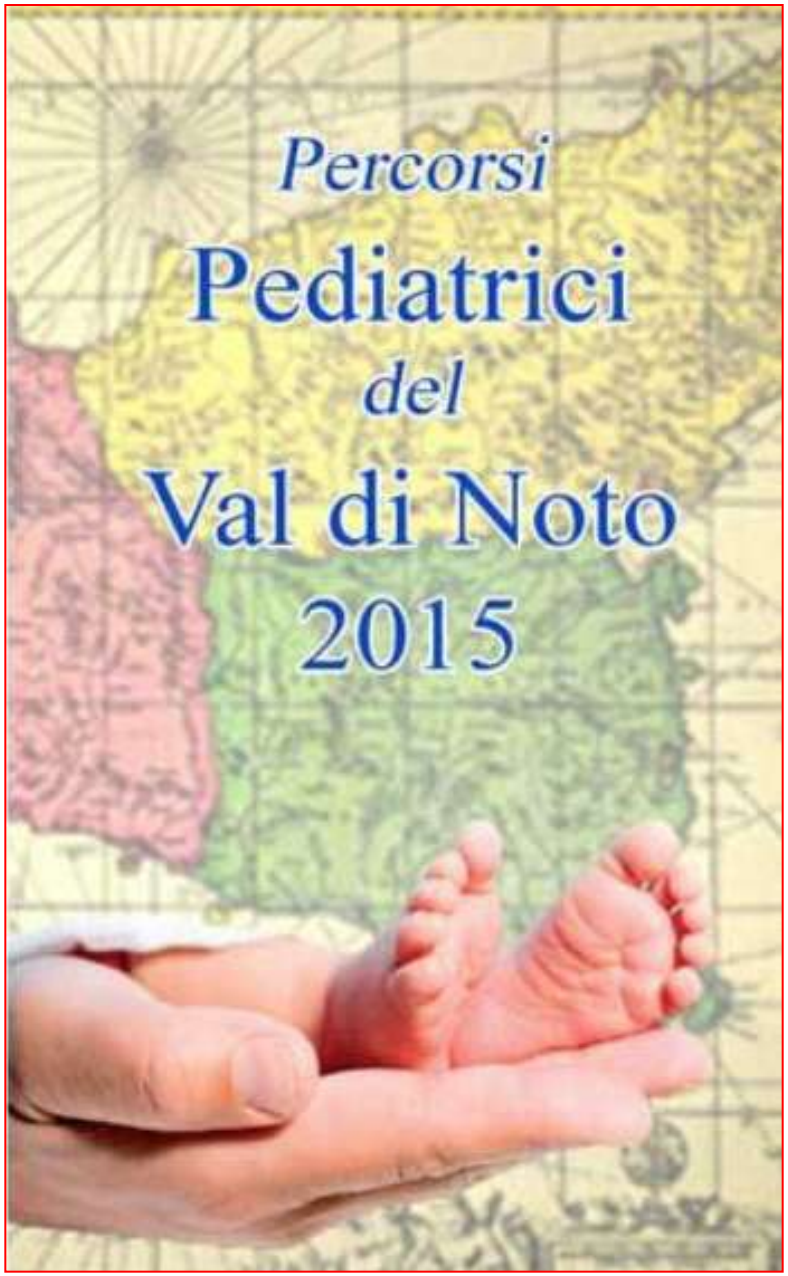


Sabato 31 Gennaio 2015

Il Pediatra e la Genetica
Coordinano: Rosario Salvo, Natalino Zisa

08.00-08.15 Registrazione dei Partecipanti

08.15-08.45 **Approccio al Bambino Dismorfico**
S. Briuglia (Messina)

08.45-09.15 **Genetica ed Endocrinopatie**
T. Arrigo (Messina)

09.15-09.45 **Ereditarietà delle Malattie Genetiche**
C. Salpietro (Messina)

09.45-10.15 **Linfoistiocitosi Emofagocitica Familiare**
M. Aricò (Ragusa)

10.15-10.20 Coffee Break

10.20-10.50 **Follow up della Sindrome di Down**
E. Moschella (Messina)

10.50-11.50 **Sindrome di Marfan, Clinica e Genetica**
M. Cutrupi, V. Procopio (Messina)

11.50-12.20 **Genetica delle Malattie Allergiche**
C. Cuppari (Messina)

12.20-12.30 *Pausa—Fast Lunch*

12.30-16.00 **Lavori di gruppo con discussione di casi clinici**

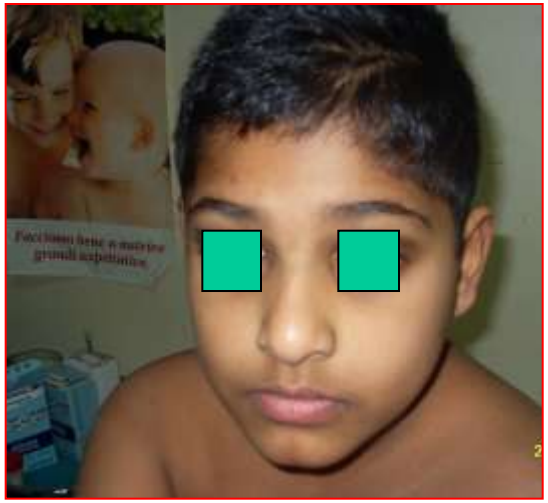
16.00-16.30 Discussione finale sui temi affrontati durante i lavori di gruppo

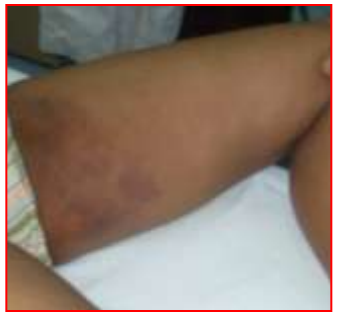
16.30-16.45 Compilazione questionario ECM e fine lavori

Accreditato per: 60 Medici **Crediti Assegnati**: 10

Discipline di riferimento:
Genetica Medica, Medicina Generale (Medici di famiglia), Pediatria, Pediatria (Pediatri di libera scelta)

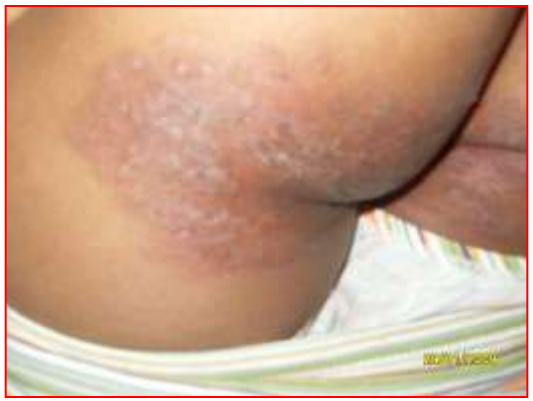
Sara Manti





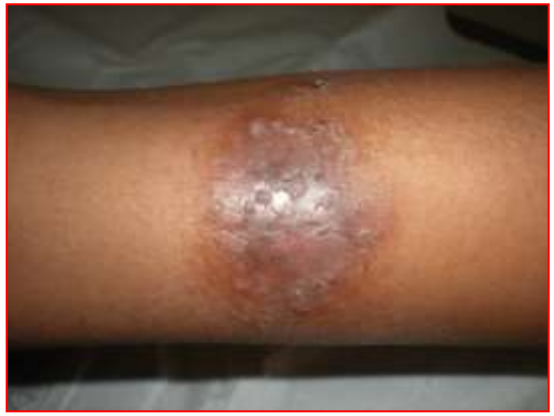
Rayan 6 anni
- 1 MESE: dermatite → latte di soia, idrolisati proteici con scarso beneficio
- 8 MESI: frequenti episodi di otiti, wheezing, diarrea, scarso accrescimento,

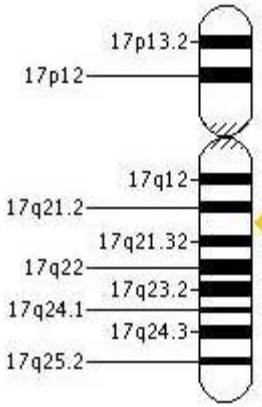
Cicli di corticosteroidi e antistaminici per *os e corticosteroidi* topici con parziali temporanee remissioni



EO:
- occhi infossati, sella nasale larga e punta del naso carnosa
- severa dermatite pruriginosa impetiginizzata
- presenza di elementi nodulari, di un particolare colore grigiastro (ascessi freddi)
- onicomicosi

Es. lab.:
Ipereosinofilia (5890 mmc), IgE 4121 UI/ml
negativi e/o nella norma: AGA, EMA, TGA, esame parassitologico delle feci, autoimmunità





SINDROME DA IPER-IGE

Tipizzazione molecolare :
Mutazioni 1144C>T del gene STAT3

TERAPIA :amoxicillina + acido clavulanico (51mg/kg in 2 somministrazioni)
TRAPIANTO MIDOLLO?

SINDROME CON IPER IgE o S. DI GIOBBE

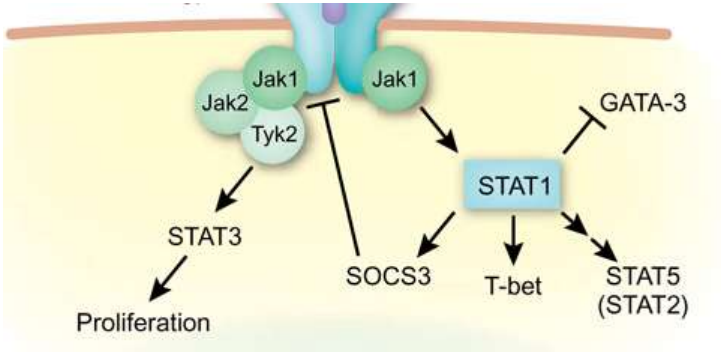
HIERIS (*Hyper-IgE Recurrent Infection Syndrome*) HIES (*Hyper-IgE Syndrome)*

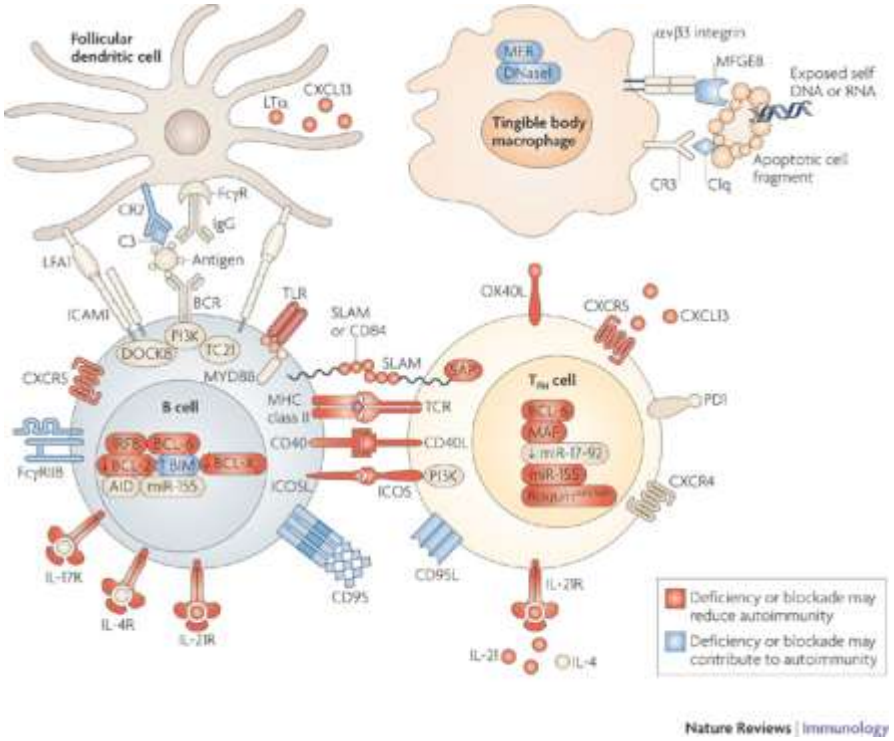
MUTAZIONI GENE STAT3 (17q21) ➡ **AD**

(5diverse mutazioni)

MUTAZIONE GENE Tyk2 (19p13.2)

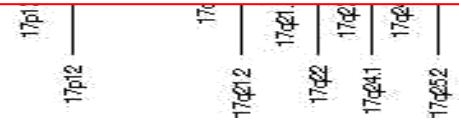
MUTAZIONE GENE DOCK8 (9p24.3) ➡ **AR**





AD-HIES 1:1.000.000 M=F

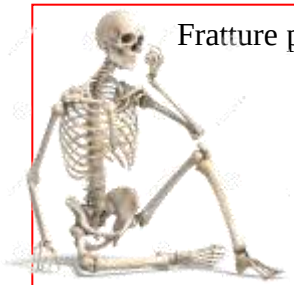
anafilassi, orticaria, angioedema, asma allergico



LIVELLI ELEVATI DI IGE NEL SIERO (>2000 IU/ML)

ASCESSI CUTANEI FREDDI RICORRENTI DA STAFILOCOCCO

FORMAZIONE DI PNEUMATOCELI



Fratture patologiche ricorrenti (ossa lunghe e coste).

Scoliosi di gravità variabile

Difetti della dentinogenesi

Alterazioni del cavo orale
(palato ogivale, rafe palatino e rughe palatine prominenti e rilevate, depressione centrale della lingua)

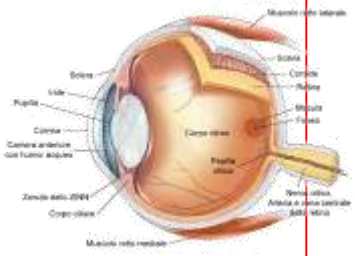
Aneurismi aortici e coronarici

Trombosi dell'arteria cerebellare e dotto venoso pervio congenito

Xantelasmi

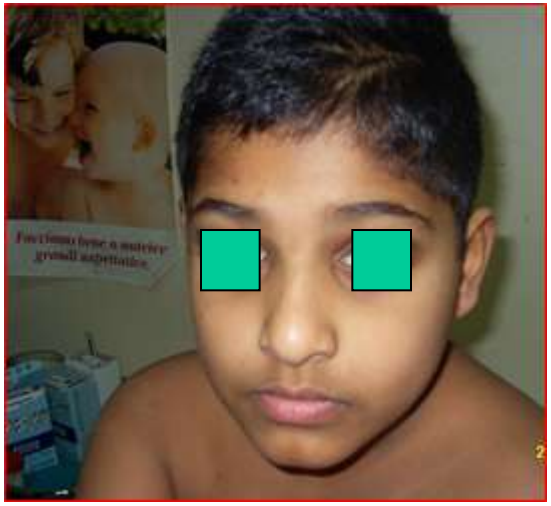
Chelasia gigante

Noduli palpebrali



Strabismo

Malattie linfoproliferative ed autoimmuni



FRONTE PROMINENTE

CUTE RUVIDA

OCCHI INFOSSATI

ASIMMETRIA FACCIALE

RADICE NASALE LARGA E PUNTA DEL NASO CARNOSA

PROGNATISMO

MUTAZIONI GENE STAT3 (17q21)

(5diverse mutazioni)

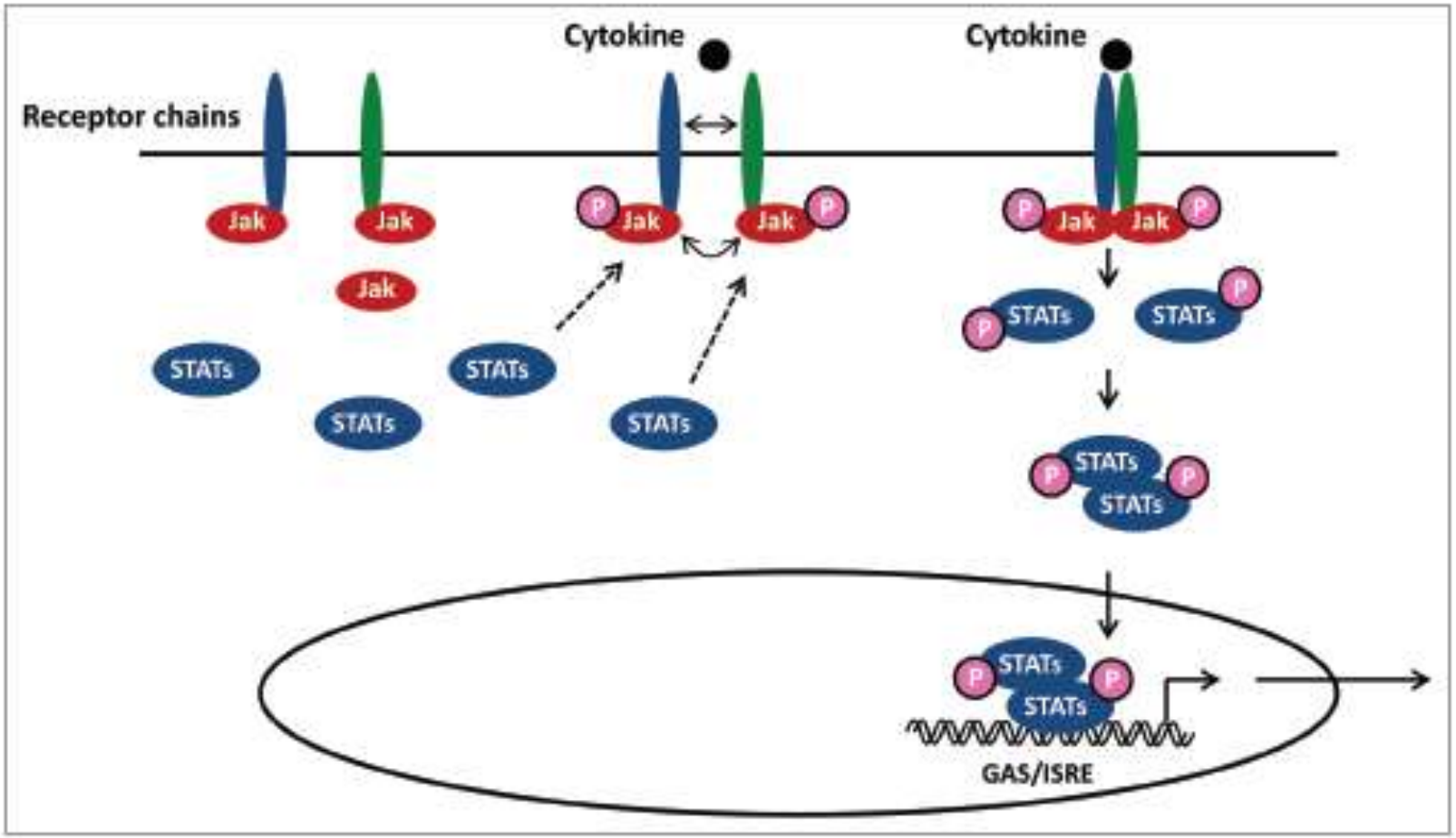


Figure 1. Principles in JAK-STAT signaling. Following receptor binding of a relevant cytokine or growth factor, the receptor undergoes homo- or hetero-dimerization and binds cytosolic JAKs (JAK1, 2, 3 or Tyk2) for receptor auto-phosphorylation and transactivation. This event allows recruitment of transcription factors belonging to the STAT family (STAT 1, 2, 3, 4, 5A, 5B or 6) that bind the cytoplasmic domain of the receptor through their SH2 domain. Phosphorylated STAT proteins subsequently undergo homo- or hetero-dimerization and translocate to the nucleus, where they induce transcriptional activation of target genes by binding to ISRE/GAS elements.

JAK-STAT 2:2, e23435; April/May/June 2013; © 2013 Landes Bioscience

MUTAZIONI GENE STAT3 (17q21)

(5diverse mutazioni)

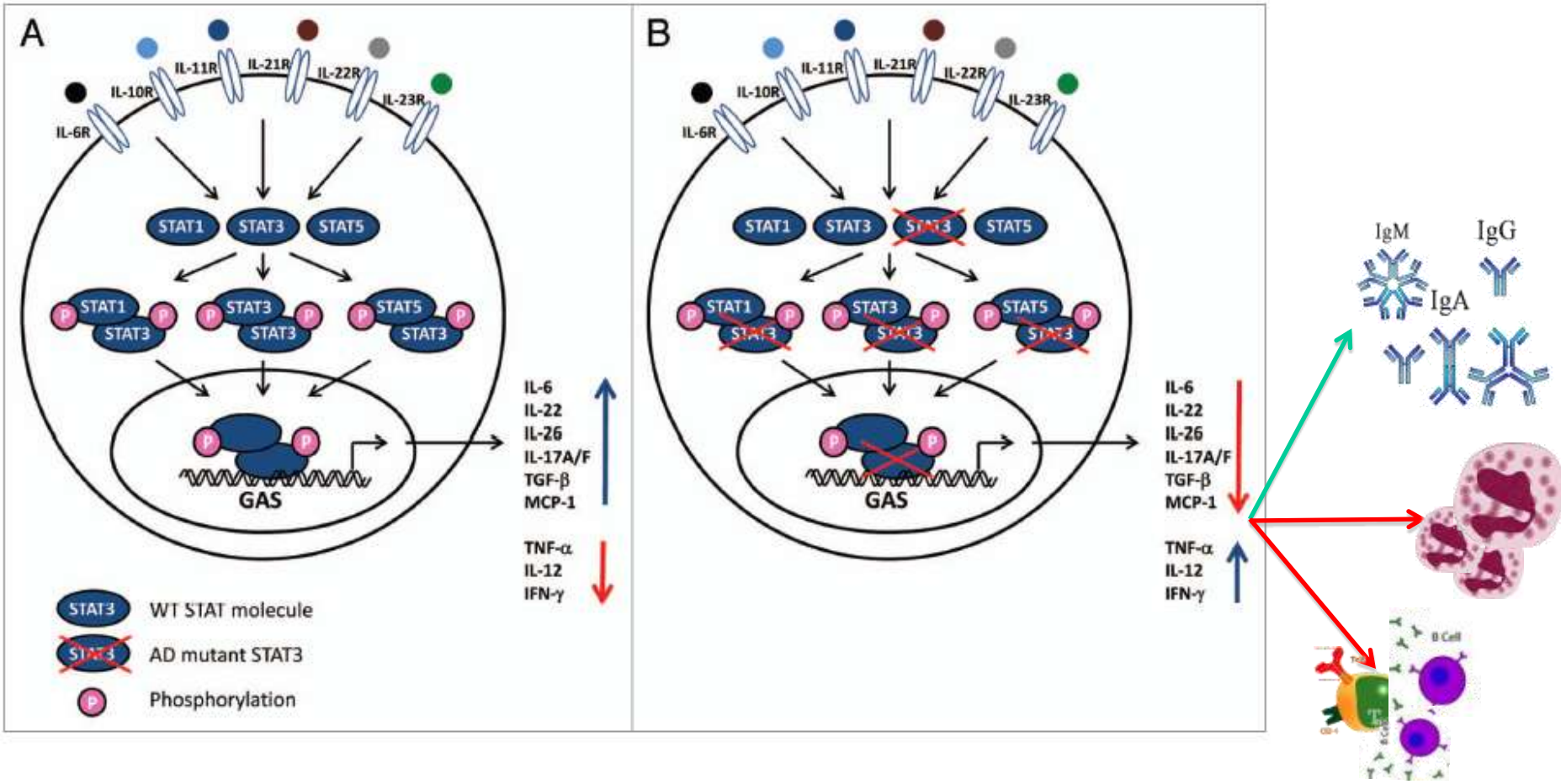


Figure 2. Impaired STAT3 function affects multiple pathways. (**A**) A wide range of cytokines and growth factors activate receptors utilizing the tyrosine kinases JAK2 and Tyk2 which trigger signaling pathways involving STAT3. Phosphorylated STAT3 can homo- or heterodimerize with other STAT3 molecules or STAT1 or STAT5, respectively. STAT complexes modulate transcription of various genes, including increased IL-6, IL-10, IL-17A/17F, IL-22, TGFβ, MCP1 production, as well as decreased TNFα, IL-12 and IFN-γ synthesis. (**B**) Mutations in STAT3 molecules can lead to dominant negative effects of the molecules, hence reducing or abolishing STAT3-dependent activities.

Table 1. Immunological and somatic phenotypes and associated pathogenesis in HIES

Clinical phenotype	Immunological abnormality
Staphylococcal cold abcesses (skin and lungs)	IL-6 ↓, IL-17 ↓, IL-22 ↓, β-defensin↓ Reduced neutrophil chemotaxis and function
Chronic mucocutaneous candidiasis	Th17 responses (IL-17A/F, IL21, IL-22)↓ Impaired antifungal immunity
Elevated serum-IgE	IL-21 signaling ↓
Atopy	IL-10 responses ↓, T regulatory cells ↓
B cell lymphoma	IL-21 signaling ↓ Disturbed B cell differentiation
Craniofacial abnormalities (craniosynostosis, childhood dentition, high-arched palate)	IL-11 signaling ↓
Pneumatocele	Increased matrix metalloprotease activity
Osteoporosis, scoliosis, fractures	Enhanced osteoclastogenesis and osteopenia
Vascular abnormalities (aneurysms, turtousity)	TGFβ signaling ↓, TNFα and RANTES production
Parenchymal brain lesions	Increased inflammation, demyelinization and astrocytosis following nerve injury

AR-HIES <1:1.000.000 M=F

Molluscum contagiosum
Papillomavirus umano

LIVELLI ELEVATI DI IGE NEL SIERO (>2000 IU/ML)

CMV
Herpes simplex e zoster

ASCESSI CUTANEI FREDDI RICORRENTI DA STAFILOCOCCO

FORMAZIONE [illegible] NEUMATOCELI

Fratture patologiche ricorrenti (ossa lunghe e coste).

Scoliosi [illegible] variabile

Difetti [illegible] ntinogenesi

A[illegible]avo orale
(palato [illegible], rafe p[illegible]o e rughe palatine prominenti e [illegible]ate, depressione centrale della lingua)

FRONTE PR[illegible]

[illegible]RUVIDA

OC[illegible]

ASIMME[illegible]ACCIALE

RADI[illegible] NASALE LARGA E PUNTA DEL NASO CARNOSA

PROGNATISMO

Paralisi del facciale

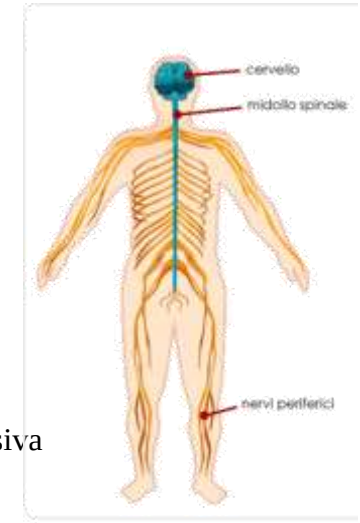
Emiplegia

Infarti cerebrali

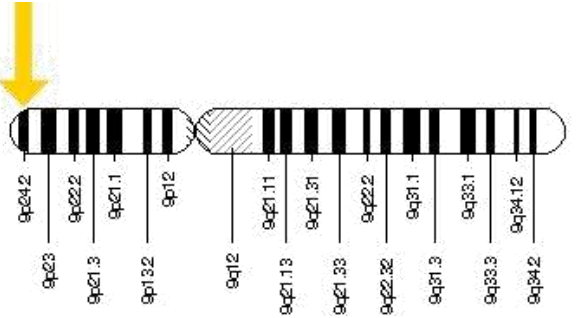
Meningiti

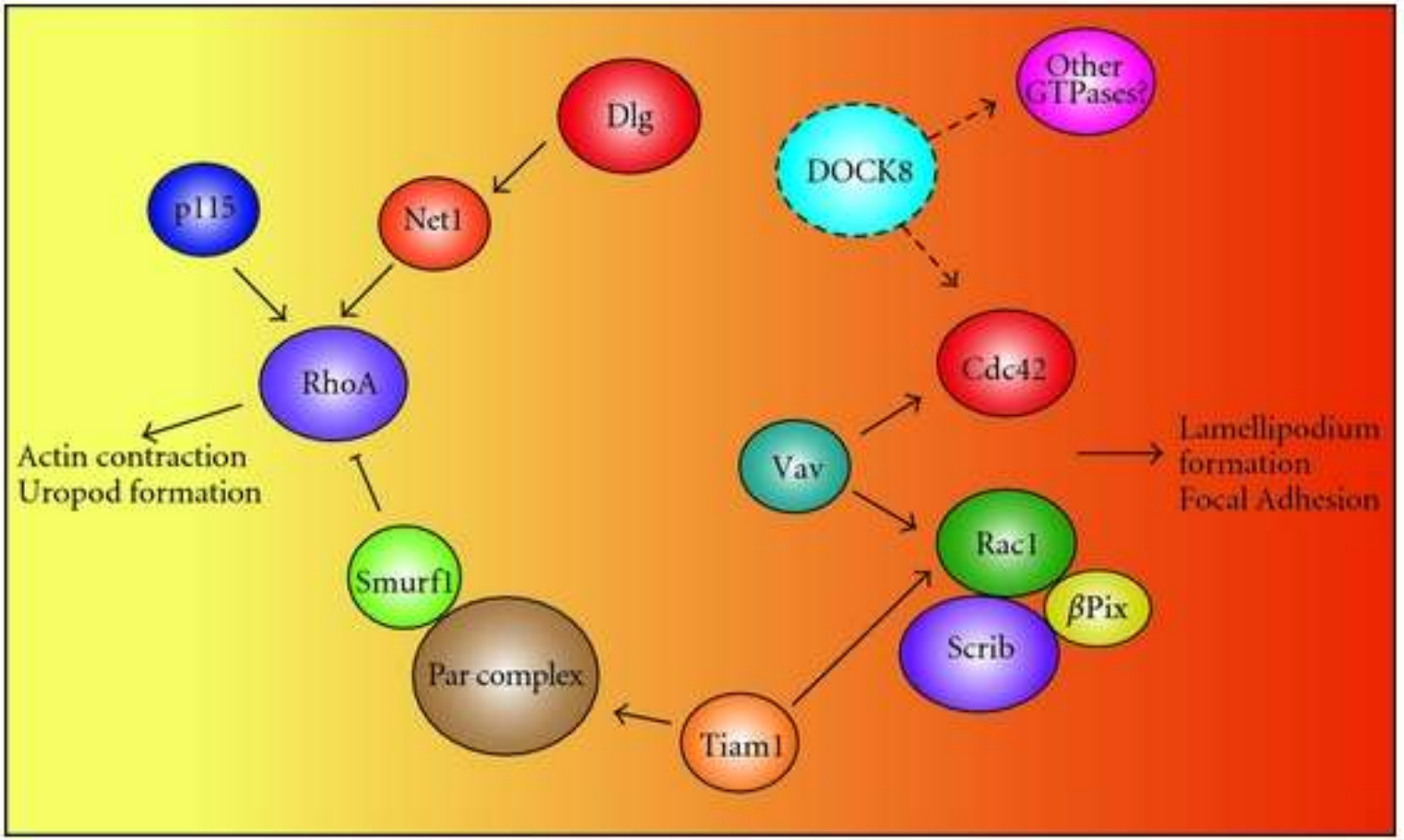
Encefaliti necrotizzanti

Leucoencefalopatia multifocale progressiva



MUTAZIONE GENE DOCK8 (9p24.3)





Nature Immunology 13, 525–52 (2012)

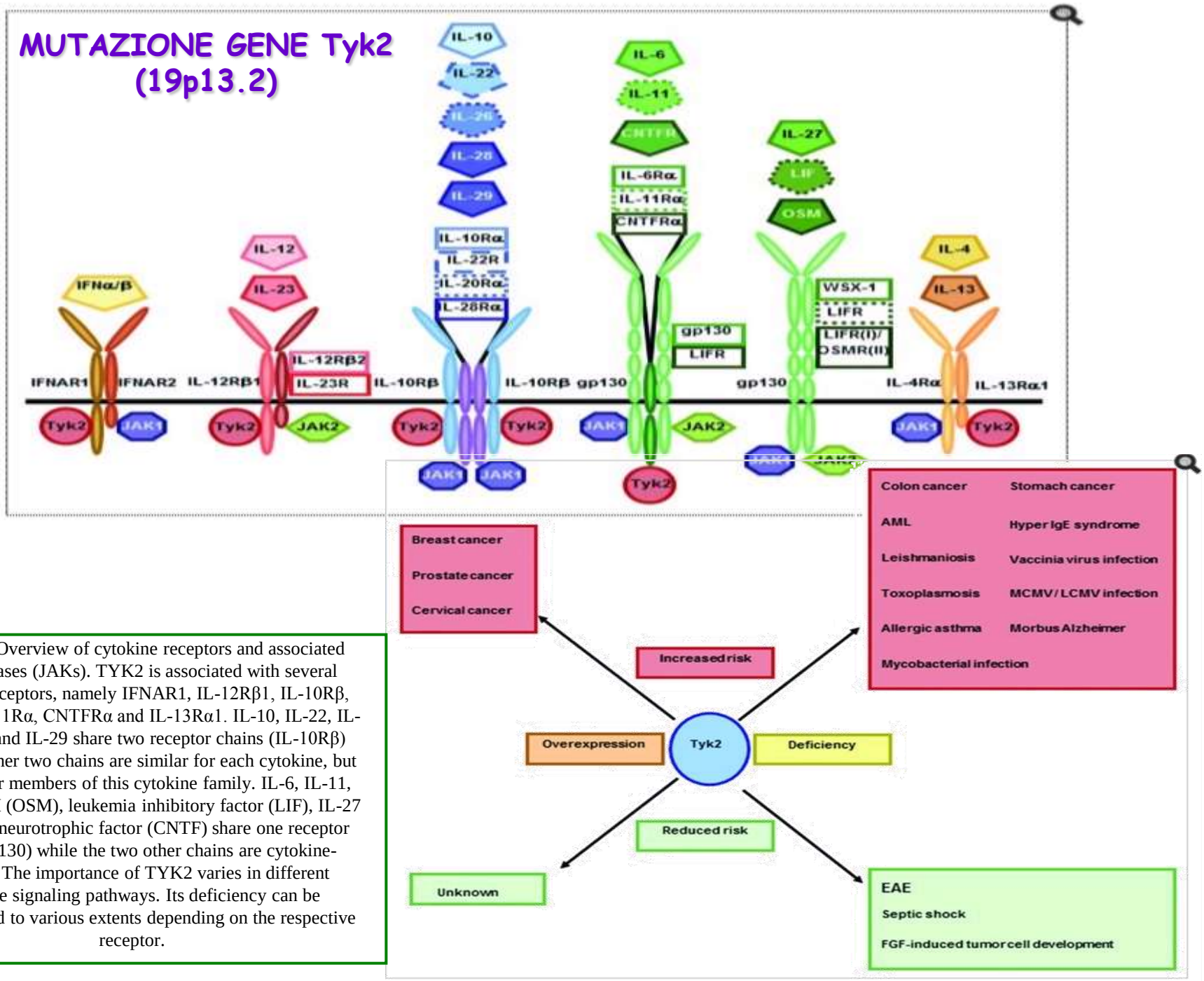


Figure 1. Overview of cytokine receptors and associated Janus kinases (JAKs). TYK2 is associated with several cytokine receptors, namely IFNAR1, IL-12Rβ1, IL-10Rβ, IL-6Rα, IL-11Rα, CNTFRα and IL-13Rα1. IL-10, IL-22, IL-26, IL-28 and IL-29 share two receptor chains (IL-10Rβ) while the other two chains are similar for each cytokine, but different for members of this cytokine family. IL-6, IL-11, oncostatin M (OSM), leukemia inhibitory factor (LIF), IL-27 and ciliary neurotrophic factor (CNTF) share one receptor chain (gp130) while the two other chains are cytokine-specific. The importance of TYK2 varies in different cytokine signaling pathways. Its deficiency can be compensated to various extents depending on the respective receptor.

Tabella 3: principali differenze cliniche tra AD-HIES e AR-HIES

	AD-HIES	AR-HIES
Tipo di ereditarietà	Autosomica dominante	Autosomica recessiva
Eczema cronico	Sì	Sì
Ascessi ricorrenti	Sì	Sì
Polmoniti ricorrenti	Sì	Sì
Pneumatocele	Sì	No
Conta assoluta eosinofili	Sì (726-2.034 / µl)	Sì marcata (2.500- 18.000 / µl)
Sintomi cerebrali	No	Sì
Vasculiti	No	Sì
Mollusco contagioso	No	Sì
Complicazioni da Herpes virus	No	Frequenti
Ricorrenti fratture patologiche	Sì	No
Scoliosi	Sì	No
Iperestensibilità articolare	Sì	No
Ritenzione dei denti primari	Sì	No
Letalità	Età adulta	Età infantile

Modificata da Grimbacher et al, Immunol Rev 2005

Tabella 1. Score diagnostico della HIES secondo Grimbacher.

Parametro clinico	Punteggio									
	0	1	2	3	4	5	6	7	8	10
Max IgE (UI/mL)	<200	200-500			501-1,000				1,001-2,000	>2,000
Ascessi cute (n° totale)	0		1-2		3-4				>4	
Pneumoniti (n° totale, documentate Rx)	0		1		2		3		>3	
Alterazioni del parenchima polmonare	NO						Bronchiectasie		Pneumatocele	
Altre infezioni gravi	NO				SI					
Sepsi	NO				SI					
Max conta eosinofili/µL	<700			700-800						
Rash neonatale	NO				SI					
Eczema(stadio peggiore)	Assente	Lieve	Moderato		Grave					
Sinusiti, otiti (n° totale max in un anno)	1-2	3	4-6		>6					
Candidosi	NO	Orale, Vaginale	Unghie		Sistemica					
Denti decidui ritenuti	0	1	2		3					
Scoliosi, max curvatura	<10°		10°-14°		15°-20°					
Fratture spontanee	0				1-2					
Iperlassità legamentosa	NO				SI					
Facies tipica	NO		Lieve			SI				
Aumentata larghezza nasale	<1 SD	1-2 SD		>2 SD						
Palato ogivale	NO		SI							
Anomalie linea mediana	NO					SI				
Linfoma	NO				SI					
Correzione per l'età	>5 anni			2-5 anni		1-2		<1		

Affetto da HIES >60

Probabilità Alta: 40-59

Probabilità Bassa: 16-39

Non Affetto: 0-15.

Grimbacher B. Am J Hum Genet 1999;65(3):735-

POLMONITI RICORRENTI

RASH NEONATALE

FRATTURE OSSEE PATOLOGICHE

FACIES CARATTERISTICA

PALATO OGIVALE

+

Th17

Possibile

IgE>1,000 IU/mL

Score clinico >30

Probabile

IgE>1,000 IU/mL

Score clinico >30

Th17 < o AF+

Definitiva

IgE>1,000 IU/mL

Score clinico >30

Th17 < o AF+

Mutazione di STAT3

J Allergy Clin Immunol 2010;125(2):424-432.

Table 2. Differential Diagnosis of Hypereosinophilia, Hyper-IgE Syndrome, Food Allergy, and Atopic Eczema

	Hypereosinophilia [16]	Hyper-IgE syndrome [2,5]	Food allergy [17-19]	Atopic eczema dermatitis syndrome [4]
Age of onset	5 months (based on 1 report)	Within a few days or weeks of life	From birth to 3 years	Early infancy
Gender predominance	Male-to-female ratio 9:1	No gender predominance	Male	No gender predominance
Prevalence	1:200 000	Incidence $< 10^{-6}$	0.1% to 7% of population	10% to 15% of the pediatric population
Systemic involvement	Cardiovascular, neurological hematological, gastrointestinal, etc	Abscesses, pneumonia, mucocutaneous candidiasis, connective tissue abnormalities, impaired deciduation of primary teeth	Respiratory (asthma, rhinitis), gastrointestinal (vomiting, diarrhea and abdominal pain), anaphylaxis	Between 50 % and 80 % of children develop other atopic diseases such as allergic rhinitis and asthma
Skin involvement	Generally, either angioedematous and urticarial lesions. or erythematous, pruritic papules, and nodules	Rash usually begins on the face and/or scalp as pink to red papules that become pustules and then break down, exuding pus, and becoming crusted	Atopic dermatitis, dermatitis herpetiformis, gluten, milk and soy enteropathies, and eosinophilic gastroenteritis, urticaria, angioedema	Rash distribution varies with age, involving cheeks and external surfaces of the arms and legs in infancy
Prognosis	Depends on the severity of ultimate organ damage Malignant blood disorders are a concern.	Benign if treatment is established early	About 80 % of children with milk and egg allergy will outgrow it by the age of 5 y; 20 % of peanut-allergic children will outgrow the allergy.	Approximately a third of children with AD and food allergy outgrow their clinical reactivity in 1-3 y.

Abbreviations: AD, atopic dermatitis; IgE, immunoglobulin E.

J Investig Allergol Clin Immunol 2008; Vol. 18(2): 131-135

Grazie