Le Iper IgE

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Serum IgE in clinical immunology and allergy

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Serum IgE was measured with the use of the Rowe modification of the Mancini technique. Serum IgE was significantly elevated in atopic and questionably atopic patients and in patients with filariasis within 2 years of diagnosis. Children with thymic hypoplasia and with cystic fibrosis had higher IgE levels than did control clinic patients. Children with variable immunodeficiency and X-linked agammaglobulinemia had significantly less IgE than did control patients, and patients with severe combined immune deficiency disease when not treated with plasma had no detectable IgE. The value of IgE determinations in groups of patients was demonstrated.

Reaginic antibody was shown by Ishizaka and associates[1, 2] to belong to a distinct immunoglobulin class, IgE. Johansson[3] demonstrated elevated levels of IgE in atopic patients. Since then, Johansson and others have confirmed and expanded these results.[4-17] The following study was undertaken to examine further the usefulness of a serum IgE determination in the practice of clinical immunology and allergy and its significance in immune deficiency and other diseases.

MATERIALS AND METHODS

The patients studied were selected from the practice of one of us (A. L. S.) and from the clinics of Children's Hospital Medical Center, Boston, Mass. Control subjects were employees and staff of the Robert B. Brigham Hospital. Sera from natives of Samoa were obtained from the Department of Medical Zoology, Walter Reed Army Institute of Research. Blood was collected by venipuncture and sera were separated after centrifugation and stored at 4° C. or −70° C.

Patient classification

Patients with a personal history of symptoms upon exposure to an allergen, an immediate family history of atopy, and positive intradermal tests to common allergens that correlated with their personal history were designated atopic. Patients with no personal history

From the Departments of Medicine and Pediatrics, Harvard Medical School, the Department of Medicine, Robert B. Brigham Hospital, and the Department of Pediatrics, Division of Immunology, Children's Hospital Medical Center.

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*Trainee supported by Training Grant AI-00366 from the National Institutes of Health.

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J. Allergy Clin. Immunol, june 1972

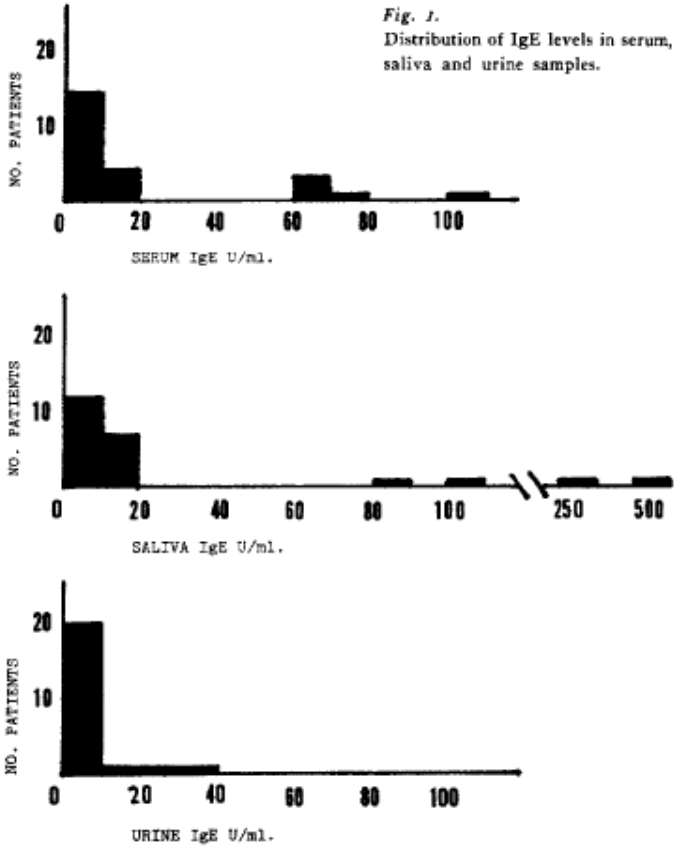


Fig. 1.
Distribution of IgE levels in serum, saliva and urine samples.

sample to 30 U/ml, with a mean value of 7.5 U/ml and median value of 6.5 U/ml.

The distribution of IgE levels in sera, saliva and urine are shown in Figure 1.

There was no obvious correlation in the IgE levels of serum, saliva, and urine in the individuals studied. In some

Acta allergologica, 1972

Patologie con IgE elevate

Patologie allergiche

- Dermatite atopica
- Asma bronchiale

Malattie neoplastiche

- Morbo di Hodgkin
- Mieloma ad IgE
- Carcinoma bronchiale

Immunodeficienze Primitive

Infezioni

- Aspergillosi polmonare
- Candidiasi sistemica
- Mononucleosi
- CMV
- Virosi respiratorie
- HIV
- Pertosse

Patologie varie

- S. Nefrosica
- Epatopatie
- Fibrosi cistica
- Malattia di Kawasaki
- Poliarterite nodosa
- S. di Guillian-Barré
- Alcolismo
- Pemfigoide bolloso
- Eritema nodoso

	Difetto genetico	Meccanismo di immunodeficienza	Meccanismo di aumento delle IgE
WAS	Deficit WASP	Anormalità citoscheletro di actina e alterata stabilità immunosinapsi	Disfunzione T-reg
IPEX	Mutazioni FOXP3	Deficit T-reg	Deficit T-reg
S.Omenn	Mutazioni RAG, ARTEMIS, IL-7R, RMRP, IL-2Rγ, ZAP70…	Ly T oligoclonali e assenza Ly B	T-reg ridotti, Ly T oligoclonali, aumentata produzione IL-4
S.DiGeorge	Delezione 22q.11.2	Ly T oligoclonali	Ly T oligoclonali
S.Netherton	Mutazioni SPINK5	Deficit di LEKTI	Deficit di LEKTI
HIES	Mutazioni STAT3, TYK2, DOCK8	Signaling citochine difettivo	Difetto di IL-21?

- **Ozcan E, Notarangelo LD, Geha RF. *Primary immune deficiencies with aberrant production of IgE*. J Allergy Clin Immunol. 2008**

Sindromi da iper IgE

Table 1

A classification of HIES

HIES type	Inheritance	Discriminant clinical findings
Type 1	Sporadic (more than 90% of cases) Familial with autosomal dominant inheritance (rare)	Skeletal and connective tissue abnormalities (characteristic facial appearance, fracture following minor trauma, retention of deciduous teeth, scoliosis, hyperextensibility), pneumatocele
Type 2	Familial with autosomal recessive inheritance	Viral infections (herpes simplex virus, molluscum contagiosum) Central nervous system involvement Some mycobacterial infections Absence of pulmonary cysts Absence of skeletal abnormalities

Current Opinion in Immunology 2009, **21**:487–492

Sindrome da Iper-IgE

Sindrome eterogenea caratterizzata da:

- **infezioni polmonari ricorrenti;**
- **ascessi da Stafilococchi;**
- **pneumatocele;**
- **candidiasi mucocutanea;**
- **eczema;**

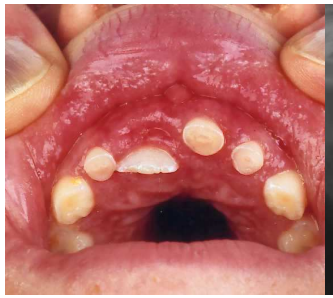
- **Livelli elevati (>2000 UI/ml) di IgE;**

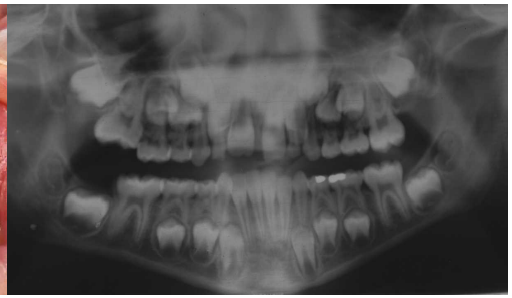
Davis SD, Schaller J, Wedgwood RJ. Lancet 1966.
Buckley RH, Wray BB, Belmaker EZ. Pediatrics 1972.

Facies tipica:

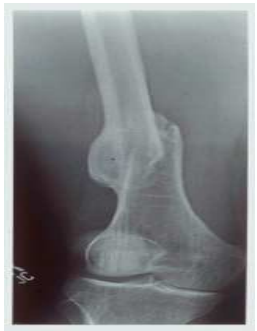
- tratti facciali grossolani,

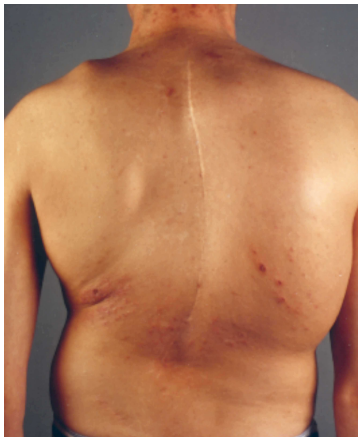
- difetti di caduta dei denti decidui,





- alterazioni ossee,





Grimbacher B, Holland SM, Gallin JI, NEJM 1999.

Sindrome da Iper-IgE: caratteristiche cliniche

Eczema	100%
Facies tipica (>16y)	100%
Ulcere cutanee	87%
Polmoniti ricorrenti	87%
Candidiasi mucocutanea	83%
Cisti polmonari	77%
Scoliosi (>16y)	76%
Ritardo caduta denti decidui	72%
Fratture patologiche	57%

Grimbacher B, Holland SM, Gallin JI, NEJM 1999.

Scoring System with Clinical and Laboratory Tests for Individuals in Kindreds with HIES

	Points[a]									
Clinical Findings	0	1	2	3	4	5	6	7	8	10
Highest serum-IgE level (IU/ml)[b]	<200	200–500			501–1,000				1,001–2,000	>2,000
Skin abscesses	None		1–2		3–4				>4	
Pneumonia (episodes over lifetime)	None		1		2		3		>3	
Parenchymal lung anomalies	Absent						Bronchiectasis		Pneumatocele	
Retained primary teeth	None	1	2		3				>3	
Scoliosis, maximum curvature	<10°		10–14°		15°–20°				>20°	
Fractures with minor trauma	None				1-2				>2	
Highest eosinophil count (cells/μl)[c]	<700			700–800			>800			
Characteristic face	Absent		Mildly present			Present				
Midline anomaly[d]	Absent					Present				
Newborn rash	Absent				Present					
Eczema (worst stage)	Absent	Mild	Moderate		Severe					
Upper respiratory infections per year	1-2	3	4–6		>6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width[e]	<1 SD	1–2 SD		>2 SD						
High palate	Absent		Present							
Young-age correction	>5 years			2–5 years		1–2 years		≤1 year		

[a] The entry in the furthest-right column is assigned the maximum points allowed for each finding.
[b] Normal <130 IU/ml.
[c] 700/μl = 1SD, 800/μl = 2 SD above the mean value for normal individuals.
[d] For example, cleft palate, cleft tongue, hemivertebrae, other vertebral anomaly, etc. (see Grimbacher et al. 1999*a*).
[e] Compared with age- and sex-matched controls (see Farkas et al. 1994).

Score: ≥ 40: diagnosi clinica di HIES;
< 20: diagnosi improbabile

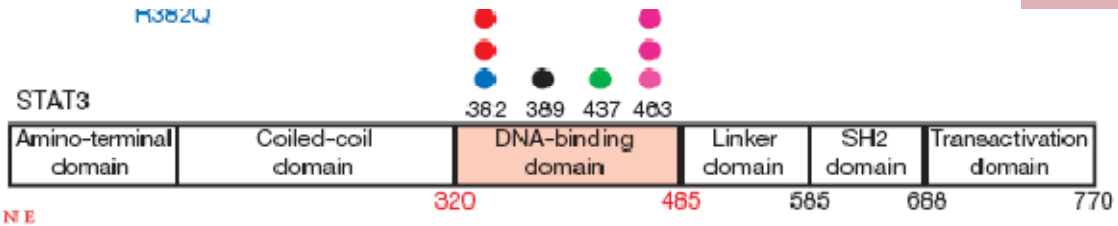
Am. J. Hum. Genet. 65:735–744, 1999

nature Vol 448|30 August 2007|doi:10.1038/nature06096

LETTERS

Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome

Yoshiyuki Minegishi[1], Masako Saito[1], Shigeru Tsuchiya[2], Ikuya Tsuge[3], Hidetoshi Takada[4], Toshiro Hara[4], Nobuaki Kawamura[5], Tadashi Ariga[5], Srdjan Pasic[6], Oliver Stojkovic[7], Ayse Metin[8] & Hajime Karasuyama[1]



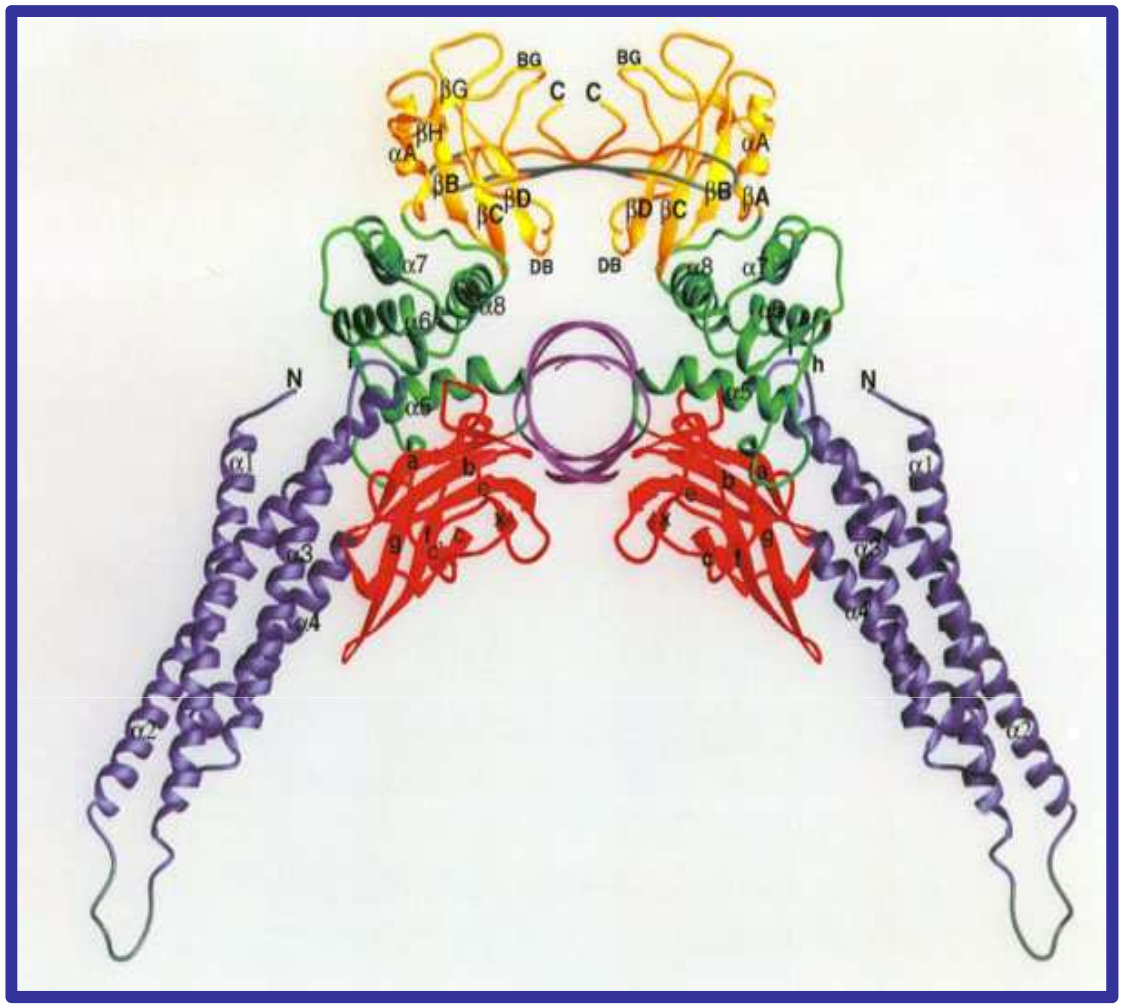
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

STAT3 Mutations in the Hyper-IgE Syndrome

Steven M. Holland, M.D., Frank R. DeLeo, Ph.D., Houda Z. Elloumi, Ph.D., Amy P. Hsu, B.A., Gulbu Uzel, M.D., Nina Brodsky, B.S., Alexandra F. Freeman, M.D., Andrew Demidowich, B.A., Joie Davis, A.P.R.N., Maria L. Turner, M.D., Victoria L. Anderson, C.R.N.P., Dirk N. Darnell, M.A., Pamela A. Welch, B.S.N., Douglas B. Kuhns, Ph.D., David M. Frucht, M.D., Harry L. Malech, M.D., John I. Gallin, M.D., Scott D. Kobayashi, Ph.D., Adeline R. Whitney, B.A., Jovanka M. Voyich, Ph.D., James M. Musser, M.D., Ph.D., Cristina Woellner, M.Sc., Alejandro A. Schäffer, Ph.D., Jennifer M. Puck, M.D., and Bodo Grimbacher, M.D.

N Engl J Med 2007;357:1608-19.

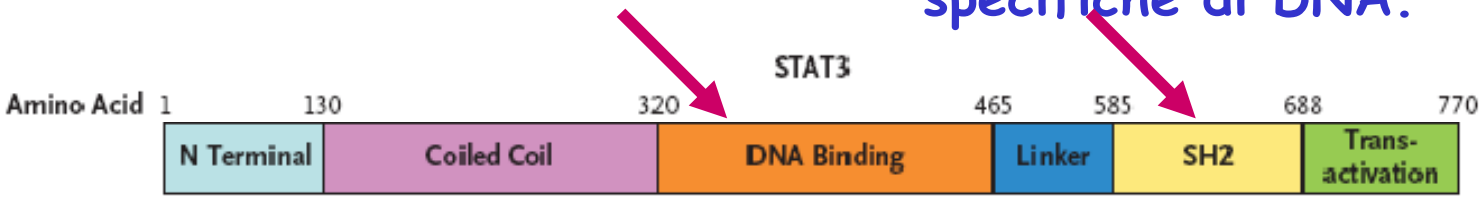


STAT3 Cytogenetic Location: 17q21.31

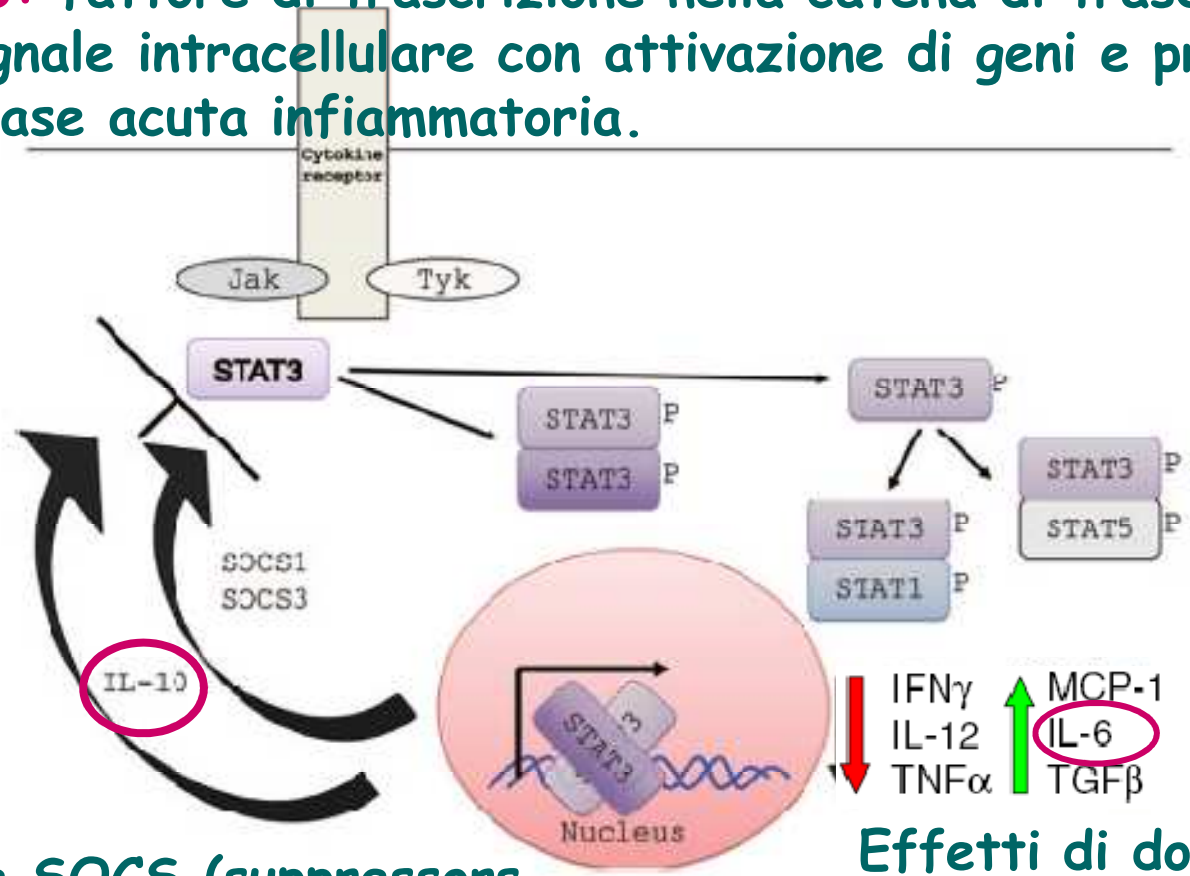
Signal transducer and activator of transcription 3 acts like homodimer, or heterodimer with STAT1.

Le mutazioni in STAT3 sono missense o delezioni a carico del dominio SH2 o del DNA-binding site.

Il dominio SH2 è necessario e sufficiente per la dimerizzazione e la traslocazione dei dimeri nel nucleo, mentre il dominio DNA-binding è necessario per interazioni con sequenze specifiche di DNA.



STAT3: fattore di trascrizione nella catena di trasduzione del segnale intracellulare con attivazione di geni e proteine della fase acuta infiammatoria.



IL-10 e SOCS (suppressors of cytokine signaling) possono down-regolare l'attività di STAT3.

Effetti di down- e di up-regulation dopo normale stimolazione di STAT3.

Nei pazienti con HIES da difetto di STAT3 ⟶ Infiammazione eccessiva ma inadeguata

ALEXANDRA F. FREEMAN AND STEVEN M. HOLLAND
(*Pediatr Res* 65: 32R–37R, 2009)

Table 2 Source and functions of key cytokines in HIES [6, 7, 22]

Cytokine	Known functions
IL-6	Produced by: mononuclear phagocytes, T and B cells, fibroblasts, hepatocytes, endothelial cells, keratinocytes, bone marrow cells
	Effects:
	Proinflammatory, activates neutrophils, activates T and B cells, potent stimulator of hepatic acute phase protein production, induces pulmonary fibrosis by fibroblast proliferation and collagen deposition
	Anti-inflammatory: inhibits further production of IL-1 and TNF-α
IL-10	Produced by primarily by Treg, monocytes, and B cells
	Effects:
	Proinflammatory: stimulates B cells and immunoglobulin production, particularly IgG4
	Anti-inflammatory; decreases production of IFN-g, IL-1B, 2, 4, 5, 6, 8, 12, TNF-α; inhibits eosinophil survival and IgE production; downregulates TNF-α synthesis
IL-17	Produced by Th17 cells and eosinophils
	Effects: activates macrophages, fibroblasts, stromal cells; induces IL-6, IL-8, IL-11, and G-CSF expression. Enhances macrophage production of nitric oxide and prostaglandin E2; role in airway remodeling
IL-21	Produced by T cells
	Effects: activates NK and CD8 cells and promotes both T and B cell proliferation. Acts with IL-4 cells to induce B cell class switching
IL-22	Produced by T cells, Th17 cells, activated NK cells
	Effects: upregulates epithelial innate molecules leading to epithelial defense; expression is induced by TLR 9; induces acute phase protein production
TNF-α	Produced by: macrophages neutrophils, NK cells, endothelial cells, mast cells
	Effects: cytotoxic antitumor immunity, induces ICAM, VCAM, and selectin expression to induce neutrophil adhesion to the endothelium and facilitate migration to the periphery; potent neutrophil activator; induces vascular leakage, negative ionotropic effects, inhibits eosinophil apoptosis
IFN-γ	Produced by T cells and NK cells; some macrophages
	Effects: key cytokine in cell-mediated immunity; increases MHC I and II expression. Induces TNF-a production, stimulates macrophage response to microbes via adherence, nitric oxide production, phagocytosis, oxidative burst, etc. Also stimulates effects of NK cells and neutrophils. Inhibits IgE production
IL-12	Produced by monocytes, macrophages; also from B cells, dendritic cells, Langerhans cells, PMNs and mast cells
	Effects: enhances growth and activity of NK cells, induces IFN-γ production, induces T cell proliferation

- **Le citochine sono prodotte in risposta a diversi stimoli cellulari e servono sia come fattori di crescita che come regolatori della risposta immune.**
- **Alcune citochine sono prodotte in risposta a stimoli dell'immunità innata, altre citochine in risposta a stimoli di cellule dell'immunità adattativa.**

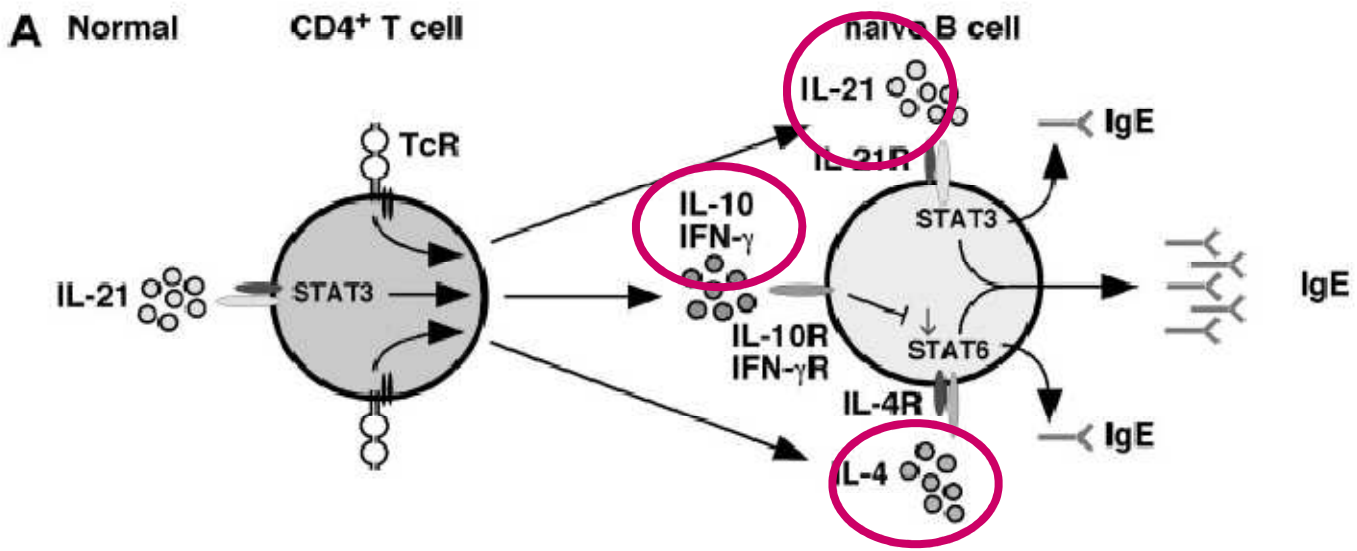
Clinic Rev Allerg Immunol
DOI 10.1007/s12016-009-8134-1

Table 1

Clinical Characteristics of STAT3 Deficiency.

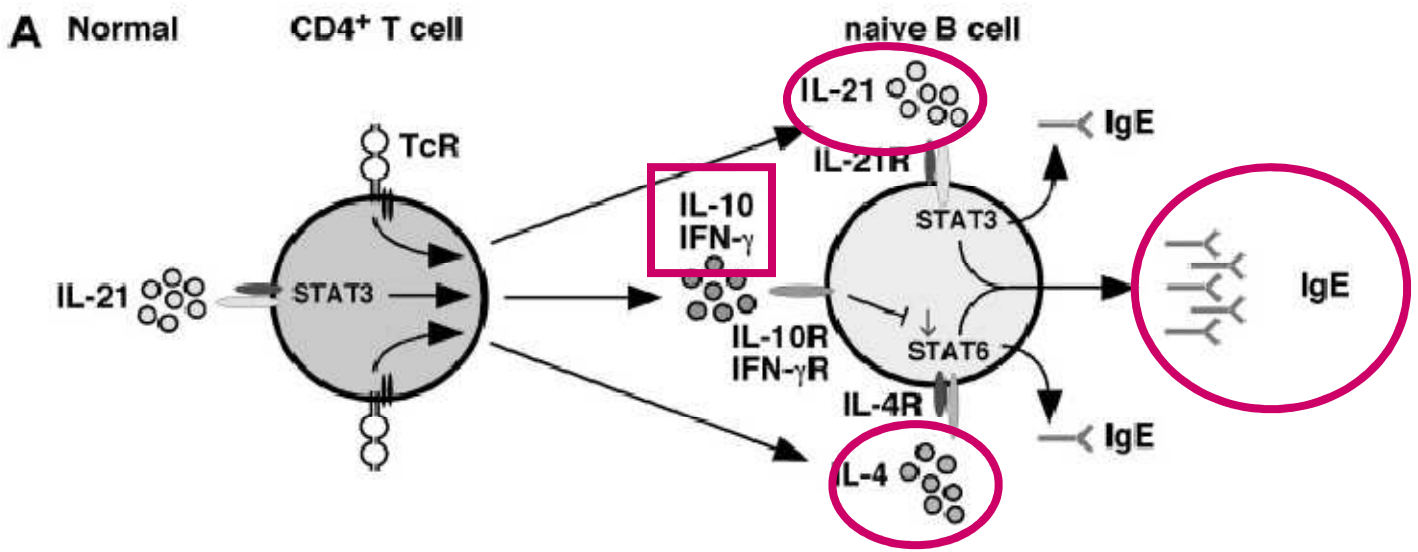
Immunologic Characteristics (% Frequency)	Non-Immunologic Characteristics (%Frequency)
Newborn rash (81%)	Characteristic face (83%)
Boils (87%)	Retained primary teeth (72%)
Recurrent pneumonias (87%)	Minimal trauma fractures (71%)
Pneumatocoeles (77%)	Scoliosis >10 degrees (63%)
Eczema (100%)	Hyperextensibility (68%)
Mucocutaneous candidiasis (83%)	Focal Brain Hyperintensities (70%)
Peak Serum IgE >2000 IU/ml (97%)	Chiari 1 Malformations (18%)
Eosinophilia (93%)	Craniosynostosis (unknown)
Increased incidence of Lymphoma	Arterial Aneurysms (unknown)

Immunol Allergy Clin North Am. 2008 May ; 28(2): 277-



I linfociti T CD4+ producono IL-4, IL-21, IL-10 e IFNγ in risposta allo stimolo via TcR.
La produzione di IL-10 e IFNγ può essere potenziato da IL-21. IL-4 e IL-21 sono in grado da sole di produrre IgE da parte di cellule B naive, via STAT3.
L'induzione di IgE da parte di IL-4 è negativamente regolata da IL-10 e IFNγ. Il risultato dell'azione reciproca tra IL-4, IL-21, IL-10 e IFNγ è la produzione di bassi livelli di IgE.

(Blood. 2008;112:1784-1793)



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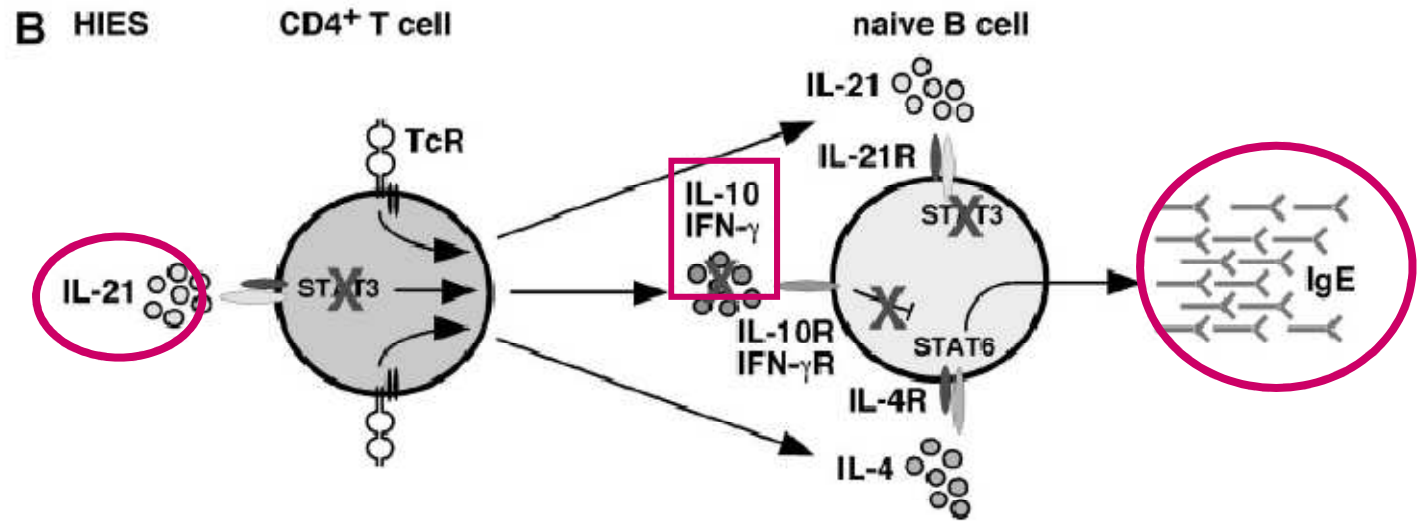
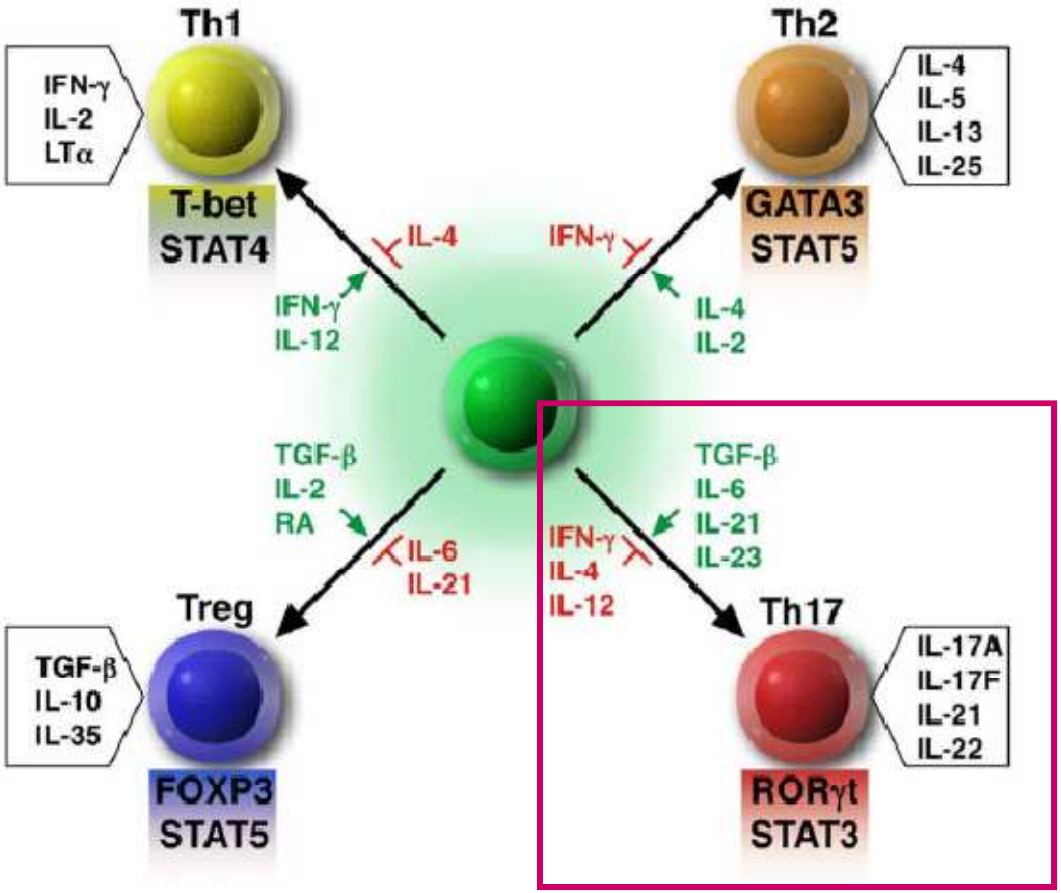


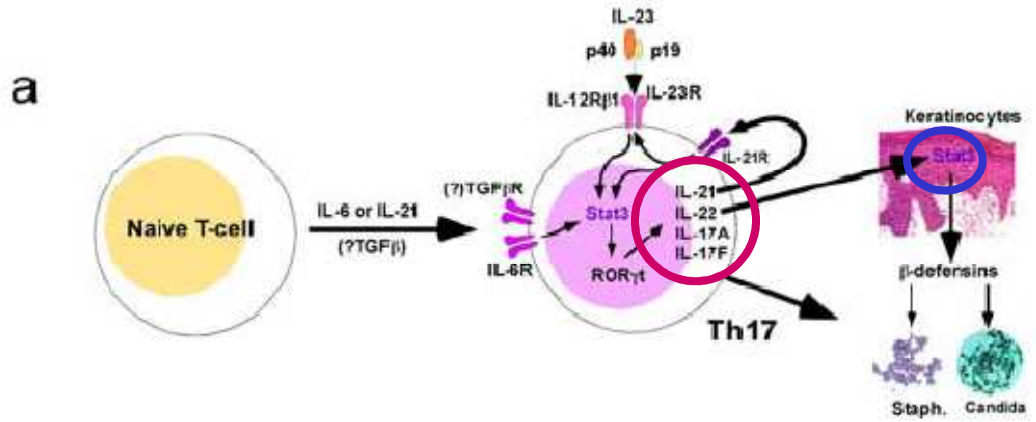
A causa di mutazioni di STAT3, la capacità di IL-21 di aumentare la produzione di IL-10 e di IFNγ da parte di linfociti T CD4+ è abrogata. Di conseguenza gli effetti soppressivi di queste citochine sulla produzione di IgE sono diminuiti. Inoltre, i linfociti B sono incapaci di rispondere alla regolazione di IL-10, che agisce attraverso STAT3. Quindi, anche se i linfociti B sono incapaci di rispondere a IL-21, la loro risposta allo stimolo di IL-4 è disregolata, risultandone una eccessiva produzione di IgE.

(Blood. 2008;112:1784-1793)



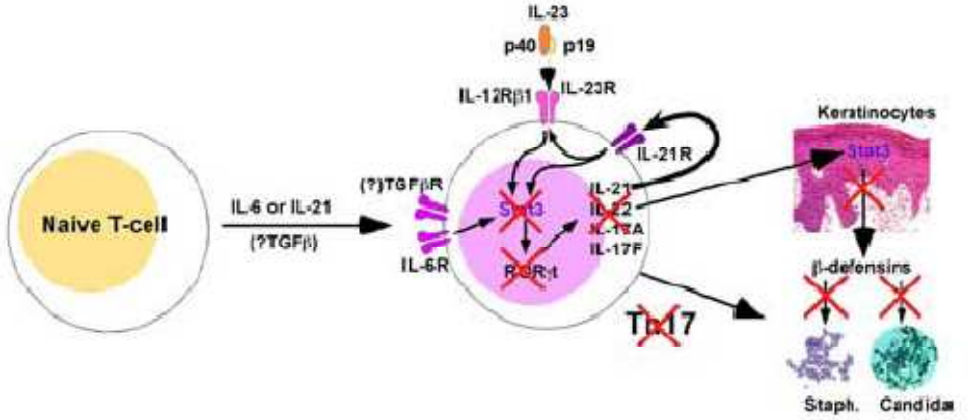
J Allergy Clin Immunol. 2009 May ; 123(5): 977–985.

Normal defence



IL-17: reclutamento neutrofili;
IL-22: induce la produzione di defensine

STAT3 deficiency (Hyper-IgE syndrome)



Ridotta produzione di linfociti Th17;
Difetto di difesa nei confronti di patogeni extracellulari

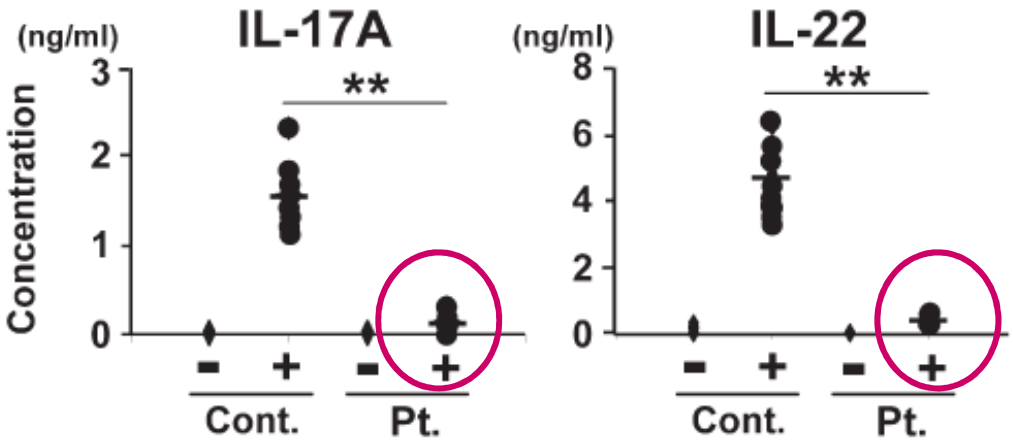
The Journal of Immunology, 2009, 182: 21–28.

Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome

Yoshiyuki Minegishi,[1] Masako Saito,[1] Masayuki Nagasawa,[2] Hidetoshi Takada,[3] Toshiro Hara,[3] Shigeru Tsuchiya,[4] Kazunaga Agematsu,[5] Masafumi Yamada,[6] Nobuaki Kawamura,[6] Tadashi Ariga,[6] Ikuya Tsuge,[7] and Hajime Karasuyama[1]

JEM VOL. 206, June 8, 2009

I cheratinociti e le cellule epiteliali bronchiali dipendono molto più fortemente rispetto ad altri tipi di cellule dalle citochine prodotte dai linfociti Th17 nella produzione di fattori antistafilococco.



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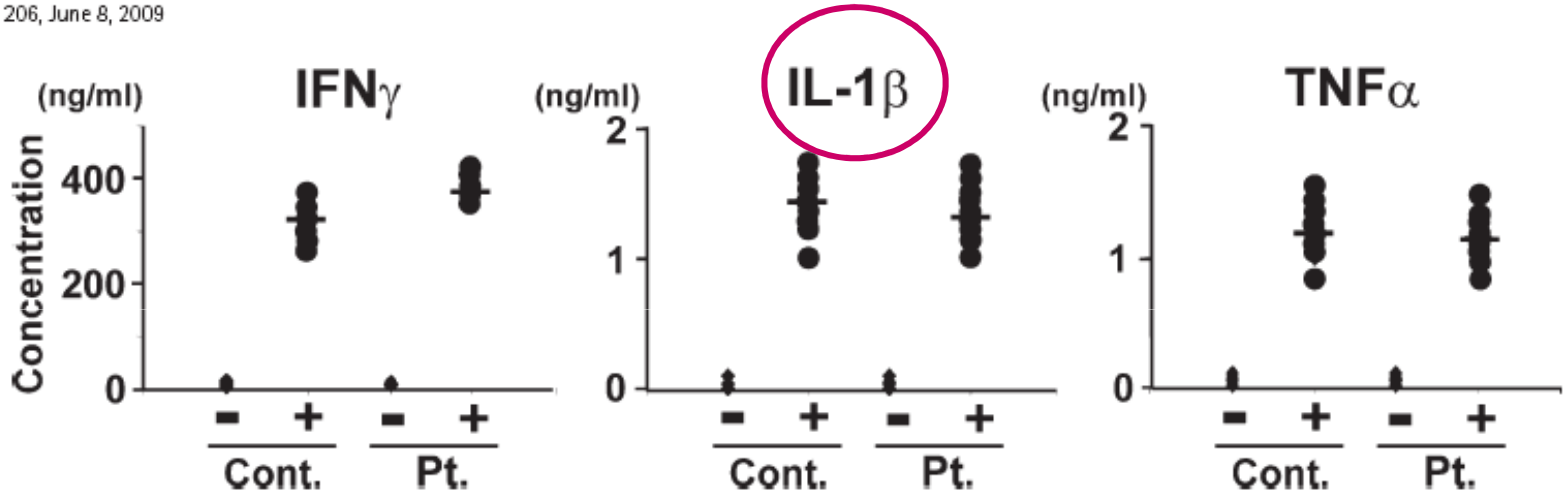
JEM VOL. 206, June 8, 2009



Nei pz. con HIES normale produzione di altre citochine proinfiammatorie, tra cui IL-1β, che è insufficiente per stimolare la produzione di fattori antistafilococchi per i cheratinociti e le cellule epiteliali bronchiali, ma sufficiente per gli altri tipi di cellule.

Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome

Yoshiyuki Minegishi,[1] Masako Saito,[1] Masayuki Nagasawa,[2] Hidetoshi Takada,[3] Toshiro Hara,[3] Shigeru Tsuchiya,[4] Kazunaga Agematsu,[5] Masafumi Yamada,[6] Nobuaki Kawamura,[6] Tadashi Ariga,[6] Ikuya Tsuge,[7] and Hajime Karasuyama[1]

JEM VOL. 206, June 8, 2009

I cheratinociti e le cellule epiteliali bronchiali sono dipendenti dall' azione sinergica delle citochine prodotte dai linfociti Th17 e dalle classiche citochine infiammatorie necessarie per la produzione di fattori antibatterici.

In contrasto, fibroblasti, cellule endoteliali e macrofagi secernono efficientemente fattori antibatterici in risposta allo stimolo delle classiche citochine infiammatorie da sole.

New mechanism of oral immunity to mucosal candidiasis in hyper-IgE syndrome

H R Conti, O Baker, A F Freeman, W S Jang, S M Holland, R A Li, M Edgerton and S L Gaffen

Abstract

Oropharyngeal candidiasis (OPC, thrush) is an opportunistic infection caused by the commensal fungus Candida albicans. An understanding of immunity to Candida has recently begun to unfold with the identification of fungal pattern-recognition receptors such as C-type lectin receptors, which trigger protective T-helper (Th)17 responses in the mucosa. Hyper-IgE syndrome (HIES/Job's syndrome) is a rare congenital immunodeficiency characterized by dominant-negative mutations in signal transducer and activator of transcription 3, which is downstream of the Th17-inductive cytokines interleukin (IL)-6 and IL-23, and hence patients with HIES exhibit dramatic Th17 deficits. HIES patients develop oral and mucocutaneous candidiasis, supporting a protective role for Th17 cells in immunity to OPC. However, the Th17-dependent mechanisms of antifungal immunity in OPC are still poorly defined. An often unappreciated aspect of oral immunity is saliva, which is rich in antimicrobial proteins (AMPs) and exerts direct antifungal activity. In this study, we show that **HIES patients show significant impairment in salivary AMPs, including β-defensin 2 and Histatins.** This tightly correlates with reduced candidacidal activity of saliva and concomitantly elevated colonization with Candida. Moreover, IL-17 induces histatins in cultured salivary gland cells. **This is the first demonstration that HIES is associated with defective salivary activity, and provides a mechanism for the severe susceptibility of these patients to OPC.**

Mucosal Immunology advance online publication 23 February 2011

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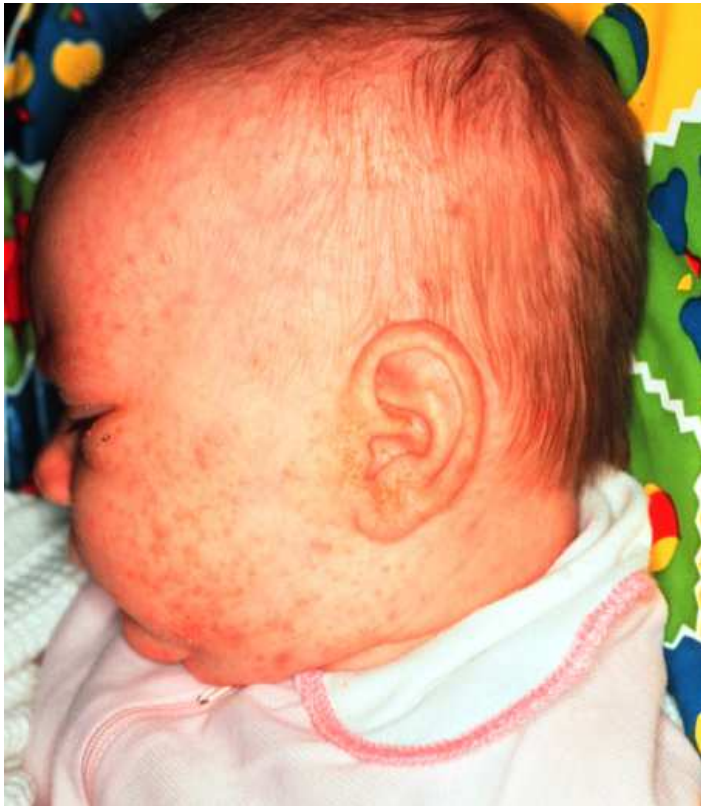
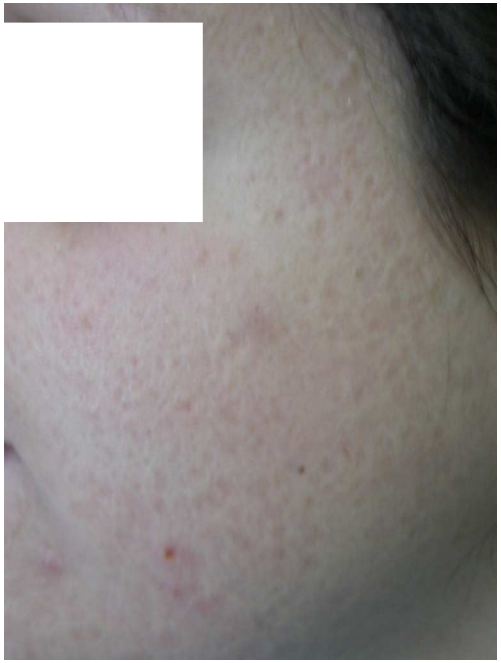
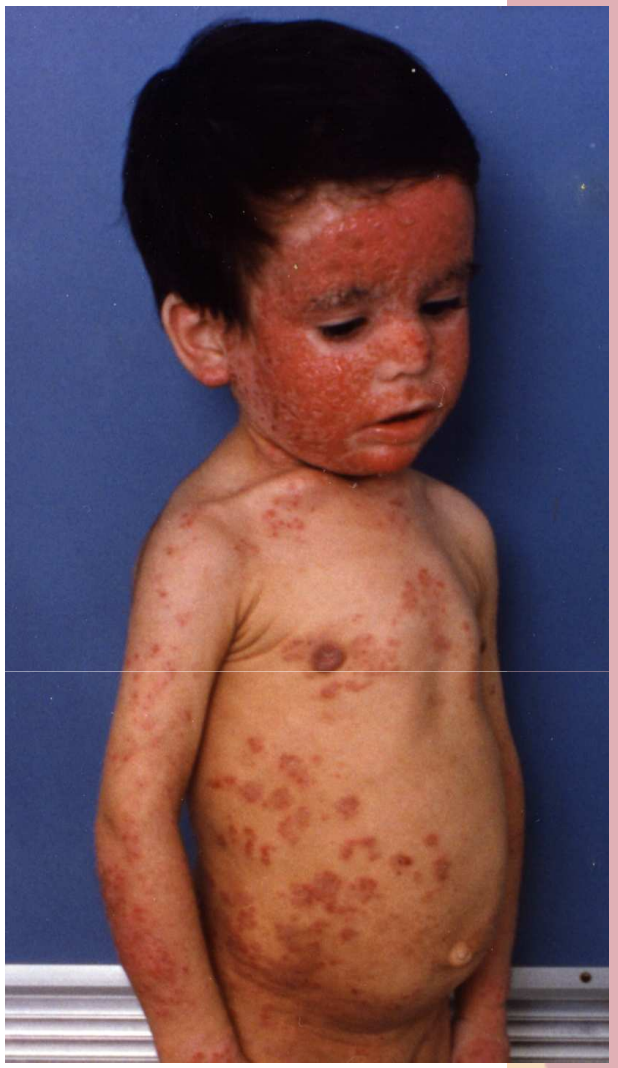
Newborn rash (81%)	Characteristic face (83%)
Boils (87%)	Retained primary teeth (72%)
Recurrent pneumonias (87%)	Minimal trauma fractures (71%)
Pneumatocoeles (77%)	Scoliosis >10 degrees (63%)
Eczema (100%)	Hyperextensibility (68%)
Mucocutaneous candidiasis (83%)	Focal Brain Hyperintensities (70%)
Peak Serum IgE >2000 IU/ml (97%)	Chiari 1 Malformations (18%)
Eosinophilia (93%)	Craniosynostosis (unknown)
Increased incidence of Lymphoma	Arterial Aneurysms (unknown)

Immunol Allergy Clin North Am. 2008 May ; 28(2): 277-







Box 1. Pathogens of STAT3 Deficiency

Frequent Pathogens

Staphylococcus aureus (lung and skin)

Streptococcus pneumoniae (lung)

Haemophilus influenzae (lung)

Candida albicans (mucocutaneous)

Secondary Pathogens of Lung

Pseudomonas aeruginosa

Aspergillus species

Scedosporium species

Nontuberculous mycobacteria

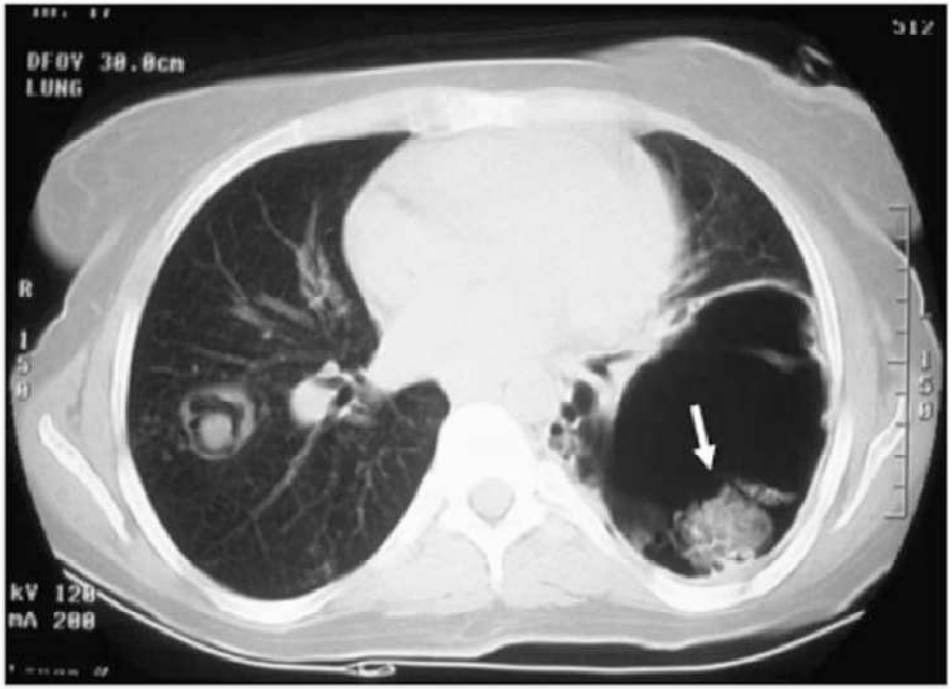
Less Frequent Pathogens

Pneumocystis jiroveci (lung)

Histoplasma (gastrointestinal tract)

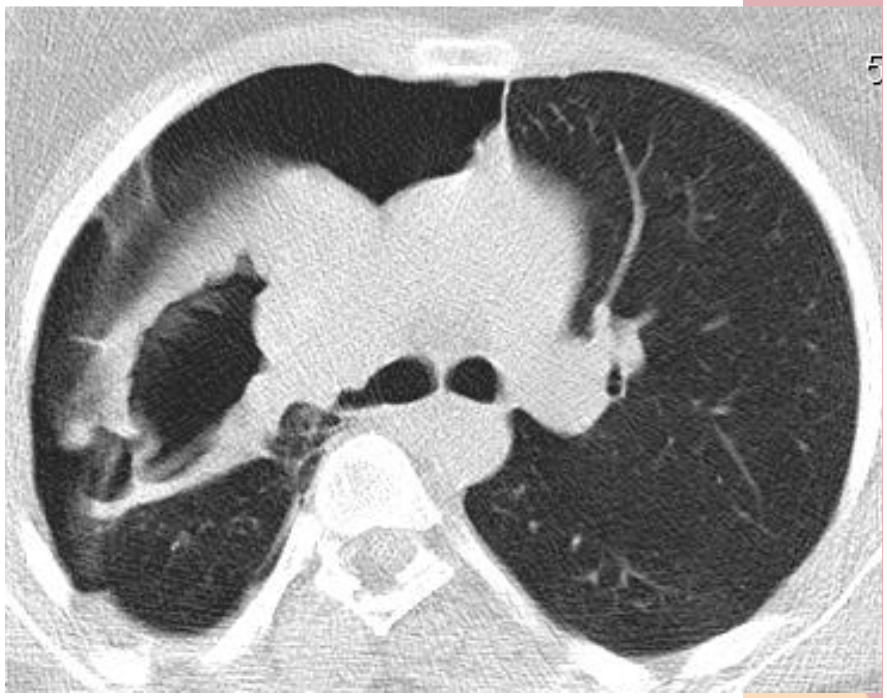
Cryptococcus (brain and gastrointestinal tract)

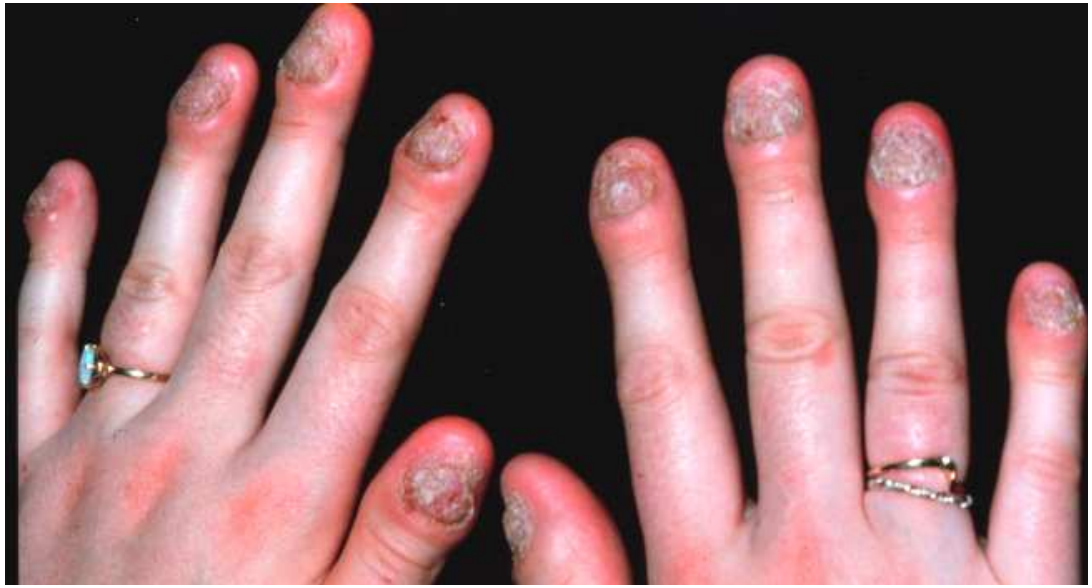
Immunol Allergy Clin North Am. 2008 May ; 28(2): 277-



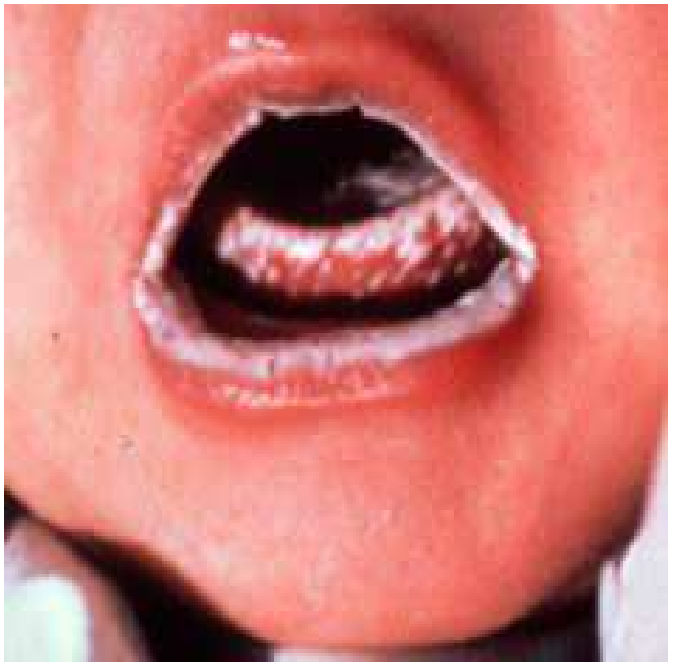
Pneumatocele con sovrainfezione fungina

Aspergillus fumigatus





Candida



Box 1. Pathogens of STAT3 Deficiency

Frequent Pathogens

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Nontuberculous mycobacteria

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Pneumocystis jiroveci (lung)

Histoplasma (gastrointestinal tract)

Cryptococcus (brain and gastrointestinal tract)

Pneumocystis jirovecii pneumonia in a baby with hyper-IgE syndrome

Ben Zion Garty · Adit Ben-Baruch · Asaf Rolinsky · Cristina Woellner · Bodo Grimbacher · Nufar Marcus

Eur J Pediatr (2010) 169:35–37

Pulmonary nontuberculous mycobacterial infections in hyper-IgE syndrome

Elizabeth Melia, BA[a]
Alexandra F. Freeman, MD[a]
Yvonne R. Shea, MS[b]
Amy P. Hsu, BA[a]
Steven M. Holland, MD[a]
Kenneth N. Olivier, MD, MPH[a]

jaci.2009.07.007

COCCIDIOIDES IMMITIS MENINGITIS IN A PATIENT WITH HYPERIMMUNOGLOBULIN E SYNDROME DUE TO A NOVEL MUTATION IN SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION

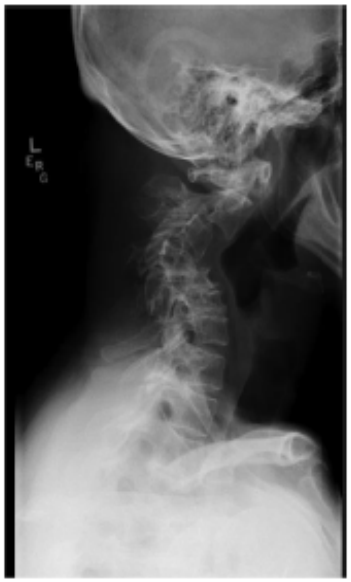
Annie E. Powers, MD, PhD, Jeffrey M. Bender, MD,† Attila Kumánovics, MD,‡§ Krow Ampofo, MD,† Nancy Augustine,‡§ Andrew T. Pavia, MD,† and Harry R. Hill, MD†‡§*

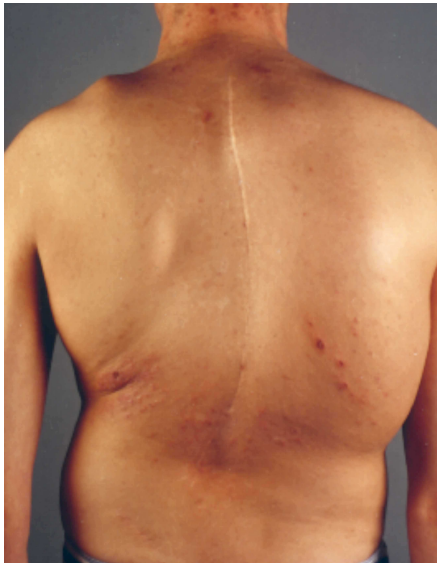
The Pediatric Infectious Disease Journal • Volume 28, Number 7, July 2009

Table II. *Effects of STAT3 deficiency on Cellular Function*

Cell Type	Defect	Human	Mice	Cytokine(s) Likely Responsible	Reference
CD4+ T cells	Th17 deficiency	Yes	Yes	IL-6, IL-21, IL-23	29 (mouse); 54–57 (human)
	Impaired IL-10 production	Yes	Yes	IL-6, IL-27 (mouse)	15 (mouse); 55 (human)
B cells	Lack of Ag-specific PC	Inferred from functional Ab deficiencyin AD-HIES	Yes	IL-6, IL-21 (mouse); IL-6, IL-10, IL-21 (human)	35 (mouse); 45, 49–51 (human)
Myeloid cells	Excessive production of proinflammatory cytokines, chemokines	Not examined	Yes	IL-10	12 (mouse)
Dendritic cells	Impaired development	Not examined	Yes	Flt3 ligand	13 (mouse)
Keratinocytes	Alopecia, dermatitis, skin ulcers	Inferred from AD-HIES	Yes	IL-22	62 (mouse)
Osteoclasts and monocytes	Increased bone resorption	Yes	Yes	IL-6 family	77 (mouse); 75 (human)

The Journal of Immunology, 2009,182: 21–28.

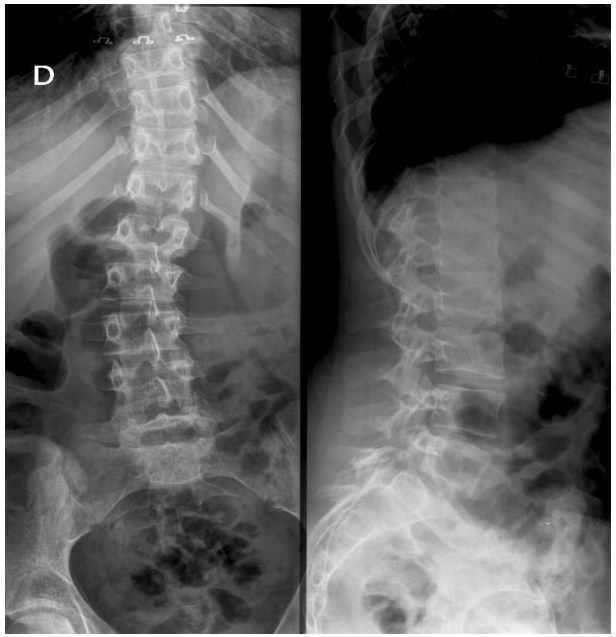


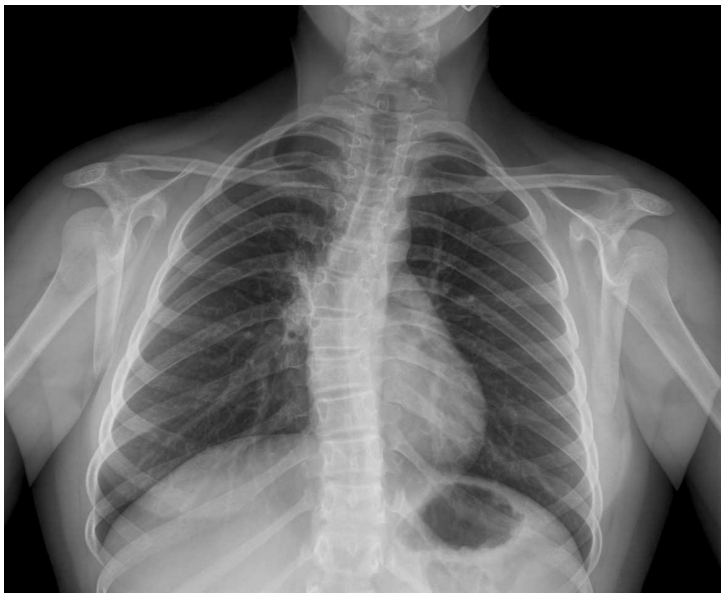


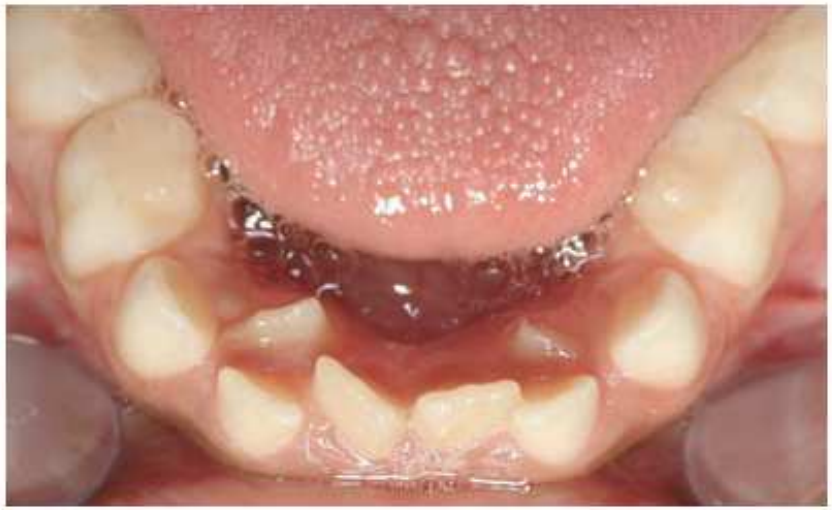
↓ IL-6

↑ TNF-α

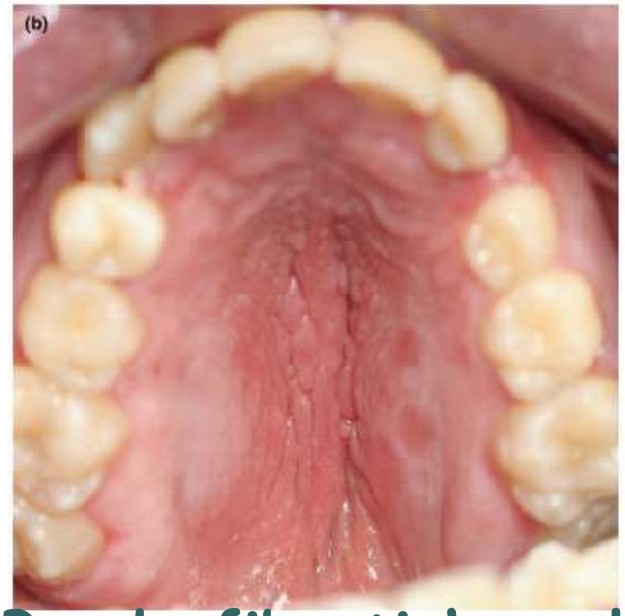
} ↑ osteoclasti



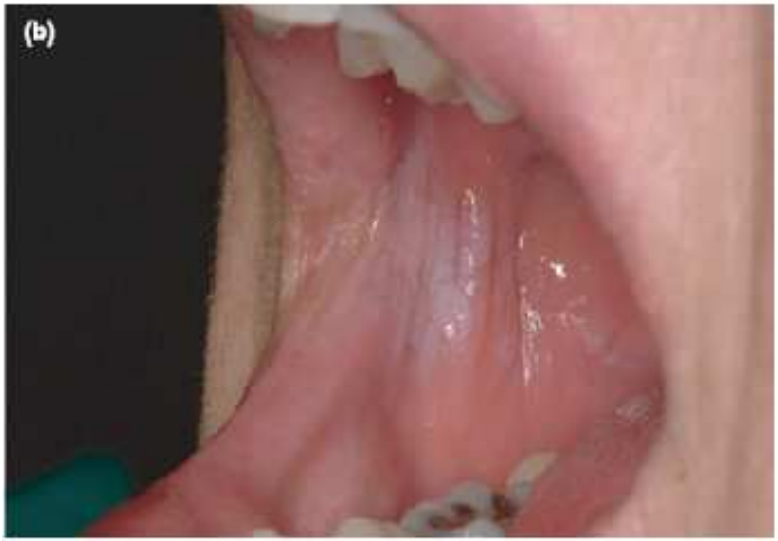




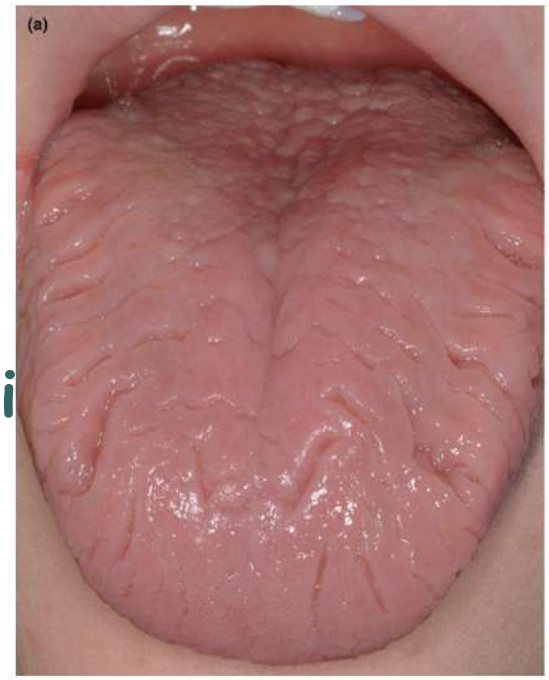
Dentizione mista



Bande fibrotiche a livello palato duro



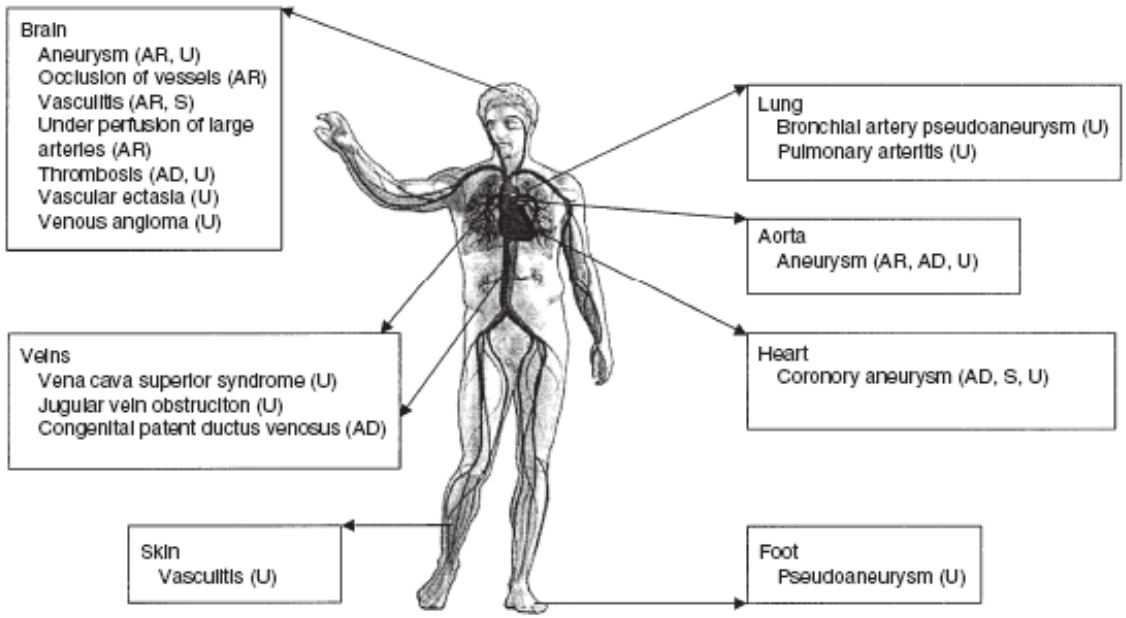
Placche cheratosiche



Fissurazioni linguali

AF Freeman[1,2], DL Domingo[3], SM Holland[1]

Oral Diseases (2009) **15**, 2–7



- difettiva angiogenesi, correlata al difetto di STAT3;
- difetto di STAT3 nei miociti cardiaci;
- ipereosinofilia;
- infiltrazione eosinofila dei tessuti (?).

H. Yavuz* and R. Chee†

2009 British Society for Immunology, *Clinical and Experimental Immunology*, **159:** 238–244

Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome

100 pz. con sospetta HIES, di cui 64 con difetto di STAT3

TABLE I. Number and percentage of patients positive for the 17 evaluated features

	all HIES		HIES STAT3 wild-type		HIES STAT3 mutated	
	No.	%	No.	%	No.	%
Recurrent pneumonia	85/100	85	24/36	66.7	61/64	95.3
Eczema	90/100	90	32/36	88.9	58/64	90.6
Recurrent skin abscesses	86/100	86	28/36	77.8	58/64	90.6
Characteristic face	82/99	82.8	24/35	68.6	58/64	90.6
Failure to shed deciduous teeth	60/86	68.9	16/31	51.6	44/55	80.0
Lung cyst formation	61/97	62.9	14/34	41.2	47/63	74.6
Eosinophilia	68/94	72.3	27/36	75.0	41/58	70.7
Newborn rash	52/86	60.5	15/29	51.7	37/57	64.9
Other unusual infections	47/94	50	13/34	38.2	34/60	56.7
Increased interalar distance	37/83	44.6	10/31	32.3	27/52	51.9
Cathedral palate	41/84	48.8	12/31	38.7	29/53	54.7
Hyperextensibility	37/87	42.5	8/32	25.0	29/55	52.7
Pathologic bone fractures	32/94	34.0	5/35	14.3	27/59	45.8
Recurrent upper respiratory infections	41/92	44.6	14/33	42.4	27/59	45.8
Candidiasis	37/91	40.6	12/33	36.4	25/58	43.1
Scoliosis	20/83	24.1	7/33	21.2	13/50	26.0
Midline anomaly	12/86	14.0	5/34	14.7	7/52	13.5

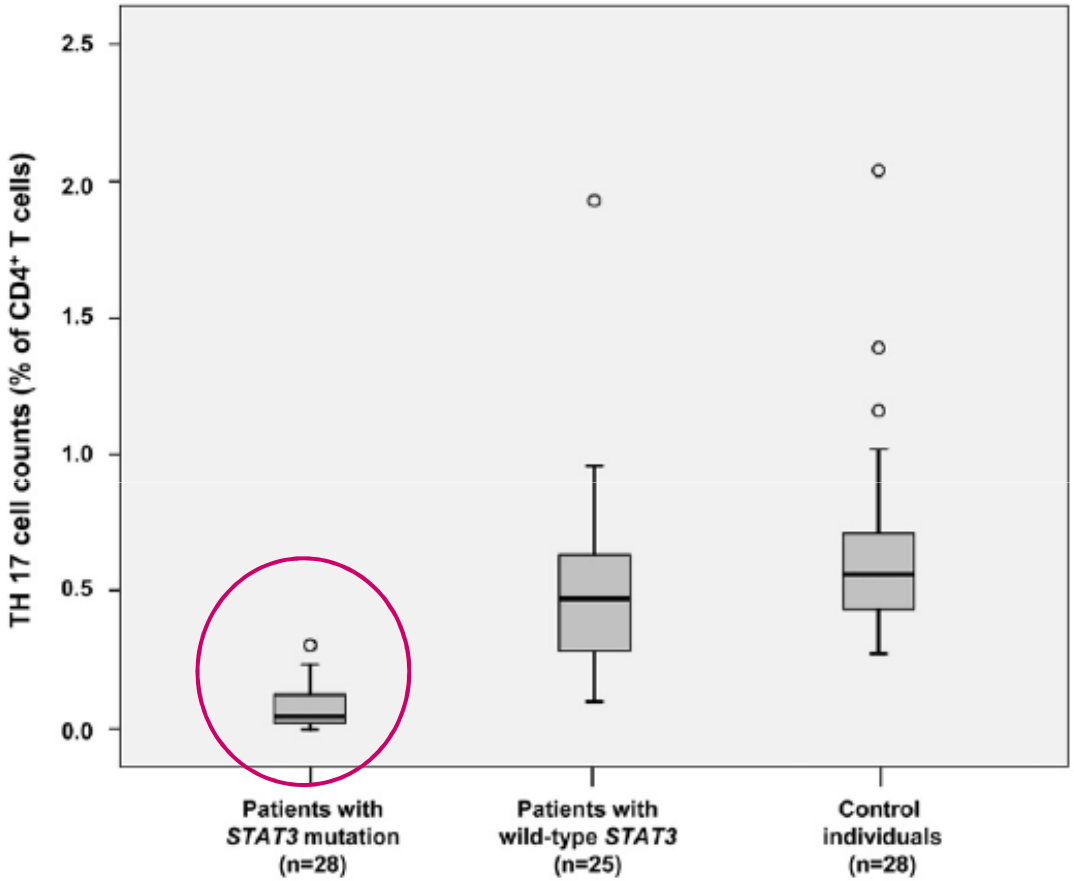
(J Allergy Clin Immunol 2010;125:424-32.)

Sindrome da Iper-IgE da difetto di STAT3: caratteristiche cliniche fondamentali

- Polmoniti recidivanti
- Eczema/ rush in età neonatale
- Fratture ossee patologiche
- Facies caratteristica
- "Cathedral palate"

(J Allergy Clin Immunol 2010;125:424-32.)

Diagnostic approach to the hyper-IgE syndromes: Immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis



Clinical implications: Differentiation of HIES from severe atopic dermatitis is a diagnostic challenge with important therapeutic implications. Clinical key findings combined with T_H17 cell counts predict patients with HIES with *STAT3* mutations.

SCHIMKE ET AL

(J Allergy Clin Immunol 2010;126:611-7.)

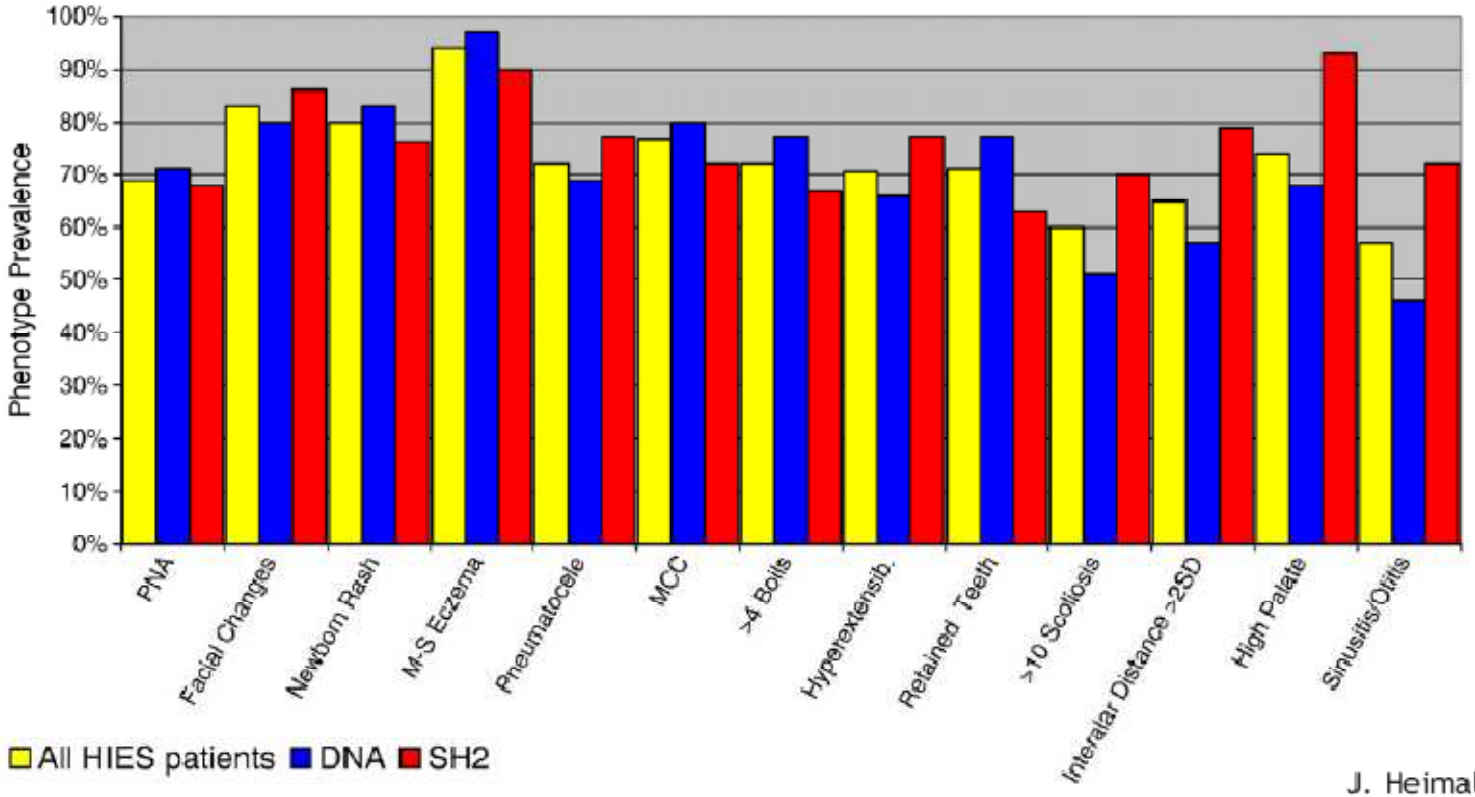
Clinical Immunology (2011) 139, 75–84

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

Paucity of genotype–phenotype correlations in *STAT3* mutation positive Hyper IgE Syndrome (HIES)



J. Heimall et al.

Diffuse Large B Cell Lymphoma in Hyper-IgE Syndrome Due To *STAT3* Mutation

Attila Kumánovics · Sherrie L. Perk
Heather Gilbert · Melissa H. Cessna
Nancy H. Augustine · Harry R. Hill

Table I Review of literature

Age	Sex	Diagnosis	Site	Stage	EBV	Outcome[a]	Citation
10	Female	Histiocytic NHL	Brain	IV	nr	Died	Bale et al. 1977 [21]
19	Male	Hodgkin lymphoma	nr	nr	nr	nr	Buckley et al. 1981[a]
7	Male	Burkitt	Retroperitoneal	IV	−	Died	Gorin et al. 1989 [50]
23	Female	Centroblastic NHL	Cervical LN	Ia	−	Alive	Einsle et al. 1990 [51]
24	Male	Hodgkin lymphoma	Mediastinal LN	I	nr	nr	Kowalchuk et al. 1996 [52]
69	Female	Mantle cell lymphoma	Generalized LN	IV	nr	Alive	Takimoto et al. 1996[b]
46	Male	DLBCL	Cervical LN	IIa	+	Died	Nester et al. 1998 [22]
10	Male	Hodgkin lymphoma	Cervical LN	III	+	Died[c]	Lin et al. 1998 [53]
14	Female	Large anaplastic NHL	nr	nr	nr	Died	Sinclair et al. 1999[b]
20	Male	DLBCL	Groin LN	III	−	Alive	Huber et al. 2000 [54]
18	Female	Cutaneous TCL	Multiple skin	nr	−	Died	Lei et al. 2000 [16]
54	Female	PTCL	nr	nr	nr	Died	Chang et al. 2002[b]
13	Female	Large T cell NHL	Neck, axilla, inguinal LN	IV	–[d]	Died	Mosseri et al. 2002 [55]
57	Female	ALCL	Cervical LN	IIIb	nr	nr	Lee et al 2003 [56]
22	Male	DLBCL	L2 vertebra, spleen	IV	–[e]	Alive	Leonard et al. 2004 [23]
4	Female	Hodgkin lymphoma	Cervical LN	II	nr	Died	Kashef et al. 2006 [57]
19	Female	PTCL	Frontal, cervical parotid	IV	nr	Alive	Onal et al. 2006 [42]
17	Male	DLBCL	Inguinal LN	nr	–[f]	Alive	Wallet et al. 2007 [58]
nr	Female	Burkitt	nr	nr	nr	nr	Engelhardt et al. 2009 [15]
nr	Female	Burkitt	nr	nr	nr	nr	Engelhardt et al. 2009 [15]
44	Male	DLBCL	Inguinal LN	IIIa	nr	Alive	Beleda et al. 2010 [19]
18	Female	Extranodal NK/T	Temporal skin	IE	+	Alive	Chang et al. 2010 [20]
48	Male	DLBCL	Parotid	IIa	−	Alive	This report

Hence, studying the underlying mechanism of lymphomagenesis in hyper-IgE syndrome patients is not only important for the management of these patients but it may also allow a better definition of the role of *STAT3* in the oncologic process.

Causes of death in hyper-IgE syndrome

Alexandra F. Freeman, MD,[a] David E. Kleiner, MD,[b] Hari Nadiminti, MD,[a] Joie Davis, APRN, APNG,[c] Martha Quezado, MD,[b] Victoria Anderson, MSN, CRNP,[a] Jennifer M. Puck, MD,[d] and Steven M. Holland, MD[a] *Bethesda, Md, and San Francisco, Calif*

TABLE II. Pathologic abnormalities observed

Patient no.	Cause of death	Pathology			
		Lung	Brain	Kidney	Other
1	Sudden; pulmonary hemorrhage secondary to *P aeruginosa* pneumonia	Cavitary; multilobular pneumonia with diffuse hemorrhage	Focal vascular ectasia with small area of hemorrhage in cerebellum	No abnormalities	Cardiomegaly with right ventricle dilation; hepatic congestion likely from right ventricle failure; chronic hepatitis B with portal fibrosis
2	Prolonged course; multi-organism pneumonia; *S prolificans* cerebritis	Multi-lobular pneumonia with budding hyphae; culture with *Scedosporium*	Cerebritis with budding hyphae	Pyelonephritis with budding hyphae	None
3	Sudden; pulmonary hemorrhage secondary to *A fumigatus*	Cavitary with local vascular invasion by *Aspergillus*	Clipped bilateral carotid aneurysms; old areas of fibrosis from previous hemorrhage	Renal tubular injury and calcification; glomerulosclerosis; 2 angiomyolipomas	Mild coronary artery atherosclerosis
4	Progressive *Pseudomonas* and *A fumigatus* pneumonia	Multi-lobular pneumonia with intra-alveolar hemorrhage, emphysematous changes	No abnormalities	Renal tubular injury and calcification; glomerulosclerosis	Stomach and duodenal intramucosal hemorrhages
5	Multiple CNS bleeds secondary to *A fumigatus* mycotic aneurysms	Cavitary with local vascular invasion by *Aspergillus*	Left MCA thrombosis and aneurysm with infiltrating fungal elements	Renal tubular injury and calcification; glomerulosclerosis	Mild coronary artery atherosclerosis
6	Sudden; pneumonia with *Aspergillus* and PJP	Cavitary with local vascular invasion by *Aspergillus*; *PJP* outside cavity with acute/chronic inflammation	No abnormalities	Renal tubular injury and calcification	Right ventricle hypertrophy with hepatic congestion

CNS, Central nervous system; *MCA*, middle cerebral artery; *PJP*, *Pneumocystis jiroveci*.

(J Allergy Clin Immunol 2007;119:1234-40)

Sindrome da Iper-IgE: strategie terapeutiche

Controllo delle infezioni:

- Detersione cute;
- Profilassi antimicrobica (es. cotrimoxazolo);
- Profilassi antifungina
- Terapia antimicrobica mirata e tempestiva delle infezioni;
- Interventi di chirurgia toracica.

Sindrome da Iper-IgE: strategie terapeutiche

Trials ed opzioni sperimentate ma ad oggi non confermate:

- **Levamisole;**
- **Interferon γ;**
- **Ciclosporina;**
- **Omalizumab.**
- **Trapianto di cellule staminali emopoietiche.**

Gennery AR, Flood TJ, Abinun M, Cant AJ. Bone marrow transplantation does not correct the hyper IgE syndrome. Bone Marrow Transplant 2000;25:1303-5.

Successful long-term immunologic reconstitution by allogeneic hematopoietic stem cell transplantation cures patients with autosomal dominant hyper-IgE syndrome

Evgenios Goussetis, MD[a]
Ioulia Peristeri, MD[a]
Vasiliki Kitra, MD[a]
Joanne Traeger-Synodinos, PhD[b]
Maria Theodosaki, PhD[a]
Katerina Psarra, PhD[c]
Maria Kanariou, MD[d]
Fotini Tzortzatou-Stathopoulou, MD[e]
Eftichia Petrakou, PhD[a]
Irene Fylaktou, MSc[b]
Emmanuel Kanavakis, MD[b]
Stelios Graphakos, MD[a]

TABLE I. Characteristics of patients with HIES

	Patient 1	Patient 2
Age at transplantation (y)	15	16
Sex	Male	Male
Skin abscesses	Multiple	Multiple
Pneumonias	>3	>3
Systemic candidiasis	Yes	No
Parenchymal lung abnormalities	No	Bronchiectasis pneumatocele
Newborn rash	Yes	Yes
Eczema	Yes	Yes
Retained primary teeth	Yes	Yes
Osteoporosis	Yes	No
Lumbar BMD *t* score/*z* score	−4.04/−1.86	Not determined
Pathologic bone fractures	No	No
Characteristic face	Yes	Yes
Scoliosis	No	No
Highest serum IgE level (IU/mL)	50,000	20,000
Eosinophilia	Yes	No
Lymphoma	High-grade NHL	High-grade NHL
Phenotype score at transplantation time	77	79
Genotype	R382Q/wild-type	R382W/wild-type

BMD, Bone mineral density; *NHL*, non-Hodgkin lymphoma.

Allogeneic HSCT for patients with AD-HIES presenting progressive lung disease or lymphoproliferative disease should be considered, despite the possibility of long-term complications, such as GVHD, especially if an HLA-identical sibling is available.

Sindrome da Iper-IgE: strategie terapeutiche

Trials ed opzioni sperimentate ma ad oggi non confermate:

- Levamisole;
- Interferon γ;
- Ciclosporina;
- Omalizumab;
- Trapianto di cellule staminali emopoietiche.

Presa in carico da equipe multidiscliplinare

Sindromi da iper IgE

Table 1

A classification of HIES

HIES type	Inheritance	Discriminant clinical findings
Type 1	Sporadic (more than 90% of cases) Familial with autosomal dominant inheritance (rare)	Skeletal and connective tissue abnormalities (characteristic facial appearance, fracture following minor trauma, retention of deciduous teeth, scoliosis, hyperextensibility), pneumatocele
Type 2	Familial with autosomal recessive inheritance	Viral infections (herpes simplex virus, molluscum contagiosum) Central nervous system involvement Some mycobacterial infections Absence of pulmonary cysts Absence of skeletal abnormalities

Current Opinion in Immunology 2009, **21**:487–492

Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, Frosch M, Bergmann M, Davis J, Belohradsky BH, Grimbacher B: **Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity**. *J Pediatr* 2004, **144**:93-99.

Immunity 25, 745–755, November 2006 ©2006 Elsevier Inc. DOI 10.1016/j.immuni.2006.09.009

Human Tyrosine Kinase 2 Deficiency Reveals Its Requisite Roles in Multiple Cytokine Signals Involved in Innate and Acquired Immunity

Human Tyk2 Kinase Deficiency: Another Primary Immunodeficiency Syndrome

Immunity 25, November 2006 ©2006 Elsevier Inc. DOI 10.1016/j.immuni.2006.10.007

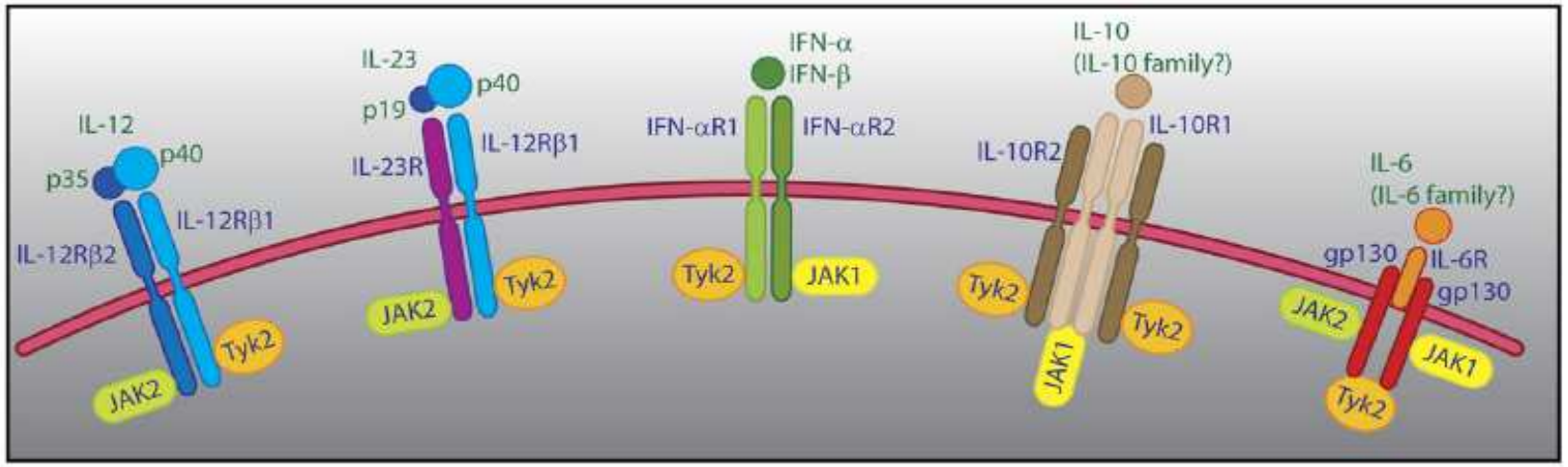


Figure 1. Cytokines and Receptors that Utilize Tyk2

TIK2
Cytogenetic Location: 19p13.2

Le JAKs chinasi giocano un ruolo fondamentale nei meccanismi di trasduzione del segnale.

TIK2 è una JAK chinasi.

E' ubiquitaria. E' fondamentale nel "signaling" di IL-12 e IFN tipo I, ma ha anche effetti anche nella trasduzione di IL-23, IL-10 e IL-6.

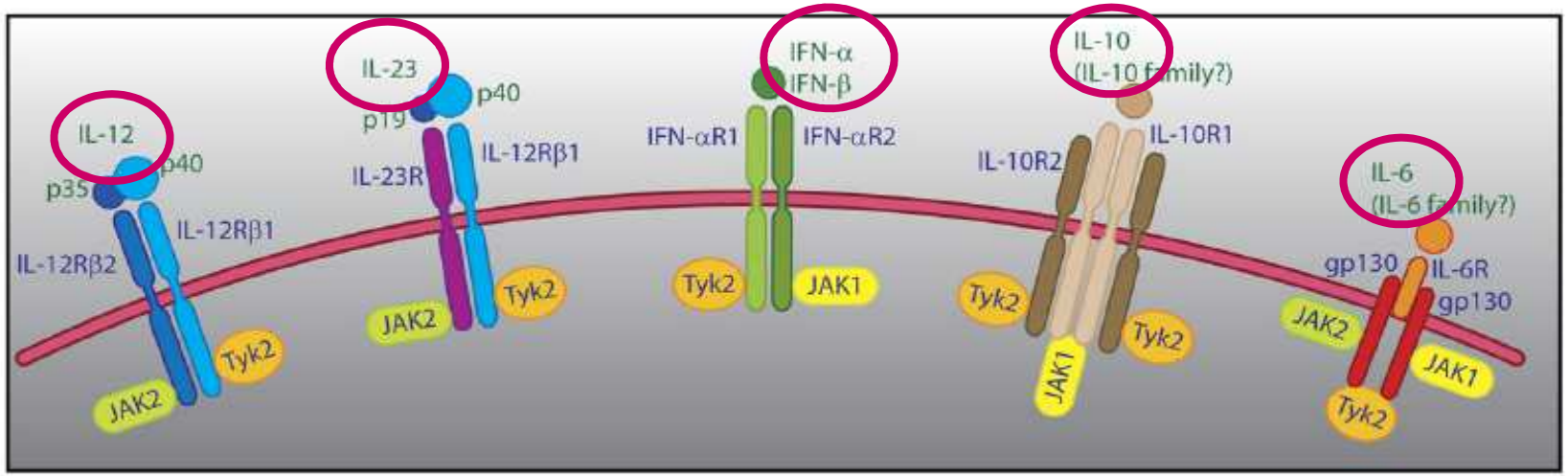
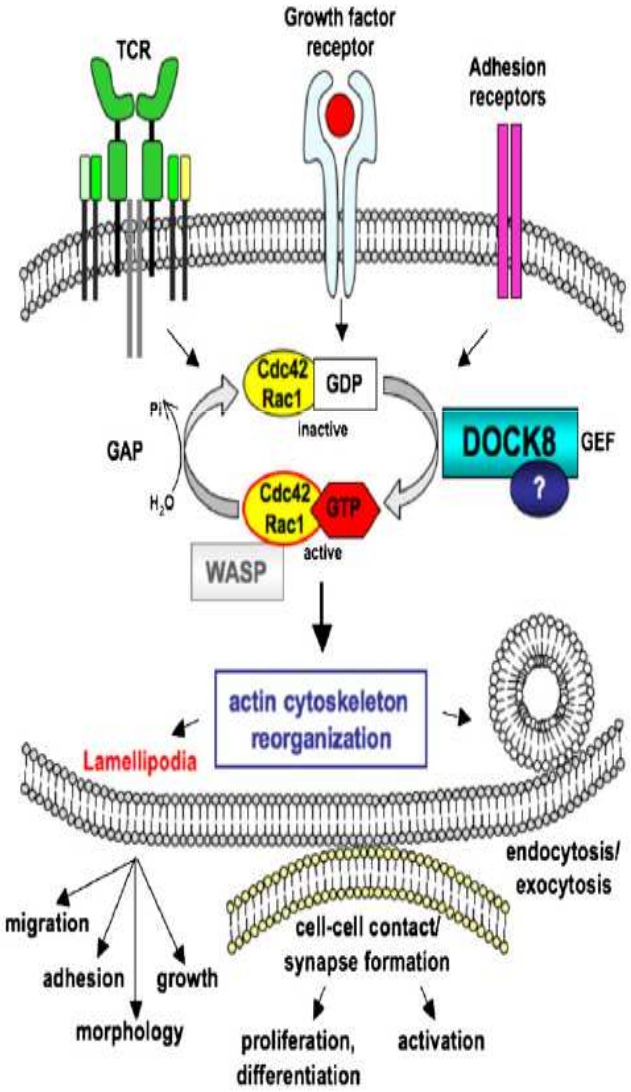


Figure 1. Cytokines and Receptors that Utilize Tyk2

Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome



DOCK8

Cytogenetic Location: 9p24.3

Proposto ruolo cruciale di DOCK8 nei processi di attivazione, proliferazione e differenziazione dei linfociti T.
Ma sembra anche giocare un ruolo importante nell'organizzazione del citoscheletro.

(J Allergy Clin Immunol 2009;124:1289-302.)

Box 2. Clinical Characteristics of AR-HIES

Eczema

Boils

Recurrent pneumonia without pneumatoceles

Sepsis

Mucocutaneous candidiasis

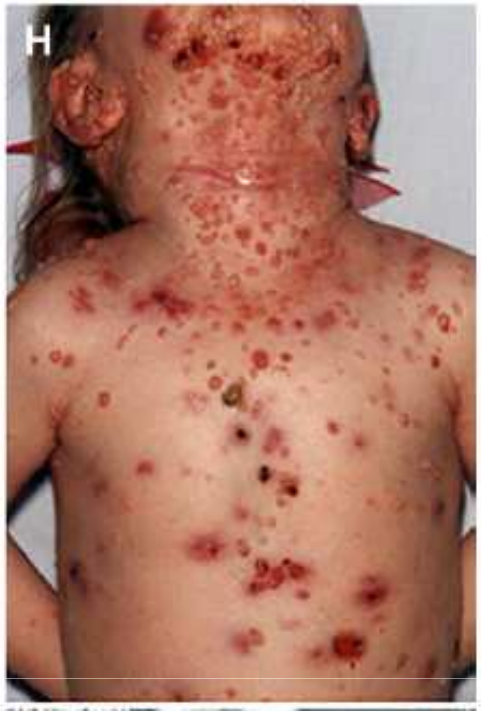
Skin viral infections

Neurologic symptoms

Vasculitis

Increased serum IgE

Eosinophilia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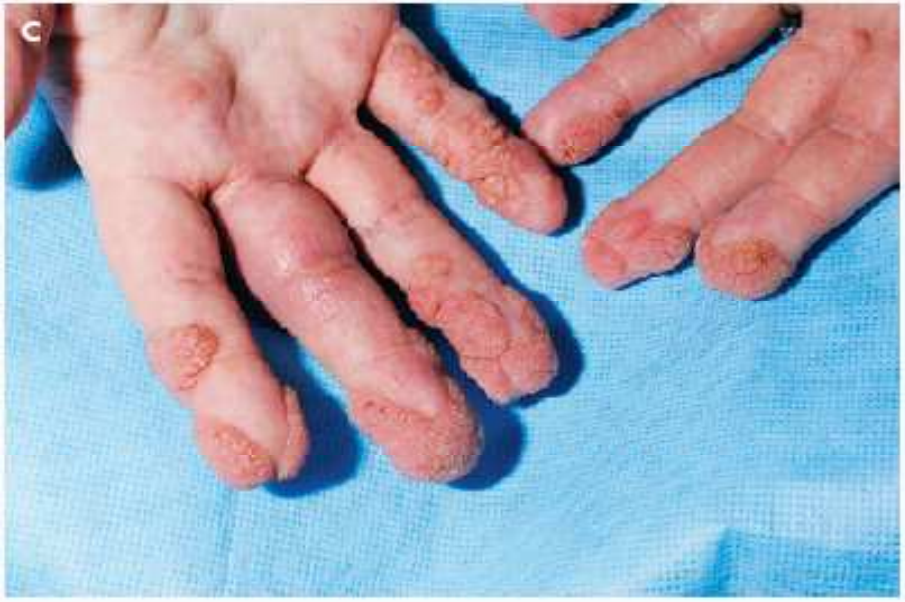
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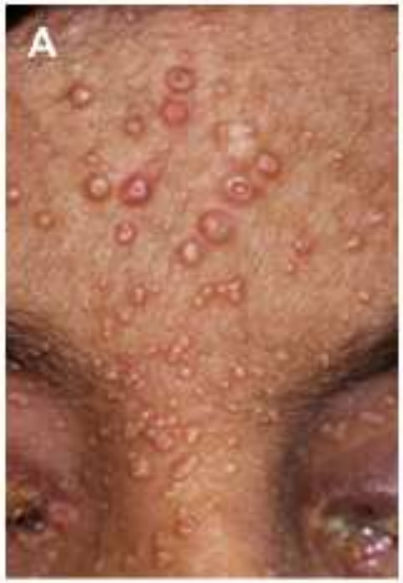
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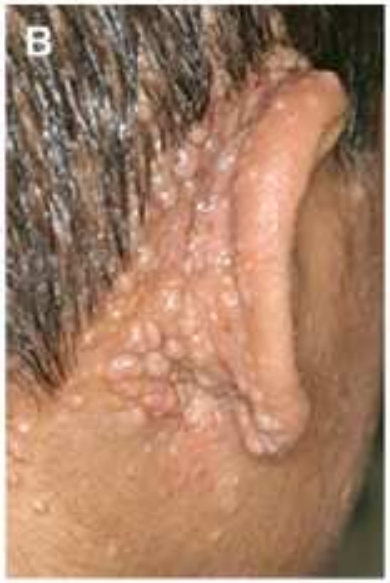
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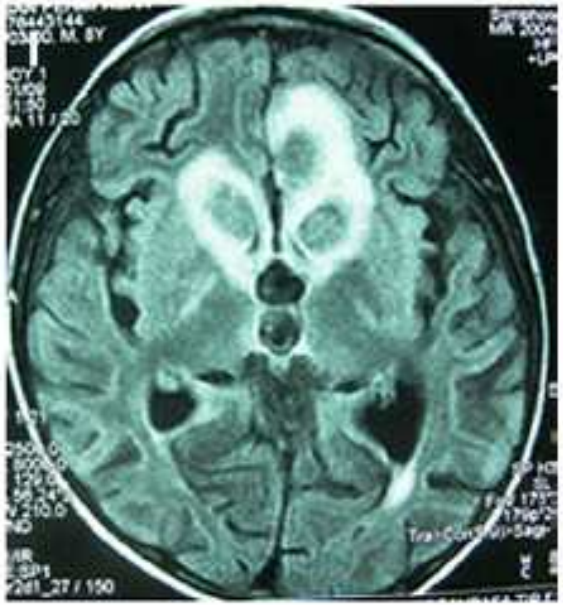
I

Sindrome da Iper-IgE autosomica -recessiva: strategie terapeutiche

Controllo delle infezioni:

- Detersione cute;
- Profilassi antimicrobica;
- Profilassi antifungina;
- Profilassi antivirale;
- Terapia antimicrobica mirata e tempestiva delle infezioni.

Bone Marrow Transplant. 2010 Jul 12.

Curative treatment of autosomal-recessive hyper-IgE syndrome by hematopoietic cell transplantation.

Gatz SA, Benninghoff U, Schütz C, Schulz A, Hönig M, Pannicke U, Holzmann KH, Schwarz K, Friedrich W. University Children's Hospital Ulm, Ulm, Germany.

Abstract

..... Here, we report on lasting control over the disorder in **two patients** by **hematopoietic cell transplantation** (HCT). Both patients were suffering from extensive long-lasting cutaneous viral complications, in particular from disfiguring molluscum contagiosum infections, when treated at the **age of 10 and 17 years**. Donors were matched unrelated, and conditioning was carried out with a combination of fludarabine, melphalan and BM-targeted radioimmunotherapy. Both patients developed stable, full donor cell chimerism, with the exception of persistent low-IgA serum levels and the exception of normal immune functions. Over the course of several months, cutaneous manifestations of viral disease resolved completely and both patients remain clinically well and free of infectious complications at 4 and 2 years, respectively, after transplantation. **This represents the first report indicating HCT to be curative in patients with AR-HIES, which should be considered early before life-threatening complications develop, which include malignancies.**

Successful engraftment of donor marrow after allogeneic hematopoietic cell transplantation in autosomal-recessive hyper-IgE syndrome caused by *dedicator of cytokinesis 8* deficiency

In summary, we report a child with *DOCK8* deficiency who underwent allogeneic HCT after myeloablative conditioning and demonstrated full donor chimerism early after transplant. These results suggest that HCT may be a viable option to treat *DOCK8* deficiency. Unfortunately, the death of the patient precluded further follow-up of immune function and clinical status.

Because *DOCK8* is expressed in both hematopoietic and nonhematopoietic tissues, further experience and long-term follow-up will be needed to determine whether correction of the hematopoietic compartment is sufficient to protect *DOCK8*-deficient patients from infection and cancer.

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Conclusioni e riflessioni (1)

La Sindrome da Iper IgE è rimasta un'enigma per decadi dopo la sua iniziale descrizione clinica.

L'identificazione di mutazioni genetiche nel patway JAK-STAT ci ha permesso di comprendere numerosi aspetti sia eziologici che patogenetici, dalle infezioni polmonari all'eczema, agli aneurismi.

La possibilità di una diagnosi genetico-molecolare certa ha consentito di ottenere diagnosi più precoci.

Conclusioni e riflessioni (2)

Ancora una volta, lo studio dei soggetti con sindrome da Iper IgE così come di molte altre Immunodeficienze primitive ci ha dimostrato il "potere" degli "experimenta naturae" nella comprensione dei meccanismi del complesso sistema immunitario.

La migliore comprensione dei meccanismi patogenetici delle diverse caratteristiche cliniche consente la pianificazione di strategie terapeutiche più razionali ed efficaci.