11ORF30/LRRC32 (GARP)
Chinese	ref. 47	1p21.3 5q11.1 20q13.3	FLG TMEM232/SLC25A46 TNFRSF6B/ZGPAT
European EST	ref. 48	11q13 19p13.2 5q31	OVOL1 ACTL9 KIF3A/IL4/IL13
Japanese	ref. 53	2q12 3p21.33 3q13.2 6p21.3 7p22 10q21.2 11p15.4 20q13	IL1RL1/IL18R1/IL18RAP GLB1 CCDC80 the MHC region CARD11 ZNF365/EGR2 OR10A3/NLRP10 CYP24A1/PFDN4



LA FILAGGRINA NELLA DA



LE MUTAZIONI DEL GENE DELLA FILAGGRINA

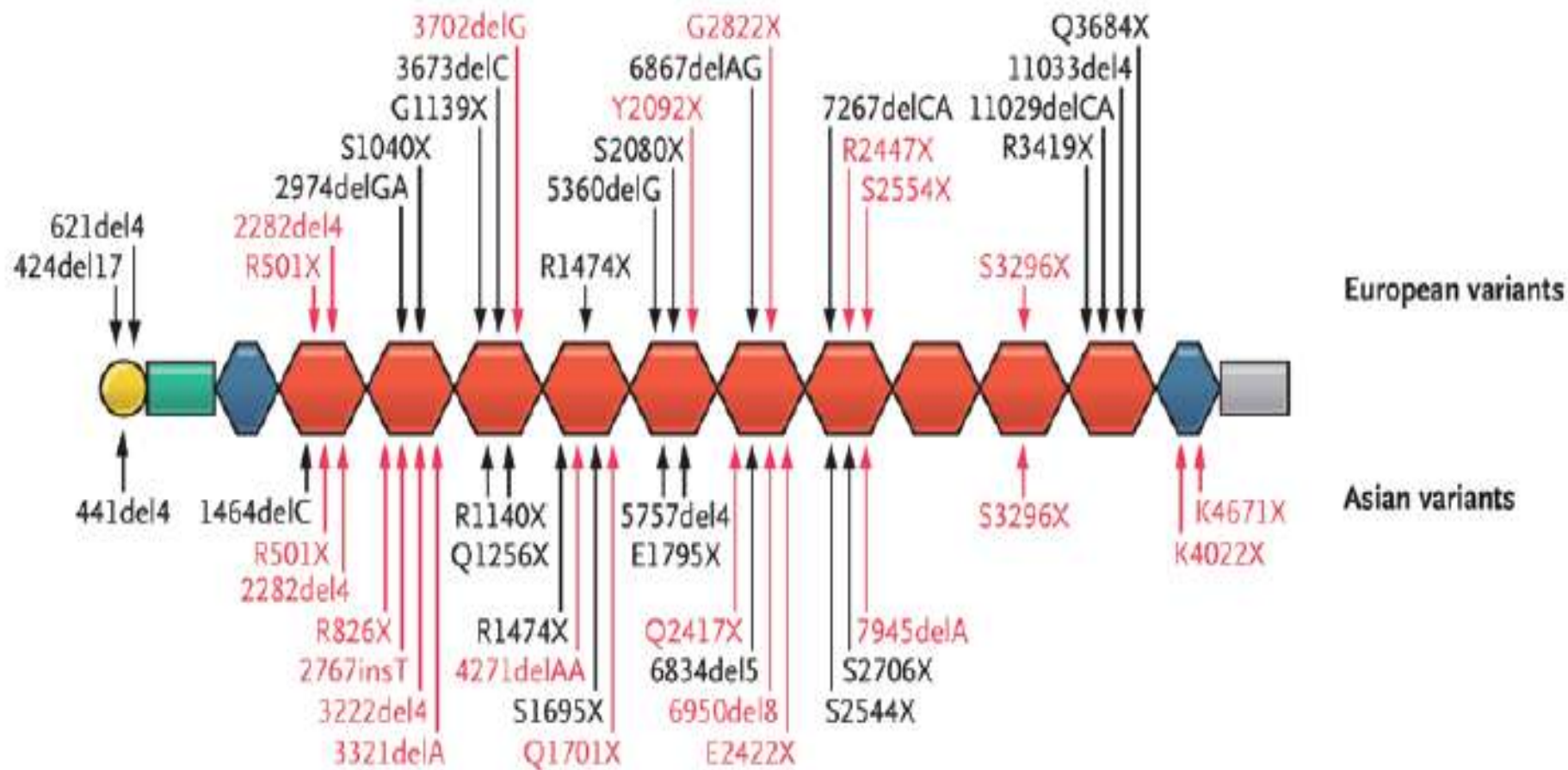


TABLE I. Comparison of clinical and biophysical features of patients with AD with (AD_{FLG}) and without ($AD_{NON-FLG}$) filaggrin mutations*

	Clinical features	Biophysical features
AD_{FLG}	Palmar hyperlinearity	Severe decrease in NMF
	More persistent	pH
	↑ Allergic sensitization	IL-1 β
	↑ Risk of asthma	Type 1 interferon-mediated stress response
	↑ Severity of AD	
	↑ Eczema herpeticum	
$AD_{NON-FLG}$	No palmar hyperlinearity	Mild decrease in NMF
	Less persistent	pH lower compared with patients with AD_{FLG}
	Less allergic sensitization	IL-1 β low compared with patients with AD_{FLG}
	Lower risk of asthma	Dysregulation of lipid metabolic processes

GENOGEOGRAFIADELLA DERMATITE ATOPICA



FENOTIPO
IPERLINEARITA' PALMARE
↓
GENOTIPO
SEGNO DI MUTAZIONE FLG

FENOTIPI DELLA DERMATITE ATOPICA

- Esordio nella prima infanzia con successiva remissione
- Esordio nella prima infanzia con eczema grave persistente
- Esordio Adolescenza-adulto con lieve-moderata eczema
- Esordio Adolescenza-adulto con eczema grave persistente

- Livelli aumentati di IgE con sensibilizzazione ad allergeni alimentari ed inalanti (estrinseca)
- Non-IgE mediata (intrinseca)
- AD con infezione da *S. aureus*/colonizzazione
- AD con storia di infezioni virali diffuse (ad esempio, eczema erpetico)



FIG 4. Clinical phenotypes in patients with AD: eczema herpeticum (A), *S aureus*-colonized AD (B), mild AD (C), and severe AD (D). Fig 4, A and B, are from Boguniewicz and Leung.¹⁰⁸ Fig 4, C and D, were contributed by Dr Emma Guttman-Yassky at the Icahn School of Medicine at Mt Sinai, New York.

5 DERMATITI A CONFRONTO

	SCORAD	Fam	PROV	IgE UI/ml	FLG	IS
	38	++	ME	130	-	=
	63	++	ME	220	MUT. R501X DEL.22 82del4	 IL-23
	92	++	ME	1500 Esclusa S. IperIgE	3321 delA 6850 del8.	 IL-23
	84 Eczema erpetico	++	ME	754	-	 IL-23  CD4
	90 Eczema impetiginizzato	+++	ME	512	-	 IL-23  IgA

GIULIA E I SUOI POLIMORFISMI

INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY

Vol 24, no. 4 (S), 0-0 (2011)

TLR2 AND TLR4 GENE POLYMORPHISMS AND ATOPIC DERMATITIS IN ITALIAN CHILDREN: A MULTICENTER STUDY.

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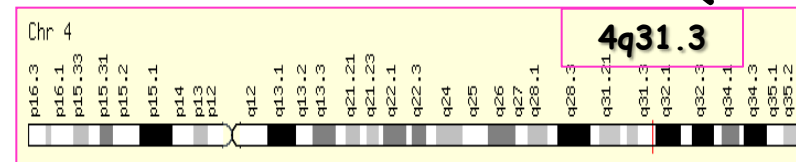
**Department of Internal Medicine, Azienda Ospedaliera Universitaria San Martino, Genoa, Italy



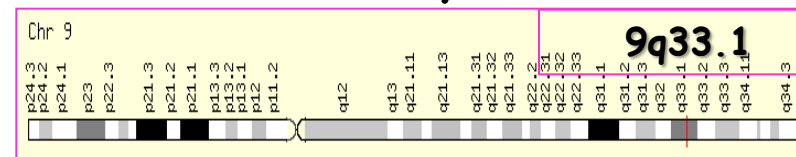
Table 1. Demographic characteristics of Italian atopic dermatitis (AD) patients and AD negative healthy control subjects

	<u>AD</u>	<u>AD negative</u>
	Number (%)	
Total	187	150
Gender		
Male	96 (51.3)	77 (51.3)
Female	91 (48.7)	73 (48.7)
Age*	8.0 (0.5-12)	9.0 (1.0-13)
SCORAD ^o	34(+/-18)	n.d.
Total IgE (kU/l)	782((+/-30)	≤3.5
AD stage		n.a.
Mild to moderate	132 (70,6%)	
Severe	55 (29,4%)	

TLR2 A-16934T; R753Q



TLR4 D299G, T399I



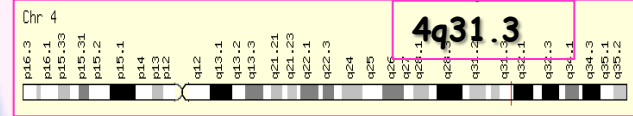
DERMATITE ATOPICA

FENOTIPO

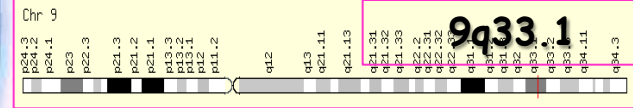


GENOTIPO

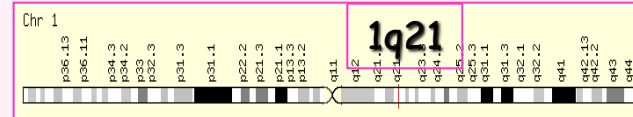
TLR2 A-16934T; R753Q



TLR4 D299G, T399I



MUT. R501X DEL. 2282del4

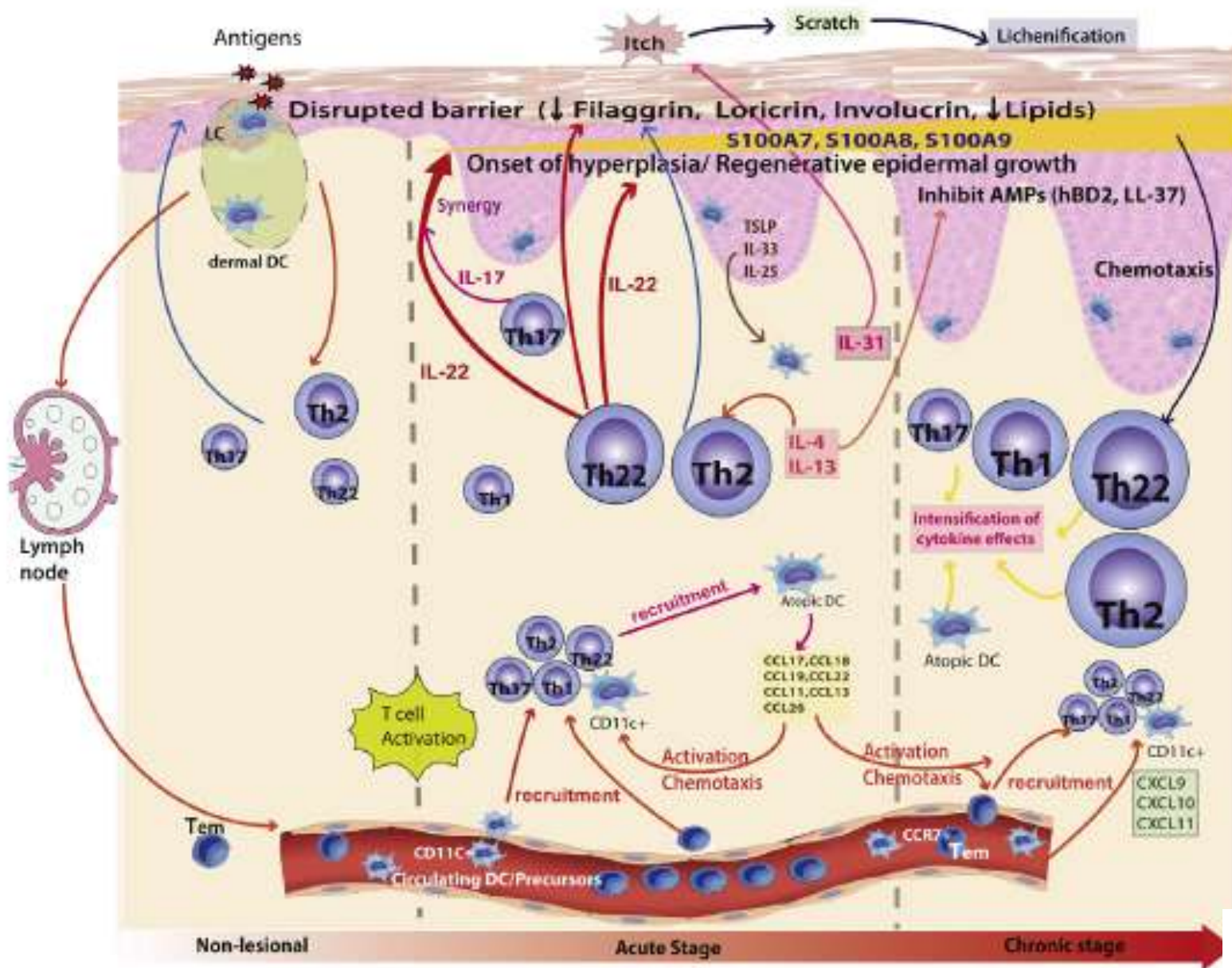


↑ **IL-23, IL-18**

↑ **gE**

↓ **VIT. D**

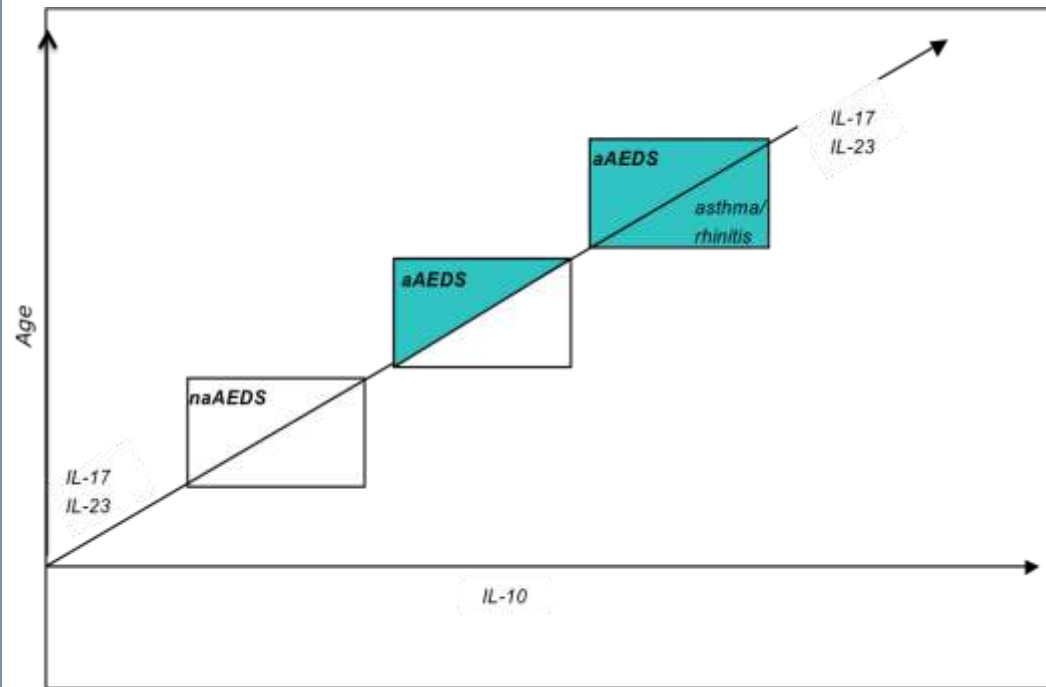
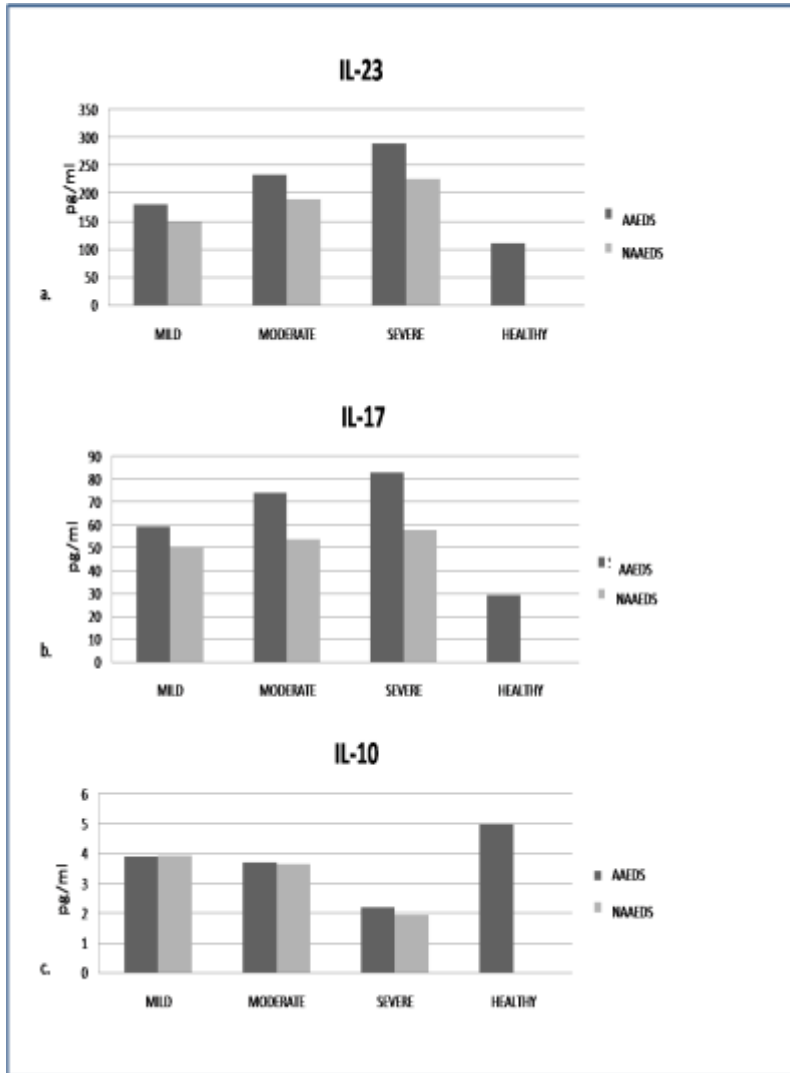
PROFILI GENETICI ED IMMUNOLOGICI E FENOTIPI DI DA



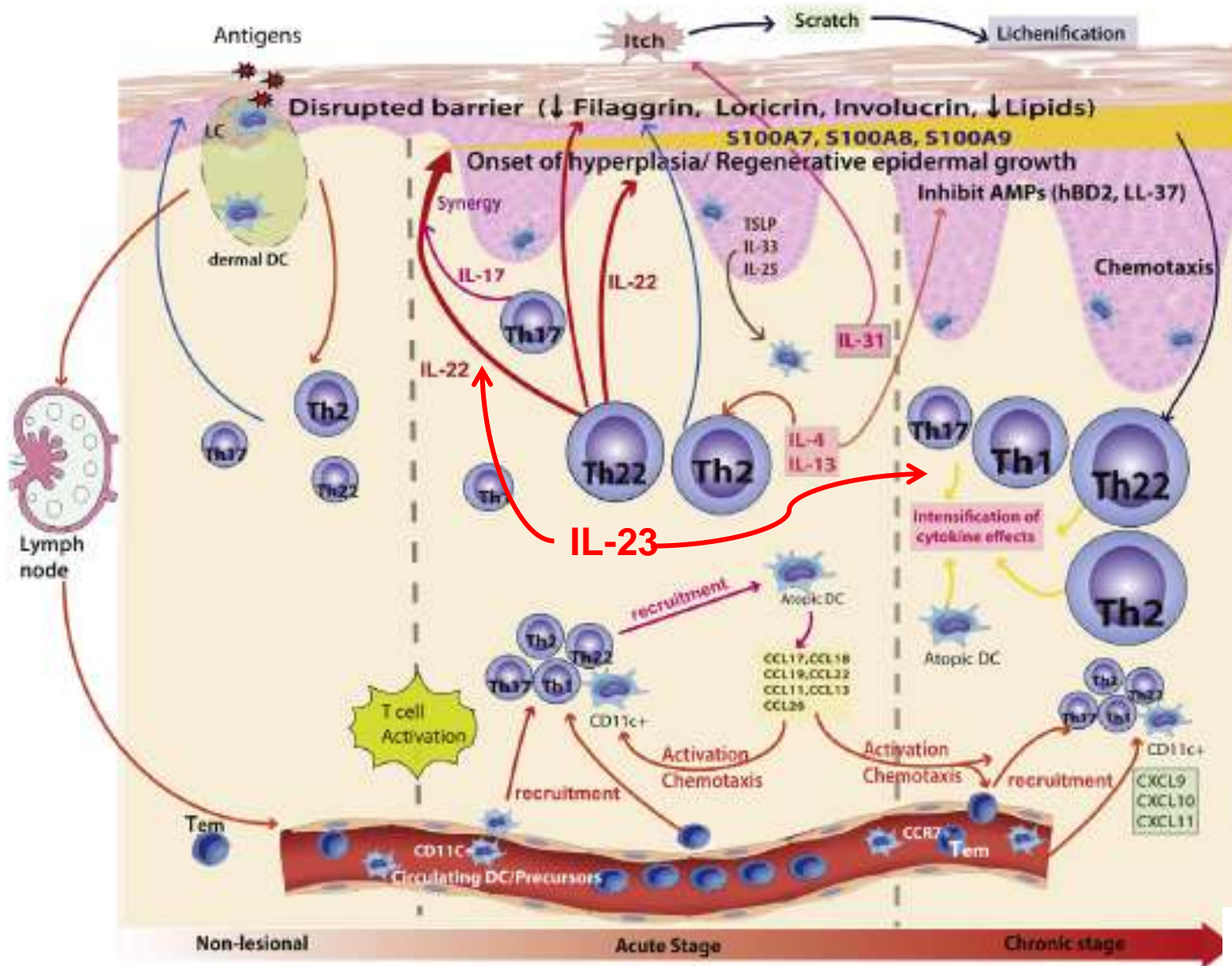
Donald Y. M. Leung, MD, PhD,^a and Emma Guttman-Yassky, MD, PhD^b

Interleukin-17, interleukin-23, and interleukin-10 serum levels in children with AEDS and their relationship with clinical severity

Leonardi Salvatore, Cuppari Caterina, Manti Sara, Filippelli Martina, Borgia Francesco, Briuglia Silvana, Cannavò Patrizia, Salpietro Annamaria, Arrigo Teresa, Salpietro Carmelo



PROFILI GENETICI ED IMMUNOLOGICI E FENOTIPI DI DA



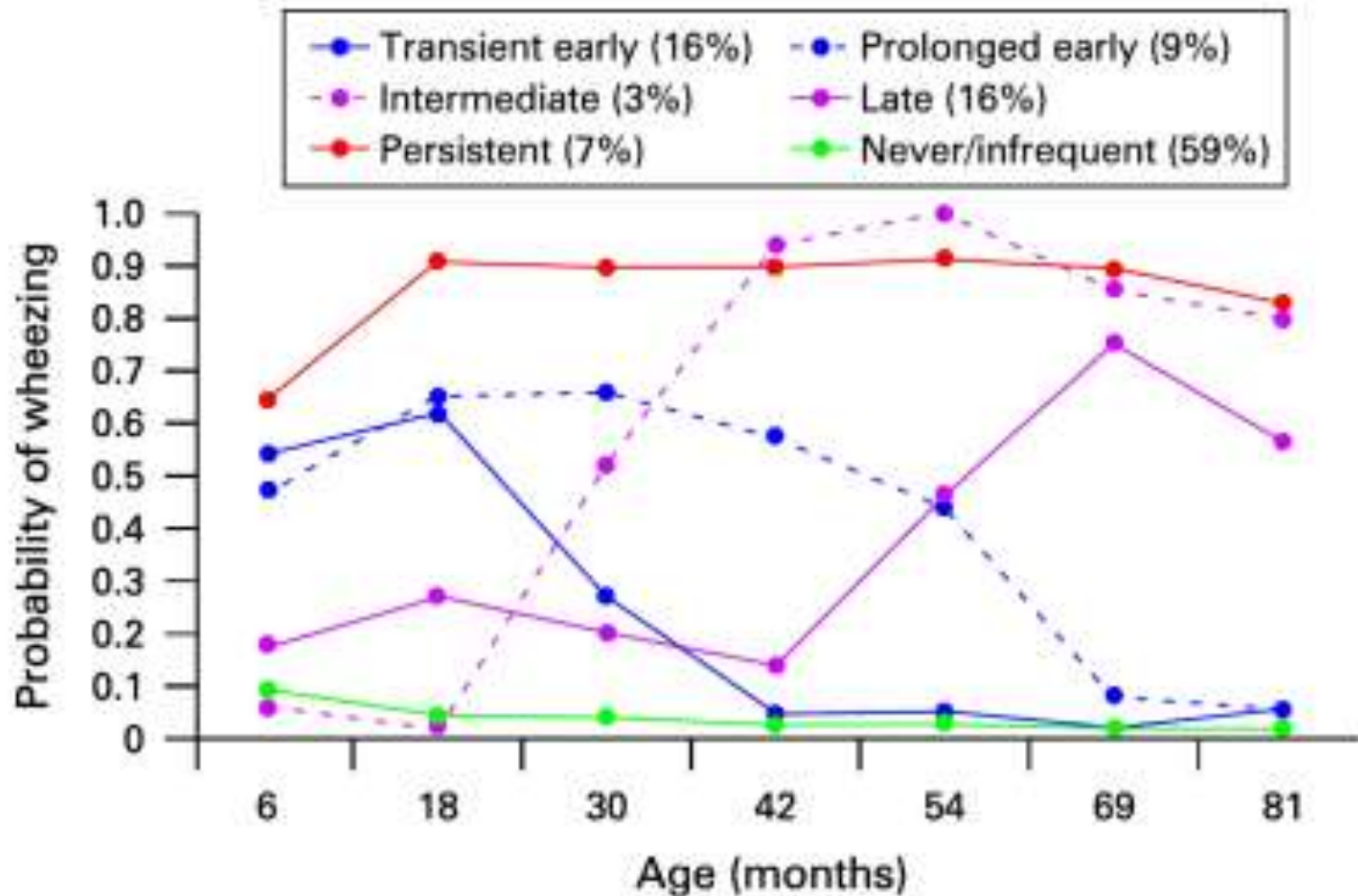
Donald Y. M. Leung, MD, PhD,^a and Emma Guttman-Yassky, MD, PhD^b



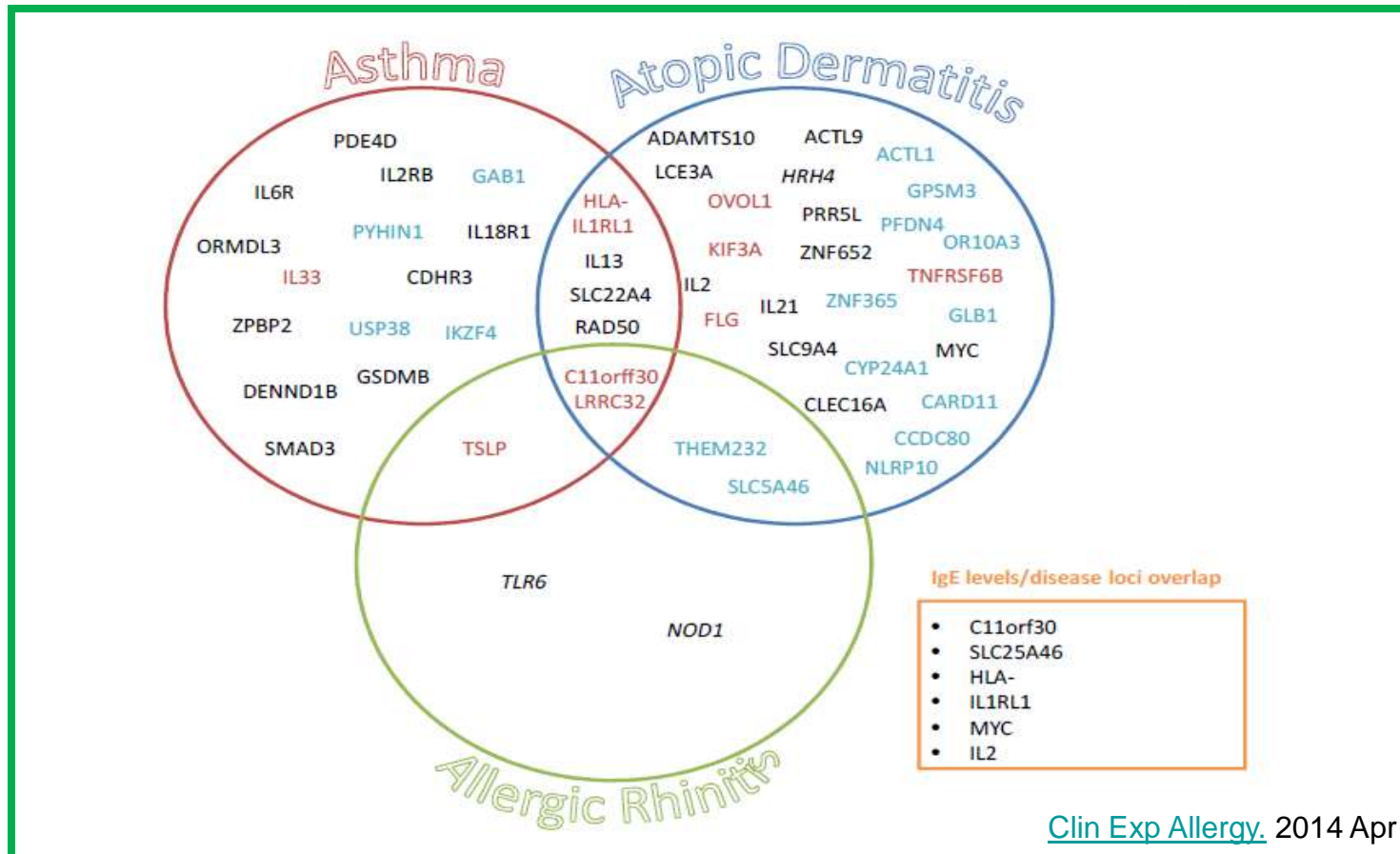
LE DIVERSE FACCE
DELL'ASMA



I FENOTIPI DEL WHEEZING



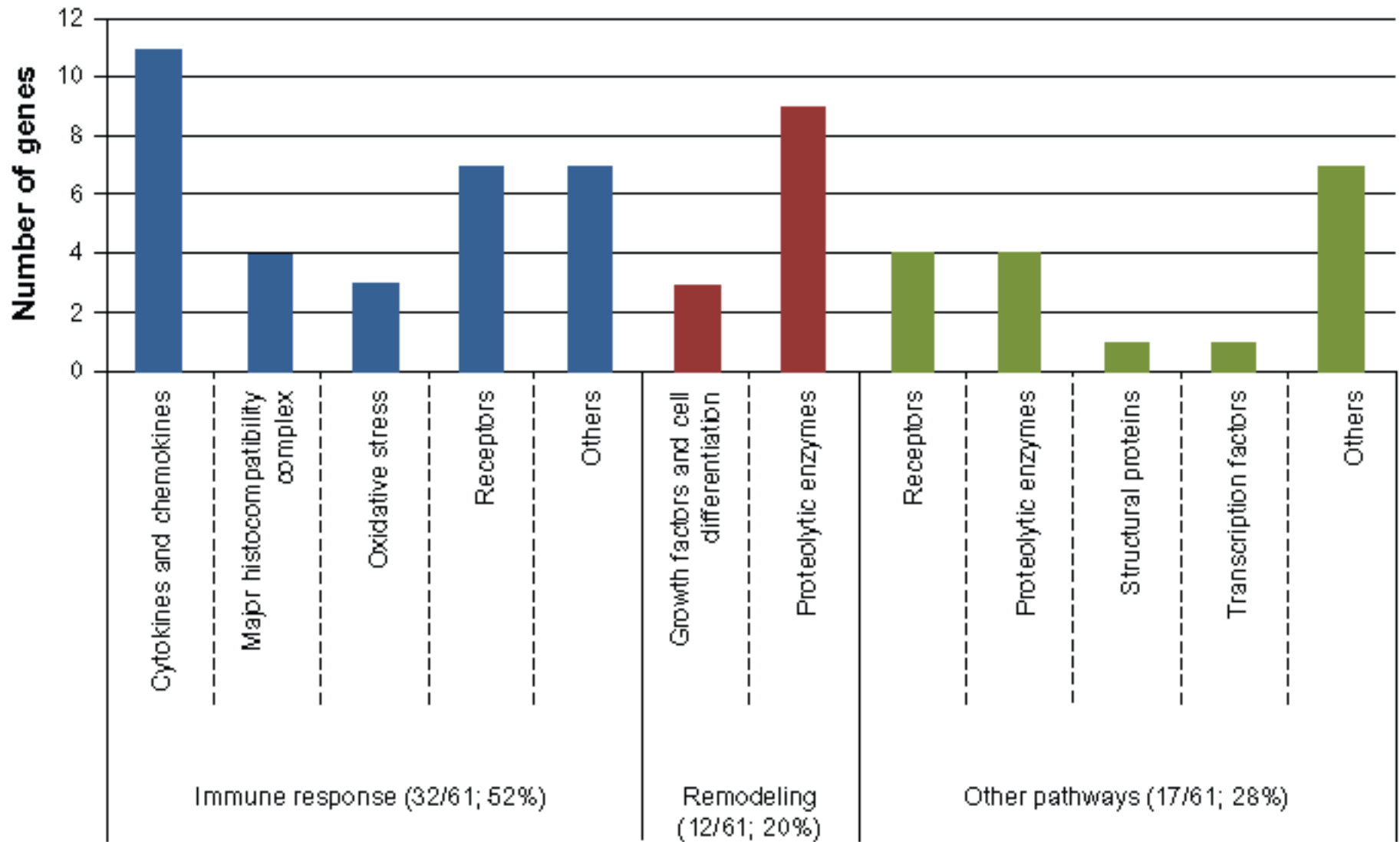
Henderson J, Granell R, Heron J et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974–80.



I geni candidati per l'asma ad oggi identificati sono numerosi (**più di 100**) e possono essere suddivisi in 4 gruppi:

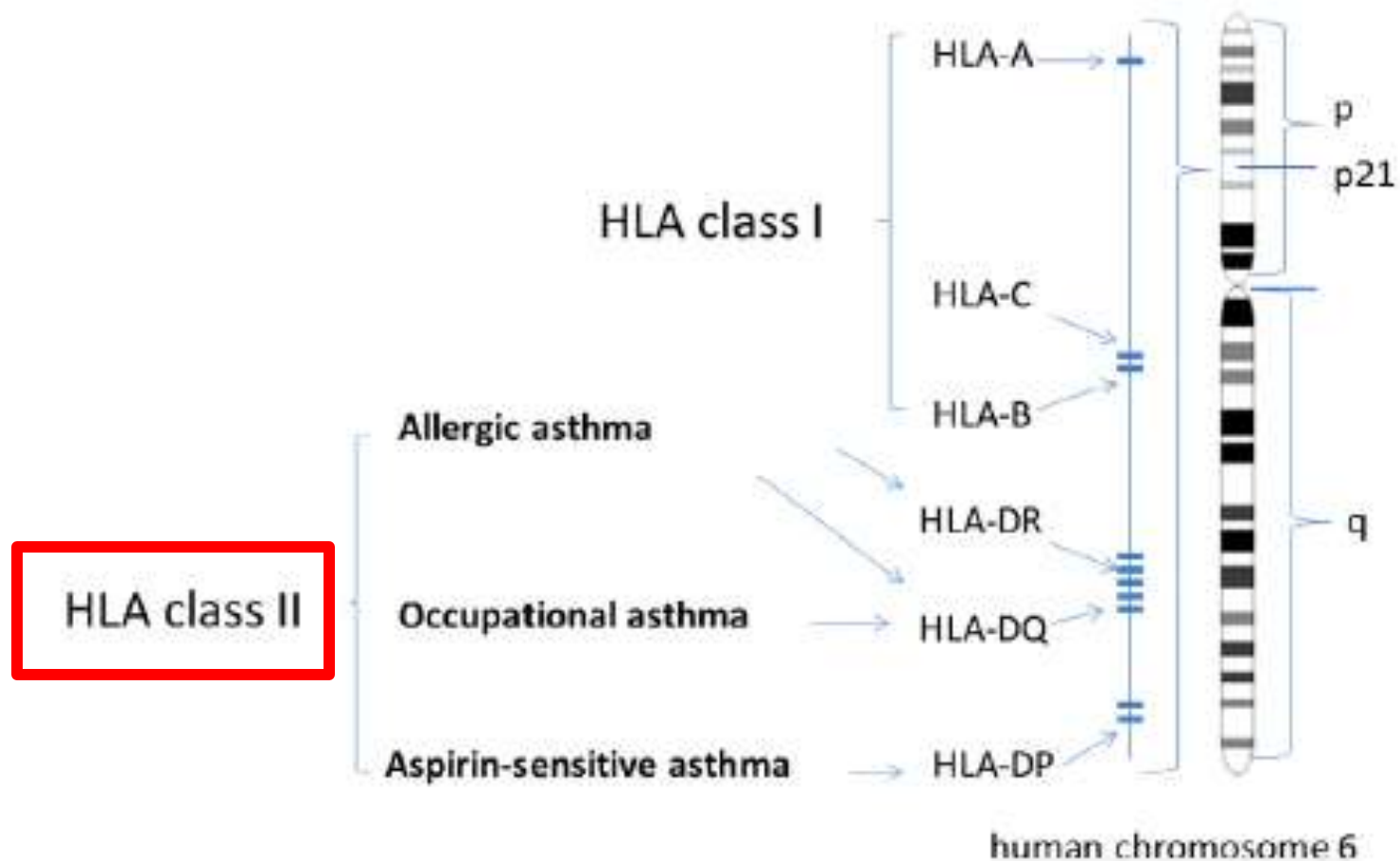
- geni coinvolti nella **presentazione dell'antigene e nell'inizio della risposta immune** (ad es. i geni del sistema HLA di classe I e II, CD14)
- geni coinvolti **nella flogosi bronchiale** (geni che codificano per le diverse citochine quali IL-4, IL-5, IL-13 ed il loro recettori)
- geni identificati tramite "positional cloning": ADAM 33, DPP10
- geni coinvolti nella **risposta al trattamento farmacologico** (ad es. geni che codificano per il recettore H2 adrenergico, per i cistenil-leucotrieni)
- E' verosimile che più alterazione a carico di più geni conferiscano la suscettibilità alla comparsa di asma

ASSOCIATED GENES WITH ASTHMA



HLA and asthma phenotypes/endotypes: A review

Eirini Kontakioti^a, Kalliopi Domvri^a, Despina Papakosta^{a,*}, Michail Daniilidis^b



Genetic variations in toll-like receptor pathway genes influence asthma and atopy

R. Tesse, R. C. Pandey & M. Kabesch

Center for Pediatrics, Clinic for Pediatric Pneumology, Allergology and Neonatology, Hannover Medical School, Hannover, Germany

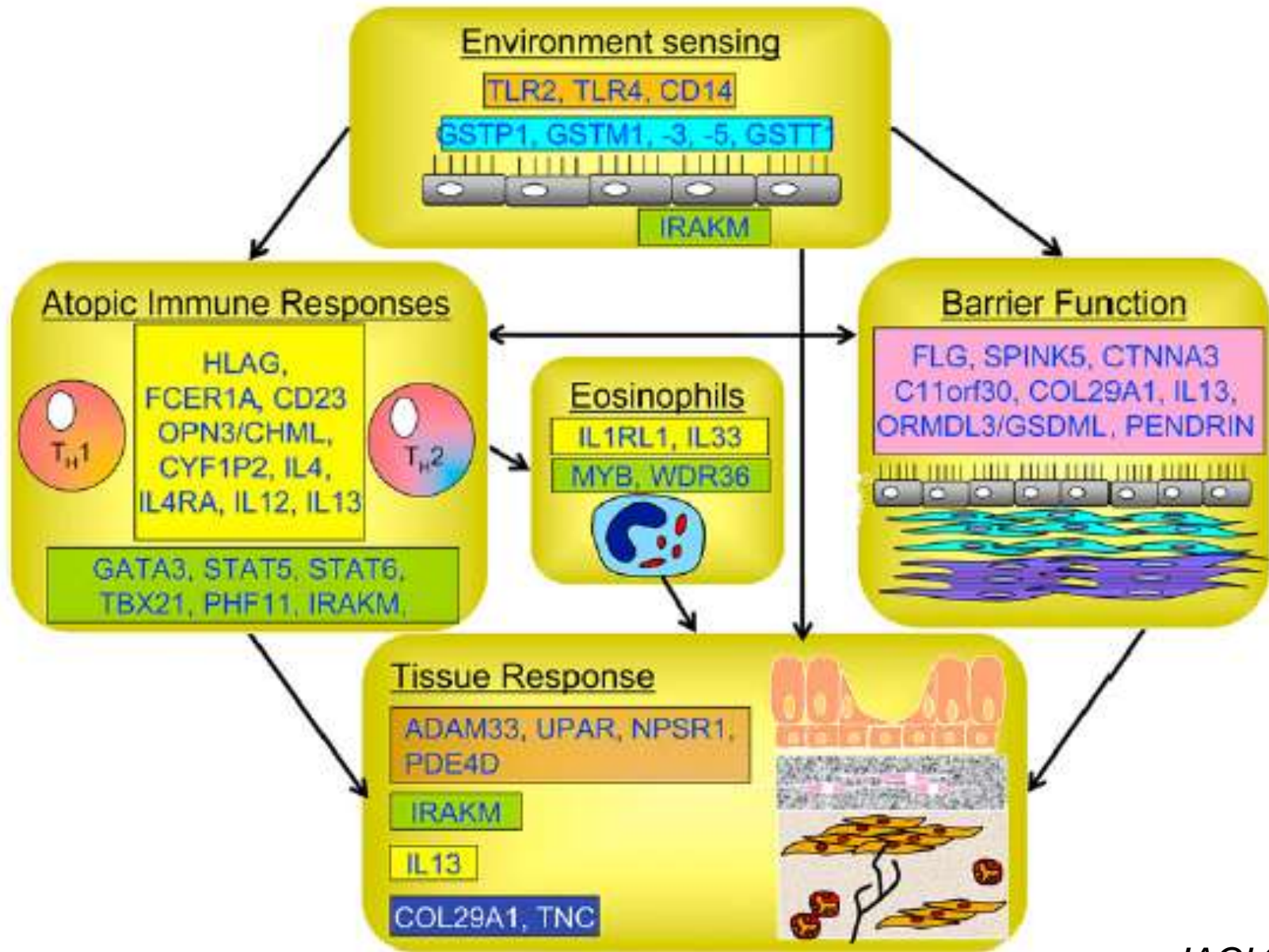


Table 1 Overview of the associations of CD14 and toll like receptors (TLRs) polymorphisms (rs numbers) with atopic disorders and other human diseases, restricted to studies with more than 200 probands

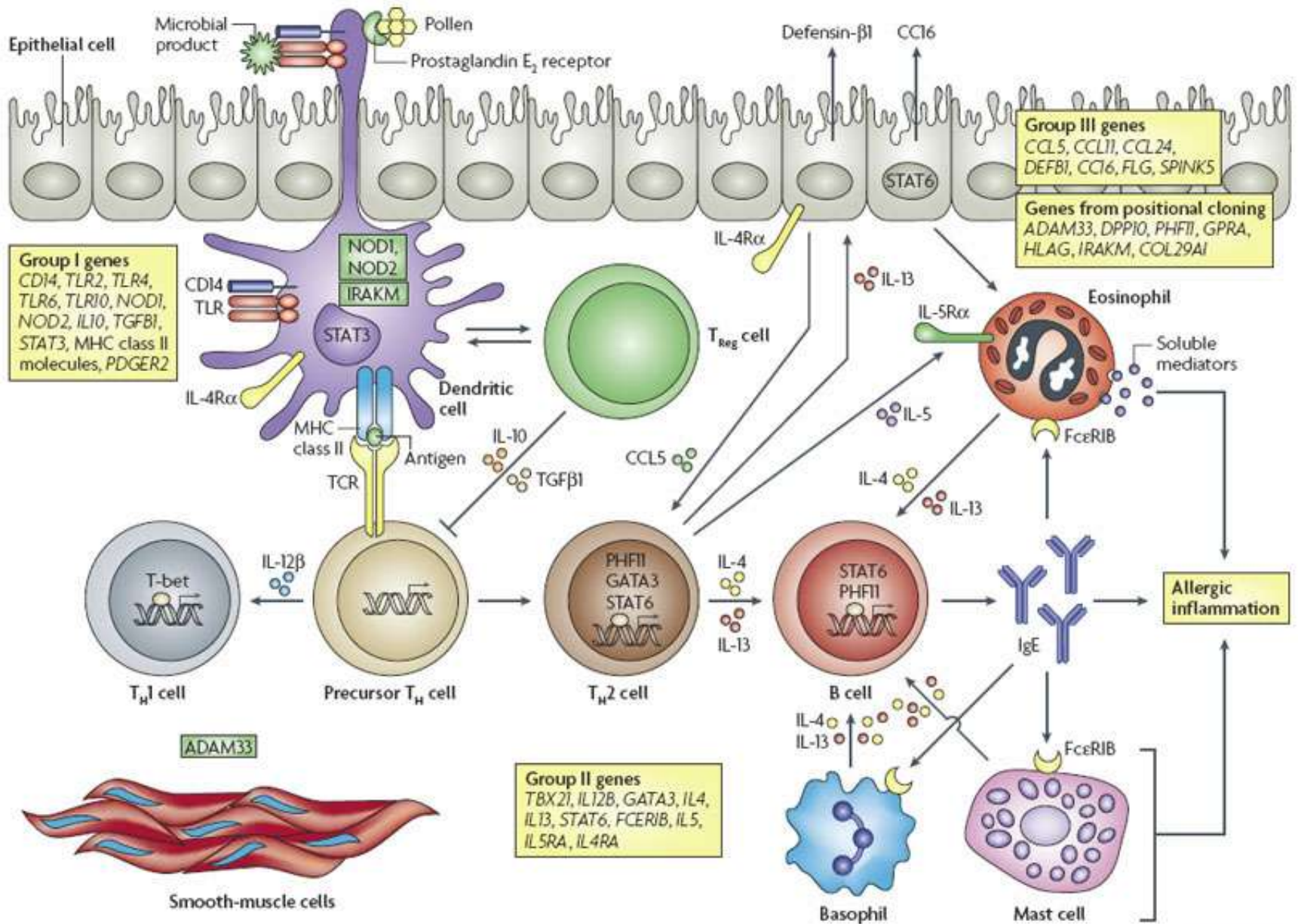
GENE	SNP rs	Association with diseases (reference number)			
		Asthma	Atopic eczema	Atopic sensitization	Infectious inflammation autoimmunity
CD14	rs2569190	No (48, 79)	Yes (50)	Yes (47, 51, 82, 83)	Sepsis (87, 88)
TLR1	rs5743595	Yes (55)	NR	NR	NR
	rs4833095	Yes (55)	NR	NR	NR
TLR2	rs4696480	Yes (38)	NR	Yes (38)	Sepsis (87)
	rs3804099	Yes (55)	NR		TB Meningitis (89)
	rs5743708	No (40)	No (56)	Yes (60)	NR
TLR4	rs4986790	Yes (37)	No (56)	No (90)	Sepsis (88); RA (91)
	rs4986791	Yes (55)	NR	NR	NR
TLR6	rs5743789	Yes (55)	No	NR	NR
	rs5743810	Yes (55)	No (92)	NR	NR
TLR7	rs5743781	Yes (66)	NR	NR	NR
TLR8	rs5744077	Yes (66)	NR	NR	NR
TLR9	rs5743836	No (55)	Yes (64)	No (65)	SLE (93)
	rs187084	Yes (55)	NR	No (65)	NR
TLR10	rs11096956	Yes (68)	NR	NR	NR
	rs4129009	Yes (55, 68)	NR	NR	NR

SNP, single nucleotide polymorphism; NR, not reported; TB, tuberculosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

GENOTIPI DIVERSI... STESSA PATOLOGIA



ASSOCIATED GENES WITH ASTHMA



4 TIPI DI ASMA A CONFRONTO

CLASSIFICAZIONE GRAVITA'
Segni clinici prima della terapia



	SINTOMI	SINTOMI NOTTURNI	FEV ₁ o PEF
<p>Livello 4</p> <p>Grave persistente</p>	<p><u>Continui.</u></p> <p>attività fisica limitata</p>	<p>Frequenti</p>	<p>< 60% predetto</p> <p>variabilità >30%</p>
<p>Livello 3</p> <p>Moderato persistente</p>	<p><u>Giornalieri</u></p> <p>attacchi influenzano l'attività</p>	<p>> 1 volta/settimana</p>	<p>60%-80% predetto</p> <p>variabilità >30%</p>
<p>Livello 2</p> <p>Lieve persistente</p>	<p>> 1 volta/settimana ma < 1 volta/giorno</p>	<p>> 2 volte/mese</p>	<p>≥ 80% predetto</p> <p>variabilità 20%30%</p>
<p>Livello 1</p> <p>Intermittente</p>	<p>< 1 volta/settimana tra gli attacchi: asintomatico e PEFnormale</p>	<p>< 2 volte/mese</p>	<p>≥ 80% predetto</p> <p>variabilità <20%</p>

FENOTIPI DELL'ASMA

ENDOTIPI DELL'ASMA

ASMA ALLERGICO

- EOSINOFILICO
- TH2 MEDIATO

RESPONSIVO A:

- Steroidi
- ITS
- Anti IgE
- Anti IL-5
- Anti IL-4/13

ASMA INTRINSECO

- EOSINOFILICO
- NEUTROFILICO
- ASSOCIATO AD AUTOAb/ SUPERAg

- steroido responsivo
- steroido resistente

ASMA NEUTROFILICO

- ATTIV. RISP. INNATA
- ECCESSIVO RECLUT. HDAC2
- INCREMENTO DELLA SOPRAVV. NEUTROFLI

- Steroido resistente
- RESPONSIVO A:
- antiossidanti
- .antibiotici
- Anti TNFa
- Regolat.HDAC (teofillina)

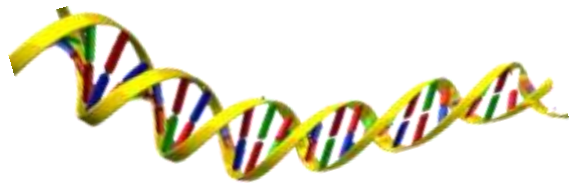
DA ECCESSIVO REMODELLING

- ALTER. INFIAMMAZ
- ANORMALE ATTIVAZ DELL'EPITELIO
- ANOMALIE MUSCOLAT
- DIFETTI DEI MECC DI RIPARAZ.

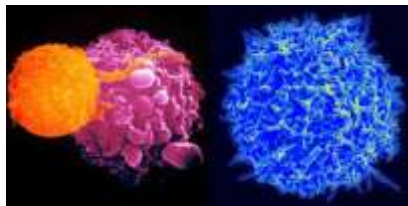
- Steroido resistente
- Terapie Possibili a livello:
- muscolare
- Epiteliale
- vasale

ASMA INDOTTO DA ASPIRINA

DALLA GENOGEOGRAFIA



ALLA IMMUNOGEOGRAFIA



TERAPIA PERSONALIZZATA

