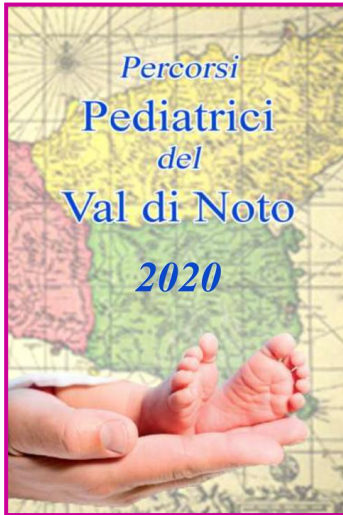


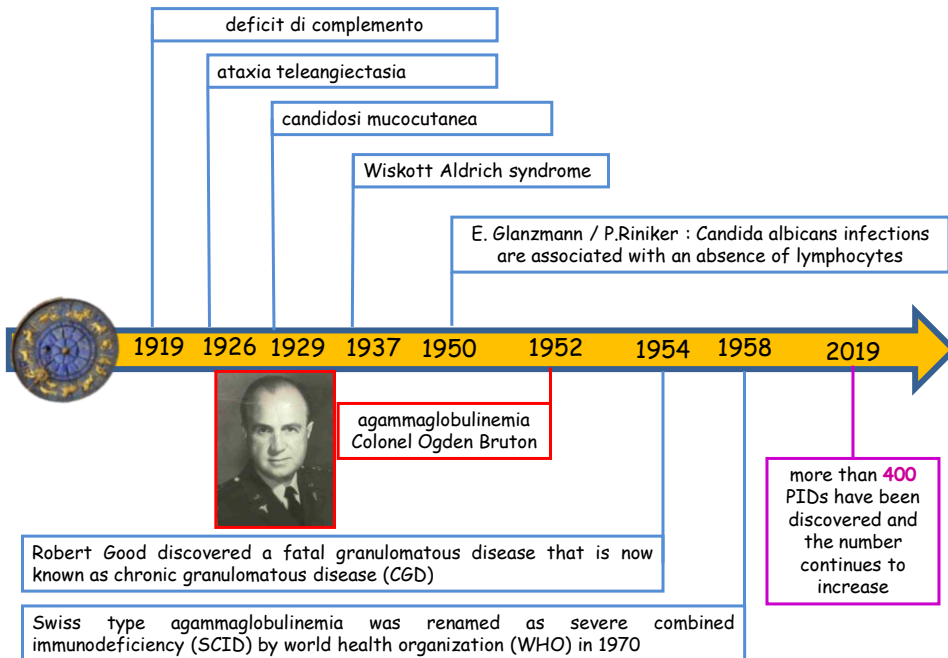


Università degli Studi di Messina  
 AOI Policlinico Universitario G. Martino  
 Scuola di Specializzazione in Pediatria  
 U.O. C. di Pediatria d'Urgenza con PS e OB  
 Centro Vaccinazioni Protette  
 Centro Malattie Genetiche Pediatriche  
 Centro IPINET (Italian Primary Immunodeficiency Network)

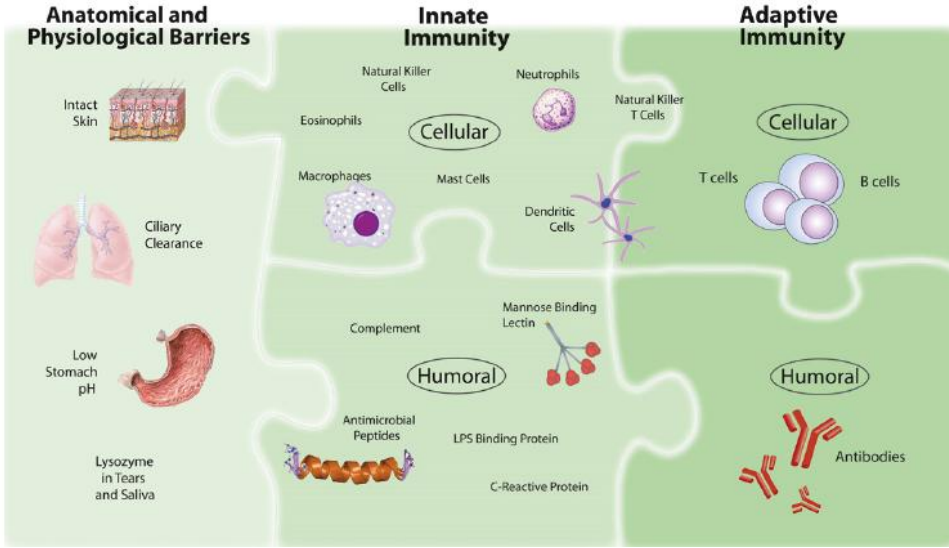


## QUANDO SOSPETTARE UN' IMMUNODEFICIENZA

Carmelo Salpietro



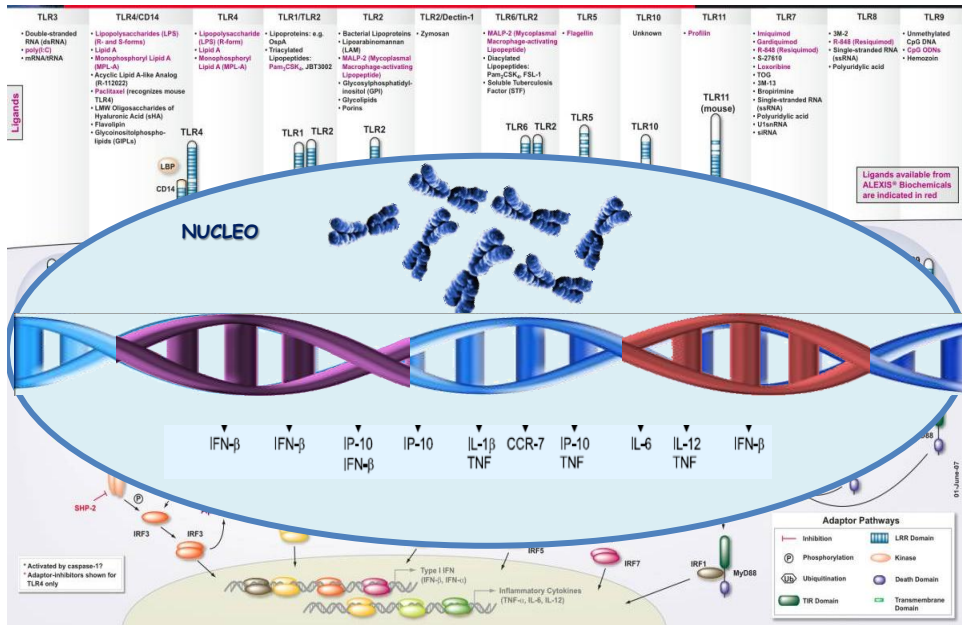
## LE COMPONENTI DEL SISTEMA IMMUNITARIO INTEGRATO



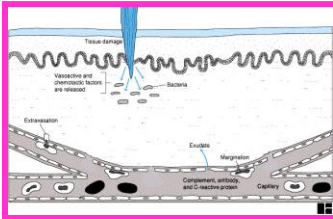
J ALLERGY CLIN IMMUNOL  
VOLUME 125, NUMBER 2

TURVEY AND BROIDE

## ANTIGENI E TLR



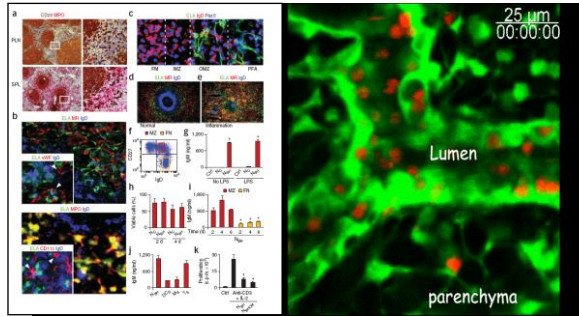
## SENTINELLE DEL SISTEMA IMMUNITARIO: I NEUTROFILI



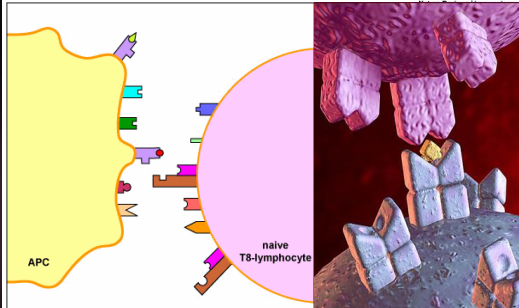
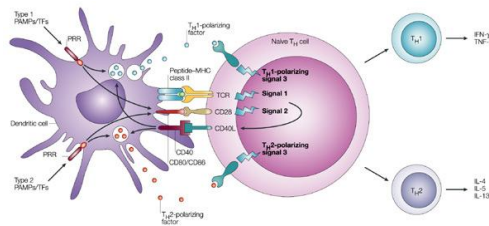
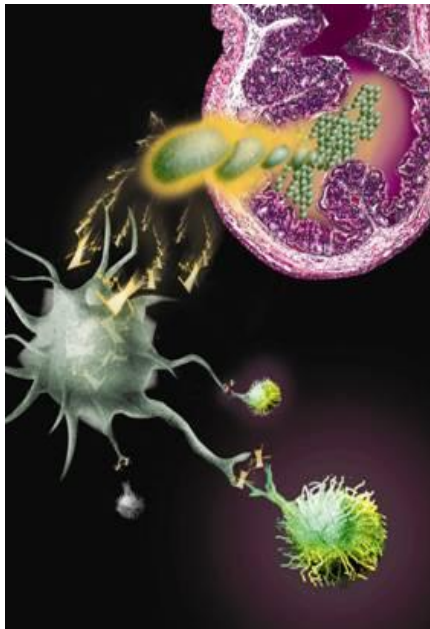
VOLUME 13 | NUMBER 2 | FEBRUARY 2012 | NATURE IMMUNOLOGY **nature immunology**

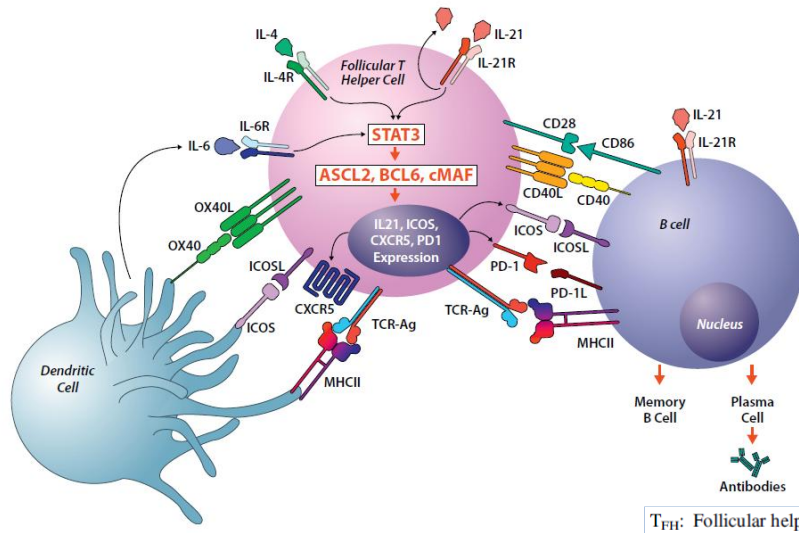
## B cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen

Irene Puga<sup>1,27</sup>, Montserrat Cols<sup>1,27</sup>, Carolina M Barra<sup>1</sup>, Bing Ho<sup>2</sup>, Linda Cassio<sup>1</sup>, Maurizio Gentile<sup>1</sup>, Laura Comerma<sup>2</sup>, Alejo Chorny<sup>2</sup>, Meimei Shan<sup>2</sup>, Wafeng Xu<sup>1</sup>, Giuliana Magri<sup>1</sup>, Daniel M Knowles<sup>4</sup>, Wayne Tam<sup>4</sup>, April Chin<sup>5</sup>, James B Russel<sup>6</sup>, Sergi Serrano<sup>6</sup>, José Antonio Lorente<sup>7</sup>, Beatriz Bellosillo<sup>8</sup>, Josep Lloreta<sup>8</sup>, Nuria Juaneperu<sup>8</sup>, Francesc Alameda<sup>9</sup>, Teresa Baró<sup>9</sup>, Cristina Diaz de Heredia<sup>9</sup>, Nuria Torán<sup>9</sup>, Albert Catalá<sup>10</sup>, Montserrat Torrebada<sup>10</sup>, Claudia Fortuny<sup>11</sup>, Victoria Cusi<sup>12</sup>, Carmen Carreras<sup>13</sup>, George A Diaz<sup>14</sup>, J Magarian Blander<sup>7</sup>, Claire-Michèle Farber<sup>15</sup>, Guido Silvestri<sup>16</sup>, Charlotte Cunningham-Rundles<sup>7</sup>, Michaela Calvillo<sup>17</sup>, Carlo Dufour<sup>17</sup>, Lucia Dora Notarangelo<sup>18</sup>, Vasilios Lougaris<sup>19</sup>, Alessandro Flebani<sup>19</sup>, Jean-Laurent Casanova<sup>20,21</sup>, Stephanie C Ganai<sup>22</sup>, Andreas Diefenbach<sup>23</sup>, Juan Ignacio Aróstegui<sup>24</sup>, Manel Juan<sup>25</sup>, Jordi Yague<sup>26</sup>, Nizar Mahlaoui<sup>24</sup>, Jean Donadieu<sup>25</sup>, Kang Chen<sup>3</sup> & Andrea Cerutti<sup>1,2,26</sup>



## INTERAZIONE CELLULA DENDRITICA/LINFOCITA





T<sub>HH</sub>: Follicular helper T

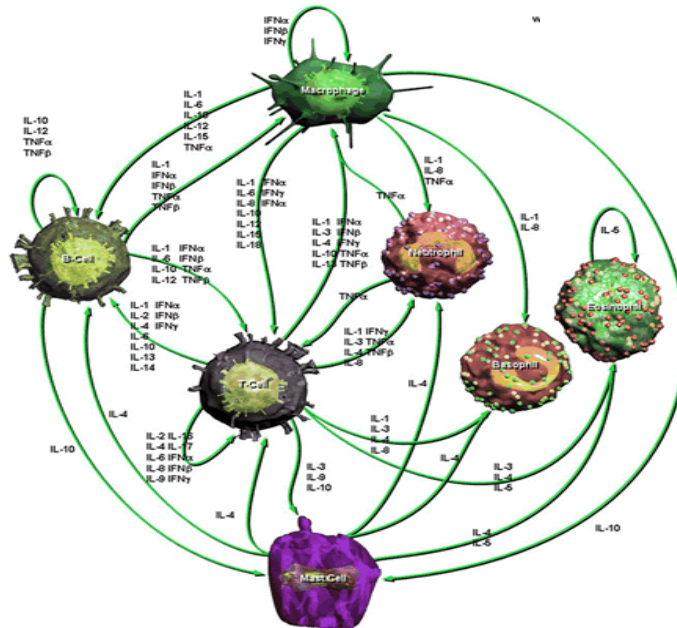
TABLE I. T<sub>HH</sub> cells are affected in patients with PIDs<sup>6</sup>

Abnormality	Defective gene
Reduced frequency of T <sub>HH</sub> cells	CD40LG, NEMO, STAT3, ICOS, BTK, IL10R, E2A
Skewing of T <sub>HH</sub> cells to the T <sub>H1</sub> phenotype	STAT1 GOF, STAT3
Defective T <sub>HH</sub> cells	SH2D1A

NEMO, NF- $\kappa$ B essential modulator.

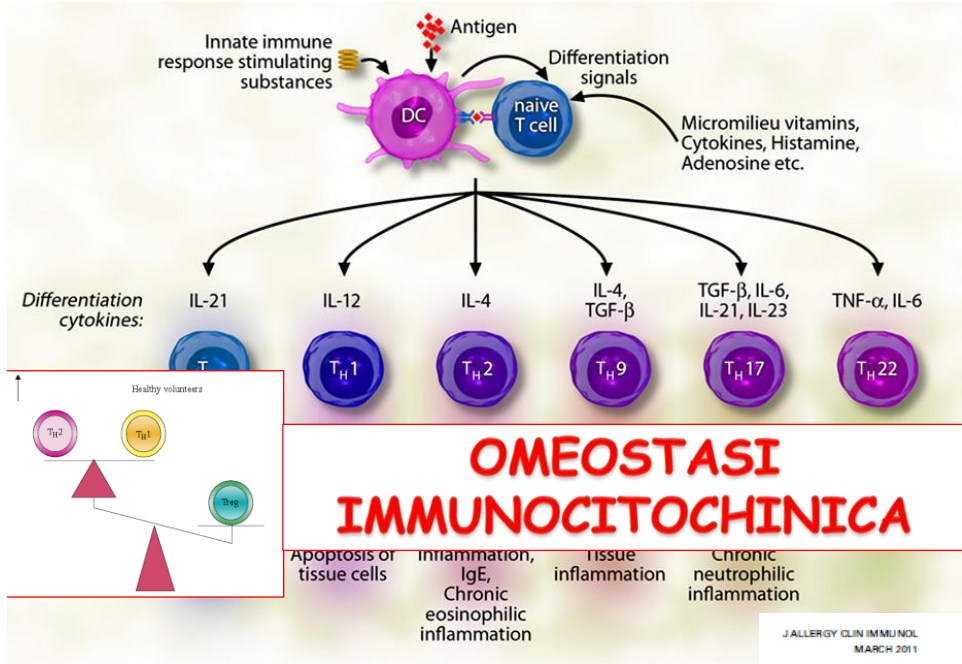
J ALLERGY CLIN IMMUNOL  
OCTOBER 2018

## NETWORK OF CYTOKINES AND CHEMOKINES

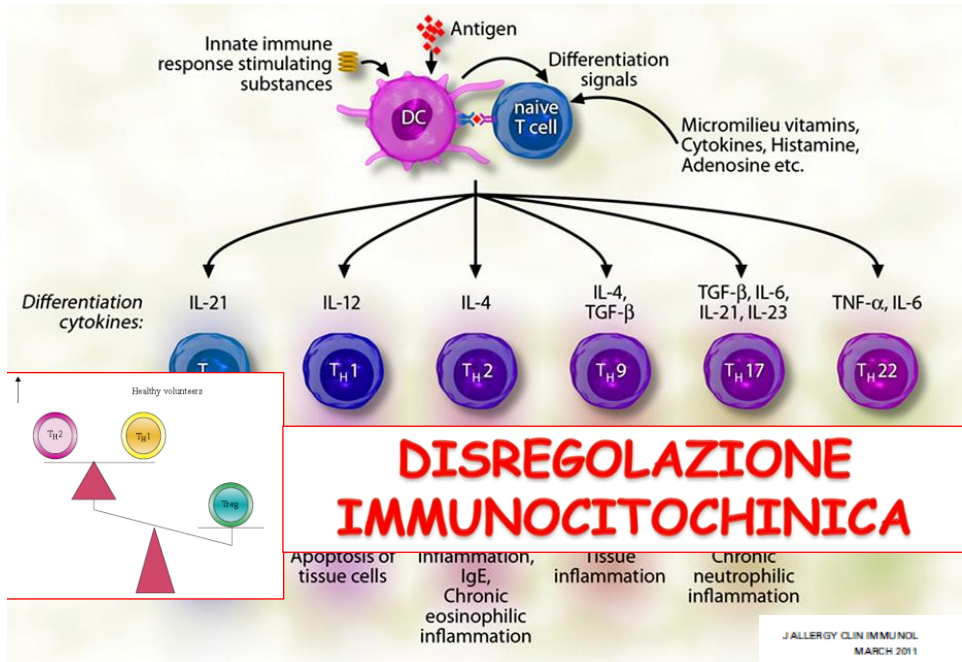


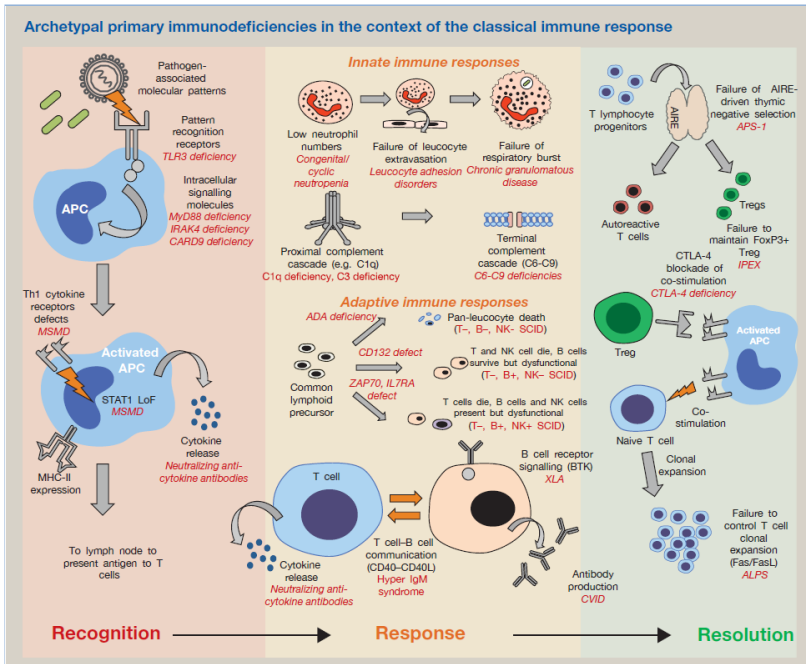


### INTERAZIONE GERME/OSPITE

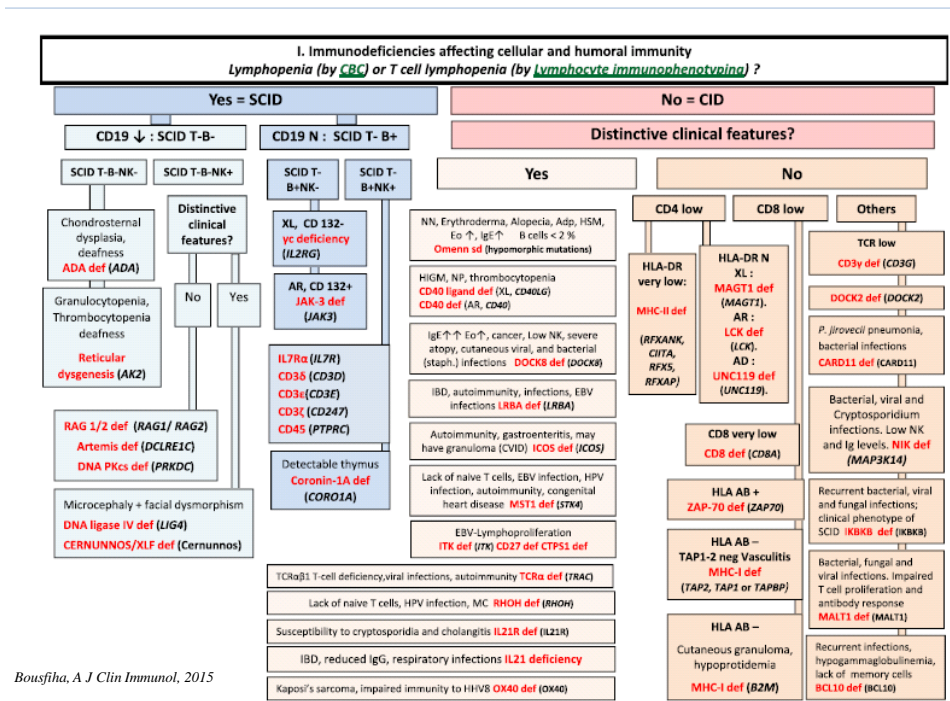


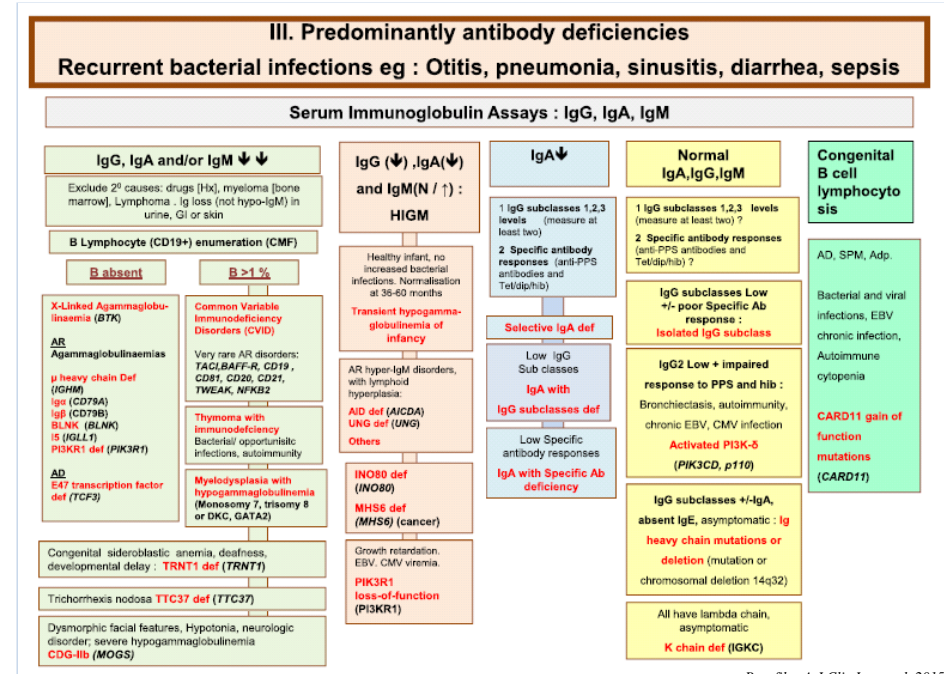
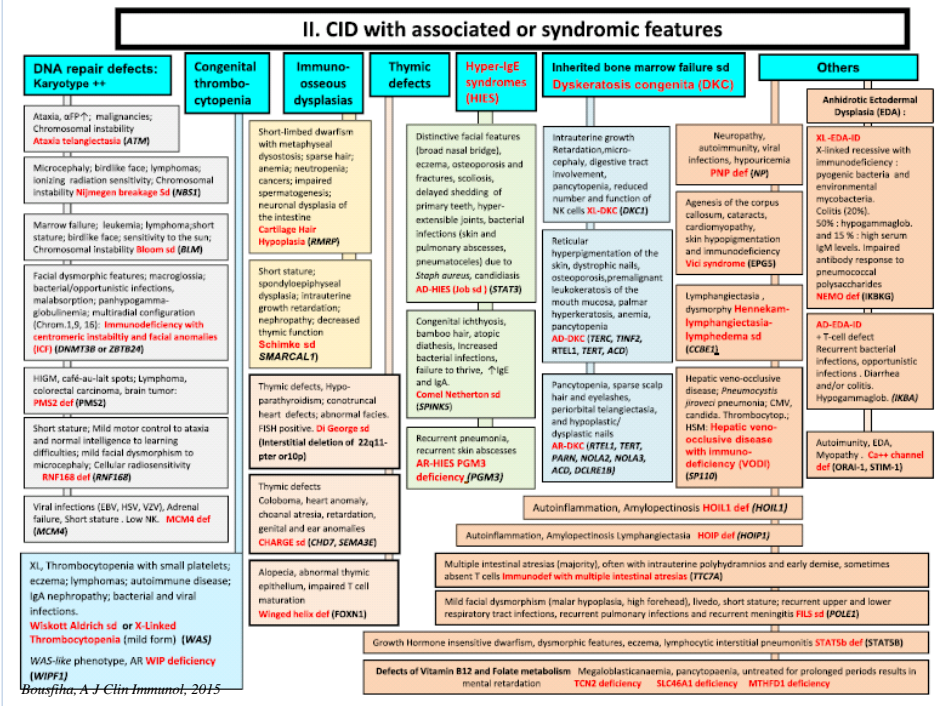
### INTERAZIONE GERME/OSPITE





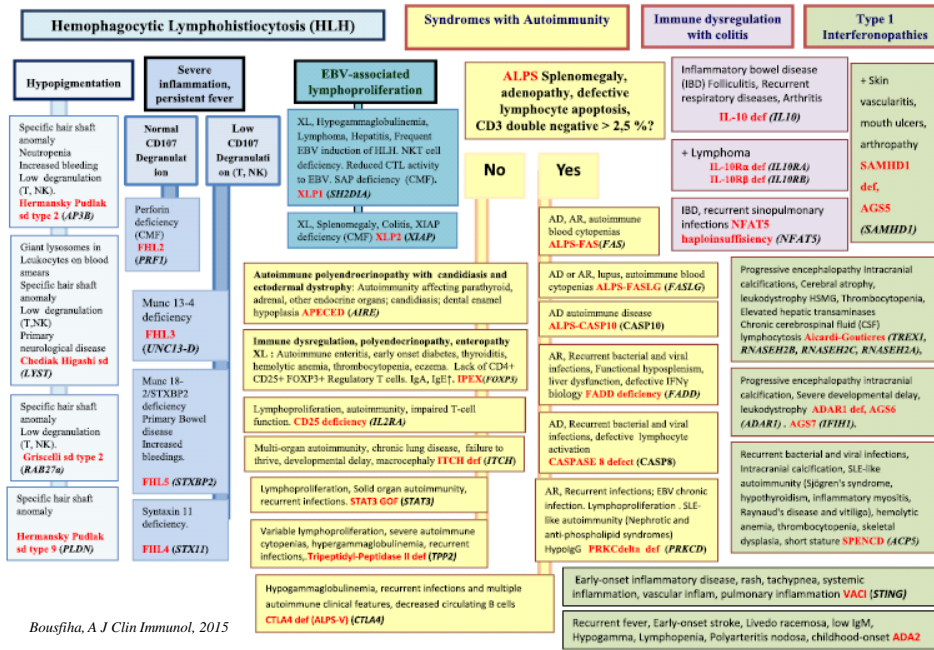
Medicine 45:10. 2017





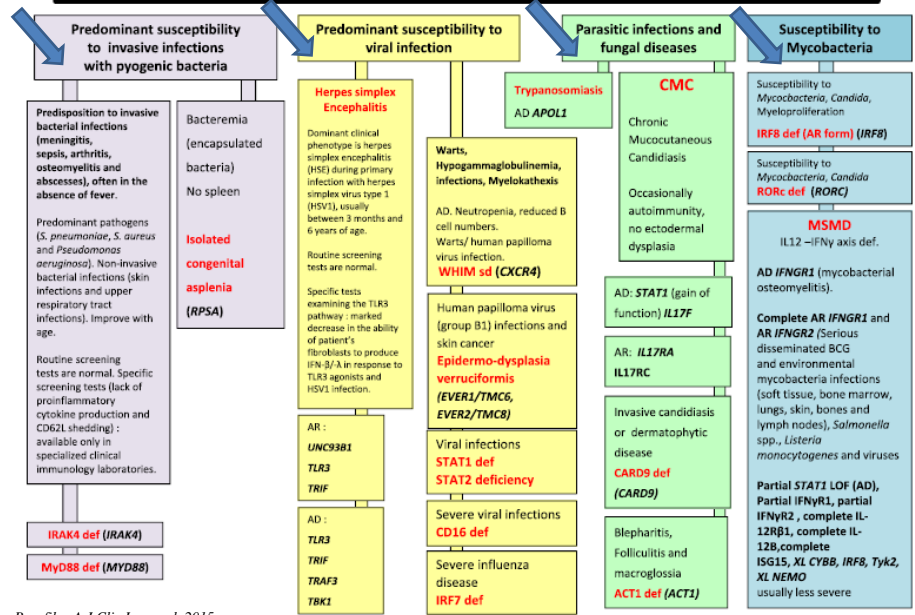
Bousfiha, A J Clin Immunol, 2015

### IV. Diseases of immune dysregulation



Bousfiha, A J Clin Immunol, 2015

### VI. Defects in intrinsic and innate immunity

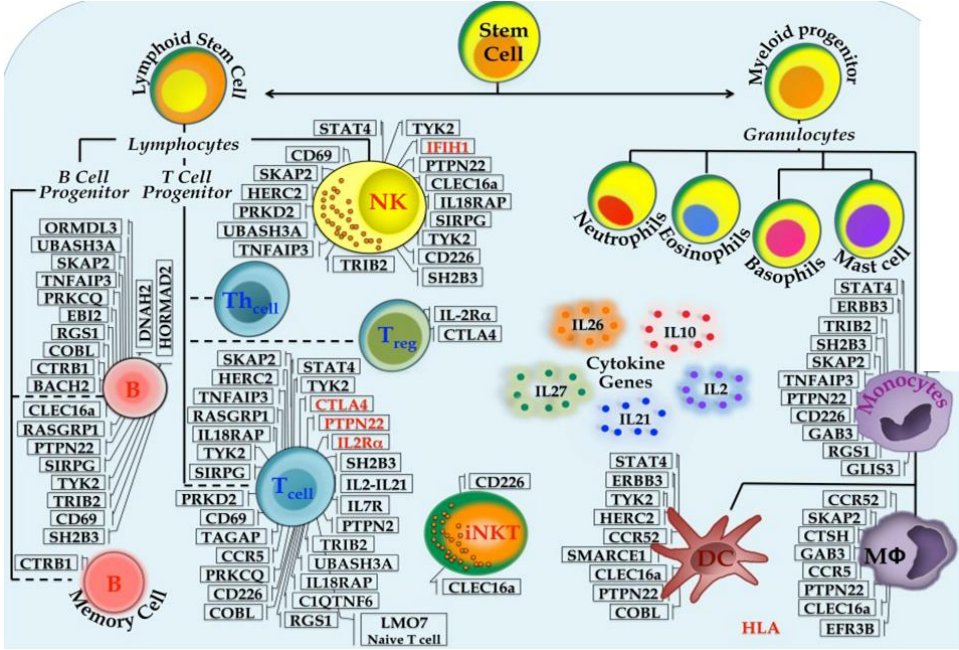


Bousfiha, A J Clin Immunol, 2015

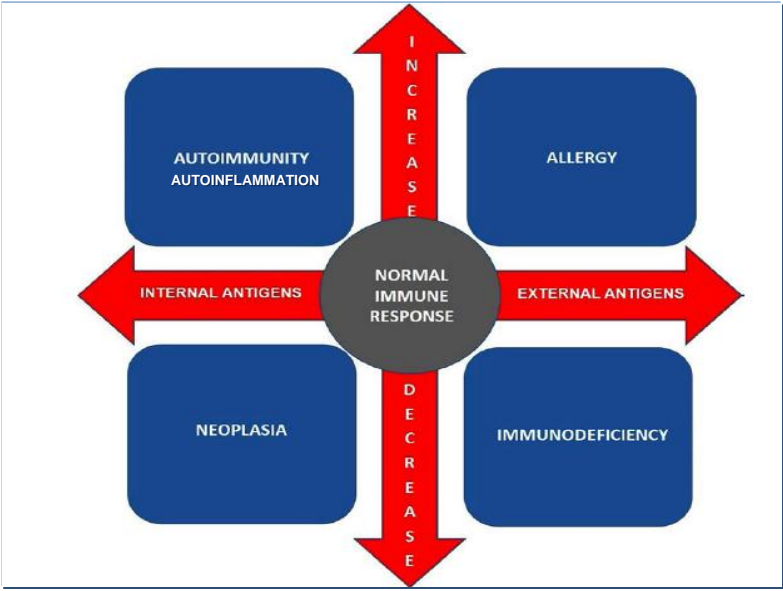
J Clin Immunol (2015) 35:727-738



# CONTROLLO GENICO DELLE CELLULE IMMUNITARIE

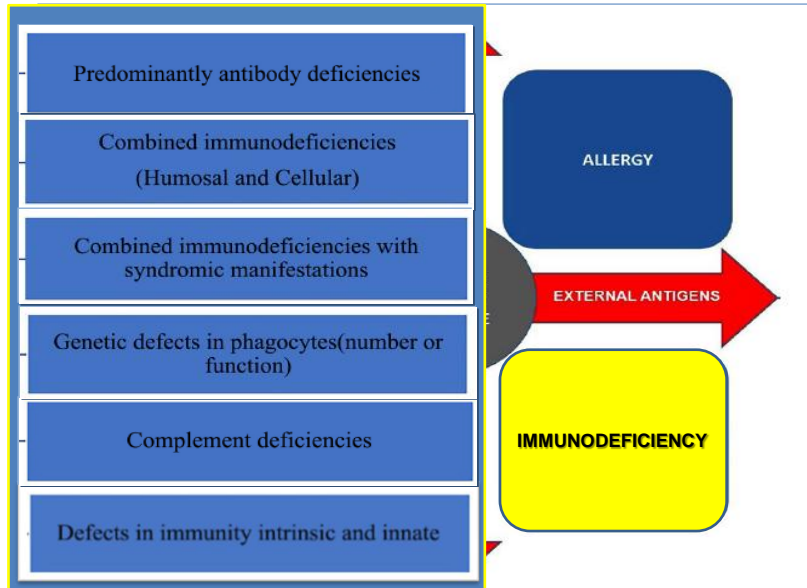


# DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE



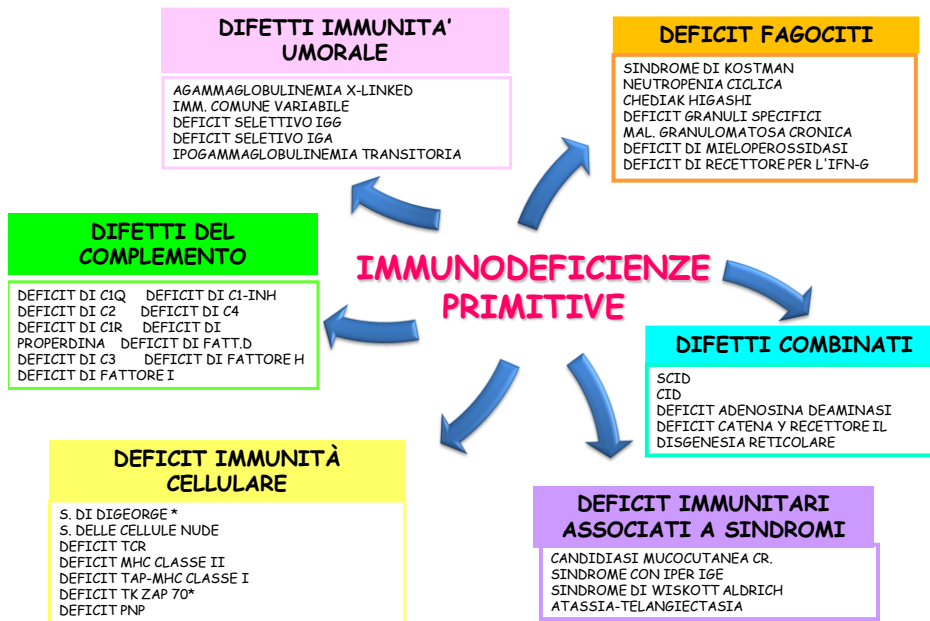
Library Journal Vol.06 No.05(2019)

## DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE



Library Journal Vol.06 No.05(2019)

## PRIMARY IMMUNODEFICIENCY

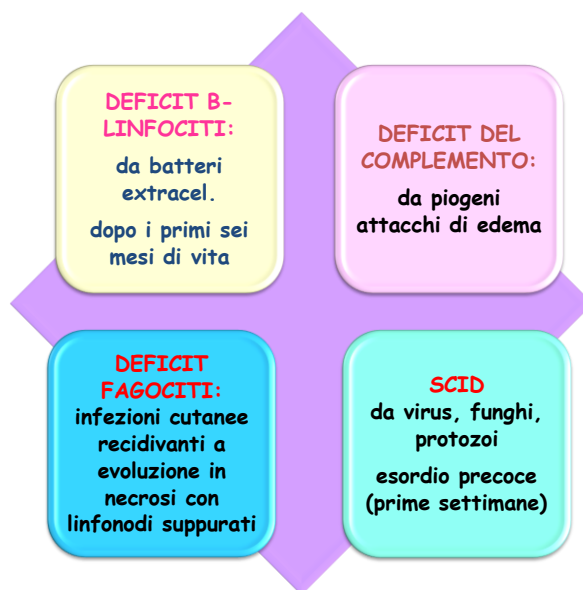


## 10 Campanelli di Allarme delle Immunodeficienze Primitive

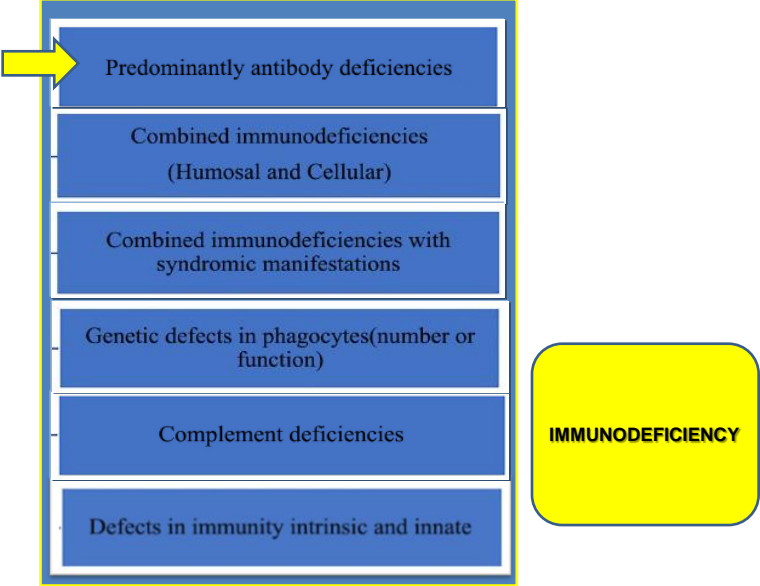


<b>1</b>	Otto o più infezioni nel corso di un anno.	<b>6</b>	Ascessi ricorrenti e profondi alla cute o agli organi.
<b>2</b>	Due o più gravi infezioni ai seni nasali in un anno.	<b>7</b>	Afte persistenti nella bocca o in altre parti del corpo dopo il primo anno di età.
<b>3</b>	Due o più mesi di trattamento antibiotico con scarsi risultati.	<b>8</b>	Necessità di ricorrere agli antibiotici per via endovenosa per combattere le infezioni.
<b>4</b>	Due o più polmoniti in un anno.	<b>9</b>	Due o più infezioni profonde come: meningite, osteomielite, sepsi.
<b>5</b>	Il bambino non riesce ad aumentare di peso o a crescere normalmente.	<b>10</b>	Presenza nella stessa famiglia di casi di immunodeficienza primitiva.

### COME ORIENTARSI



# DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE

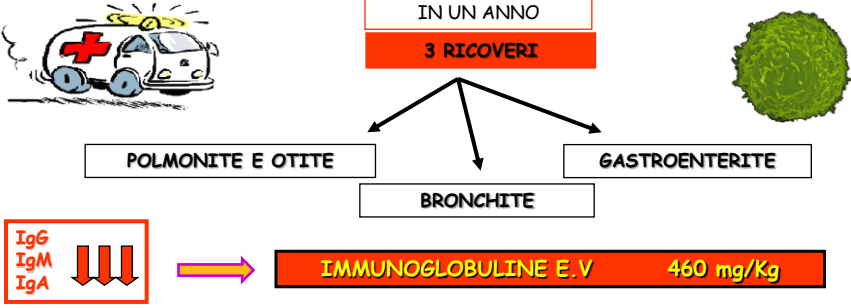


Library Journal Vol.06 No.05(2019)

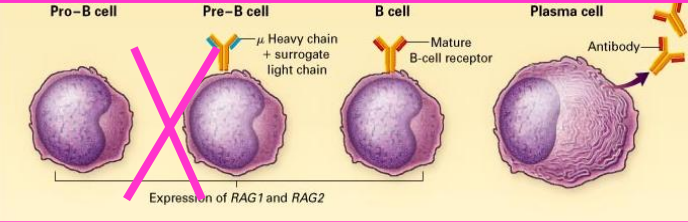
## EROS

Predominantly antibody deficiencies

A PARTIRE DAL 7° MESE DI VITA RICORRENTI EPISODI DI FLOGOSI A CARICO DELLE PRIME VIE AEREE



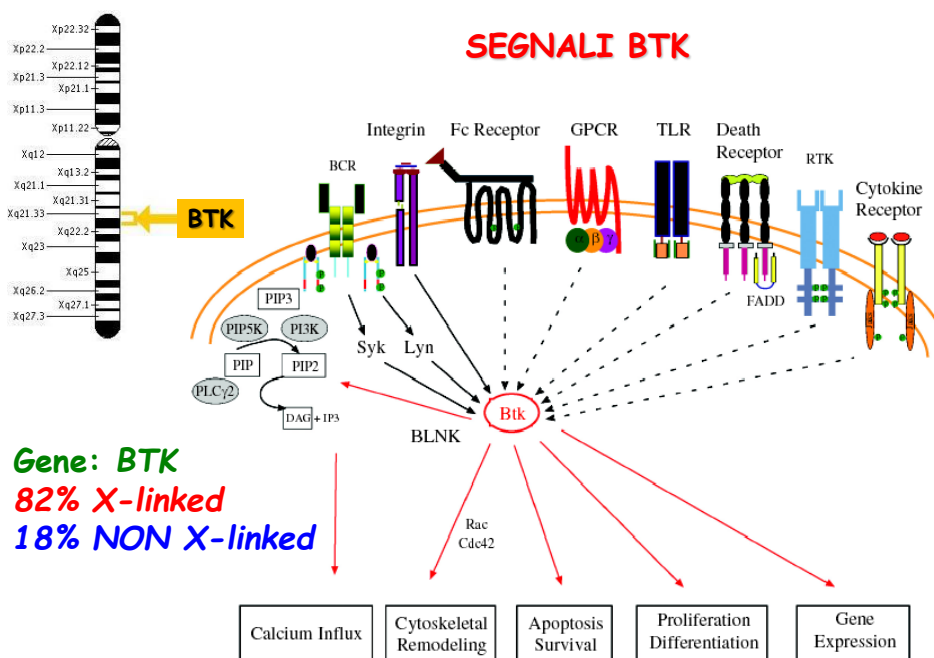
## AGAMMAGLOBULINEMIA CONGENITA (MALATTIA DI BRUTON)



### BTK

The patient has a mutation on exon 15, A504T, which changed an asparagine residue to a valine residue.





- ❑ # 300300 BRUTON AGAMMAGLOBULINEMIA TYROSINE KINASE; BTK Gene map locus Xq21.3-q22
- ❑ # 601495 AGAMMAGLOBULINEMIA 1, AUTOSOMAL RECESSIVE; AGM1 Gene map locus 14q32.33
- ❑ # 613501 AGAMMAGLOBULINEMIA 3, AUTOSOMAL RECESSIVE; AGM3 Gene map locus 19q13.2
- ❑ # 613500 AGAMMAGLOBULINEMIA 2, AUTOSOMAL RECESSIVE; AGM2 Gene map locus 22q11.21
- ❑ # 612692 AGAMMAGLOBULINEMIA 6, AUTOSOMAL RECESSIVE; AGM6 Gene map locus 17q23
- ❑ # 613502 AGAMMAGLOBULINEMIA 4, AUTOSOMAL RECESSIVE; AGM4 Gene map locus 10q23.2
- ❑ # 613506 AGAMMAGLOBULINEMIA 5, AUTOSOMAL DOMINANT; AGM5 Gene map locus 9q34.13
- ❑ # 300310 AGAMMAGLOBULINEMIA, X-LINKED, TYPE 2; AGMX2 Gene map locus Xp22

**GIOVANNI 11anni****SAMUELE 7 anni**

Fin dai primi mesi di vita infezioni recidivanti delle alte e basse vie aeree, otiti e IVU con necessita' di ricovero

**Emocromo:** GR 4660000 mmc GB 3500 mmc  
N 20% L 80% PCR 1 mg/DL VES 19

**IMMUNOGLOBULINE**

- IgA 29 (v.n. 60-270)
- IgG 423 (v.n. 707-1919)
- IgM 41 (v.n. 61-276)

**DOSAGGIO SOTTOCLASSI IG**

- IgG1 400 (v.n. 646-129)
- IgG2 104 (v.n. 337-100)
- IgG3 47 (v.n. 64- 44)
- IgG4 6 (v.n. 71-54)

**SOTTOPOPOLAZIONI LINFOCITARIE**

- CD3 71%(55-84)
- CD4 38%(31-60)
- CD4/CD8 1,65
- CD8 23%(13-41)
- CD19 22%(6-25)

- IgG tossoide 0,43 (0,11-0,5) +
- IgG difterico 0,06 (0,01-0,09) +/-
- HbsAg 12,50 (> 11 positivo)

**Emocromo:** GR 4460000 mmc GB 6800 mmc N  
50% L 43% PCR 0,01 mg/DL VES 10

**IMMUNOGLOBULINE**

- IgA 30 (v.n. 41-315)
- IgG 416 (v.n. 633-1016)
- IgM 37 (v.n. 56-261)

**DOSAGGIO SOTTOCLASSI IG**

- IgG1 400 (v.n. 571-116)
- IgG2 73 (v.n. 257-110)
- IgG3 24 (v.n. 61- 34)
- IgG4 6 (v.n. 32-25)

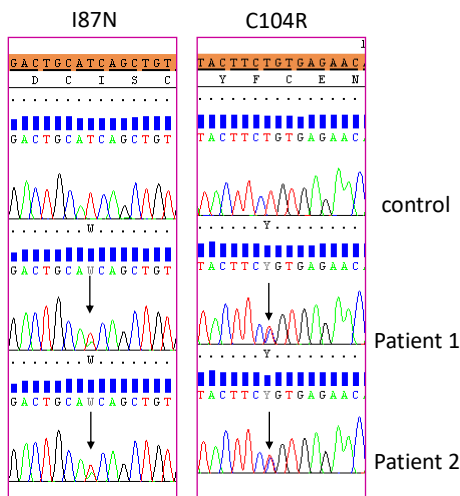
**SOTTOPOPOLAZIONI LINFOCITARIE**

- CD3 64% (55-84)
- CD4 30% (31-60)
- CD4/CD8 1.20
- CD8 25% (13-41)
- CD19 22% (6-25)

- IgG tossoide 0,83 (0,11-0,5)
- IgG difterico 0,16 (0,01-0,09)
- HbsAg 6,60 (> 11 positivo)

**A novel compound heterozygous TAC1 mutation in an autosomal recessive Common Variable Immunodeficiency (CVID) family**

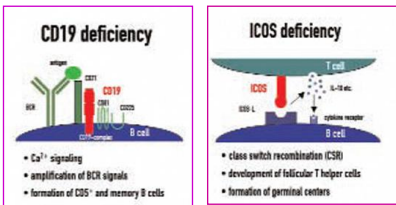
V. Lougaris<sup>1</sup>, R. Gallizzi<sup>2</sup>, M. Vitali<sup>1</sup>, M. Baronio<sup>1</sup>, A. Salpietro<sup>2</sup>, A. Bergbreiter<sup>3</sup>, U. Salzer<sup>3</sup>, R. Badolato<sup>1</sup>, A. Plebani<sup>1</sup>



Common Variable Immunodeficiency (CVID) is a primary immune disorder characterized by low immunoglobulin serum levels and increased susceptibility to infections. Underlying genetic causes are only known in less than 15% of patients and encompass mutations in the genes encoding for ICOS, TAC1, BAFF-R, CD19, CD20, CD81 and MSH5. TAC1 is the most frequently mutated gene among CVID patients. We report on two paediatric Italian male siblings with hypogammaglobulinemia and recurrent respiratory and gastrointestinal infections in association with a novel compound heterozygous TAC1 mutation. Both patients carry the I87N/C104R mutation that has not been reported yet. This results in aberrant TAC1 expression and abrogates APRIL binding on EBV B-cells. This study identifies a novel combined mutation in *TNFRSF13B* increasing the spectrum of TAC1 mutations associated with CVID.

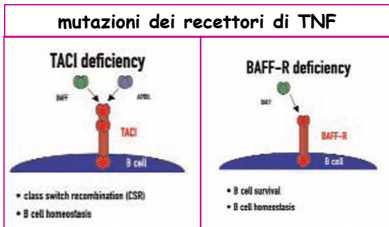
*Human Immunology In press*

Predominantly antibody deficiencies



□ difetto intrinseco delle cellule B (da mutazione di CD19; 16p11.2)

□ difetto intrinseco delle cellule T (da mutazione di ICOS; 2q33)



□ Mut. TNFRSF13B (17p11.2)

□ TNFRSF13C (22q13.1-q13.31)

**IMMUNODEFICIENZA COMUNE VARIABILE**

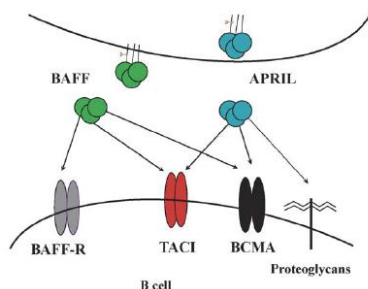
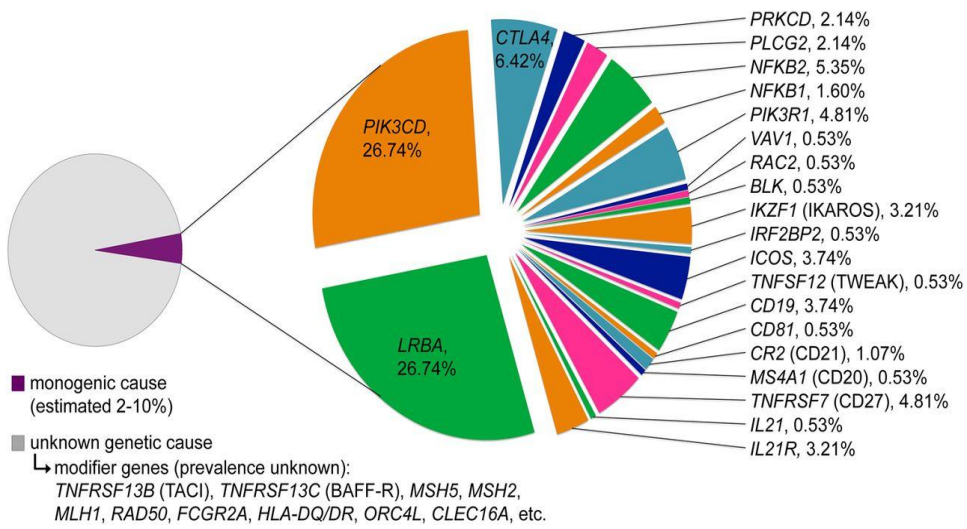


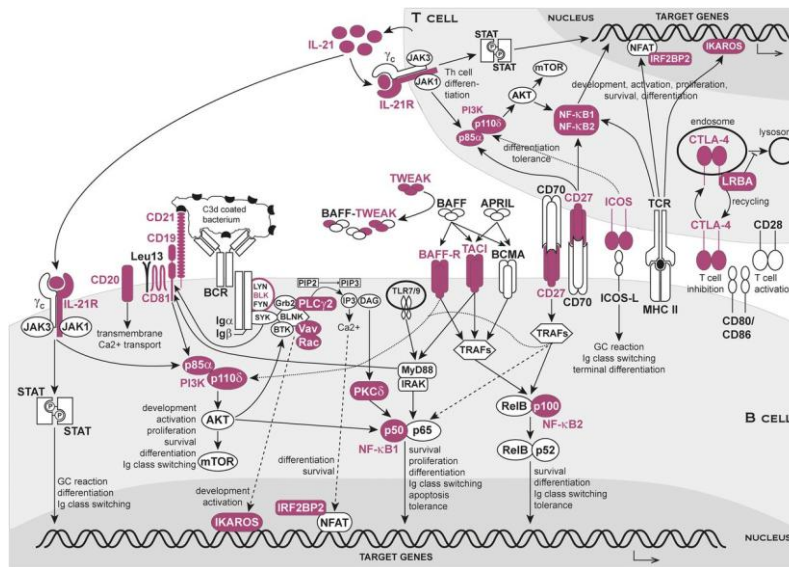
FIG 1. BAFF, APRIL, and their receptors on B cells.

Altri difetti mendeliani noti sono i deficit di MSH5, CD81 e CD20. La maggior parte dei casi è sporadico, ma si ritiene che circa il 20% possa essere familiare, a trasmissione autosomica dominante (80%) o autosomica recessiva (20%).

**GENES ASSOCIATED WITH MONOGENIC FORMS OF CVID: SUMMARY OF GENETIC, CLINICAL AND IMMUNOLOGICAL FEATURES**



**PROTEINS ENCODED BY COMMON VARIABLE IMMUNODEFICIENCY DISEASE GENES**



**AOU POLICLINICO - MESSINA**  
**UOC PEDIATRIA D'URGENZA CON Ps e OB**  
**AMBULATORIO IMMUNOALLERGOLOGIA**

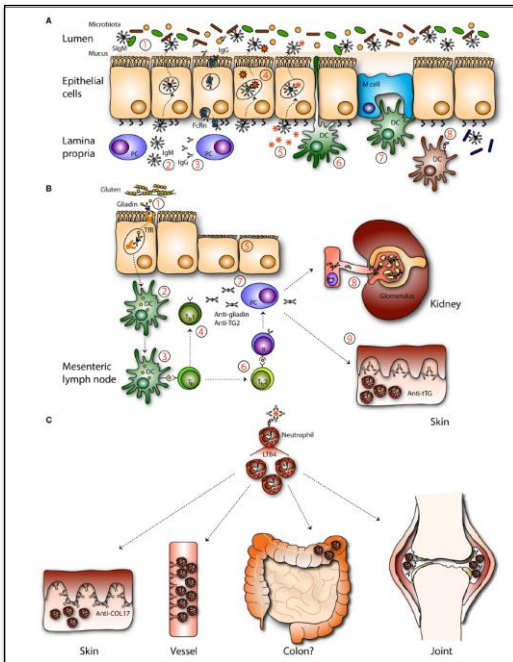
**2001-2018**  
**24.200 visite b/ni 1-6 anni**

**7431 IRR**

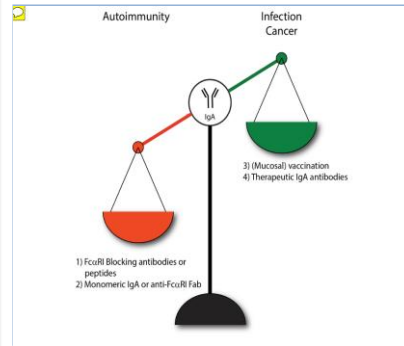


0,3% IMMUNODEFICIENZE
5,1% DEFICIT IgA
43% ATOPIA



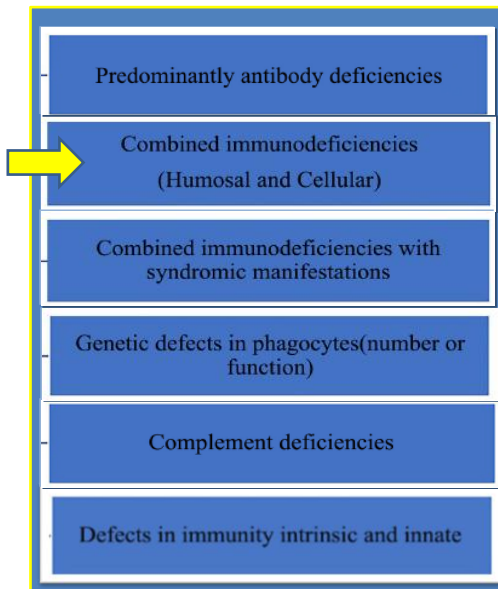


**MUCOSAL IGA DEFICIENCY**



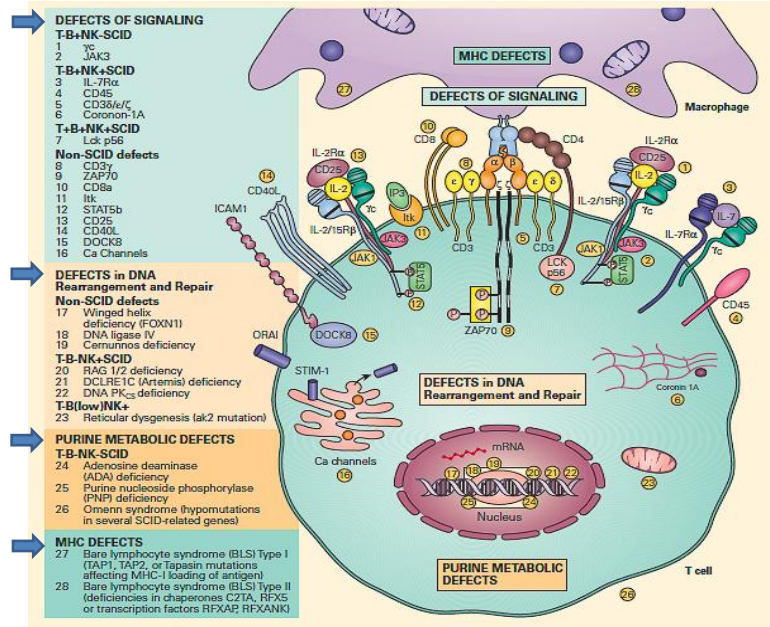
Frontiers in Immunology March 2019 | Volume 10 | Article 553

**DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE**

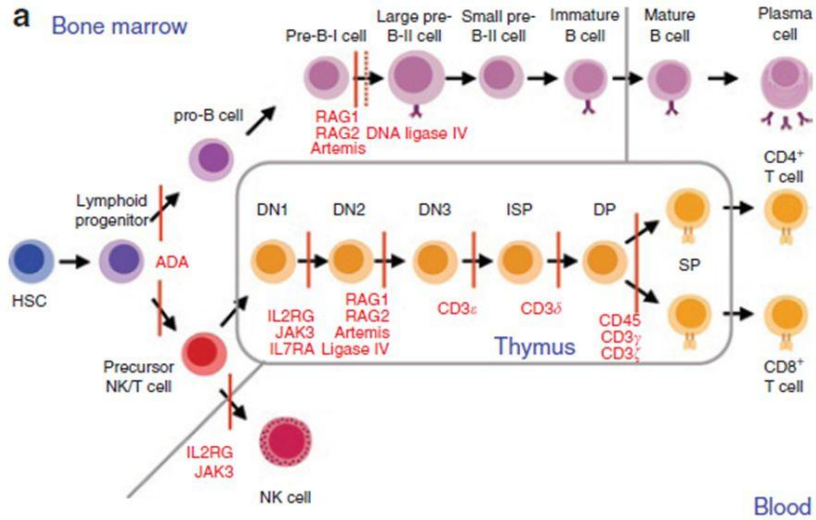


**IMMUNODEFICIENCY**

# COMBINED T CELL AND B CELL DEFECTS



## Severe Combined ID



Davide 2 mesi  
 Unigenito, Nato alla 38° settimana di gestazione  
 Parto eutocico, PN 3.250 Kg. L 50 cm  
 Perinatalità nella norma  
 Ittero fisiologico. Allattamento con formula.  
**1 mese:**  
**ERITRODERMIA E DESQUAMAZIONE CUTANEA DIFFUSA**  
**DIAGNOSI DI APLV → idrolisato spinto**



**EO:** Diarrea importante  
 Mughetto al cavo orale  
 Xerosi cutanea diffusa in corrispondenza del viso, cuoio capelluto, arti inferiori, tronco, mani; intensa desquamazione essudativa in sede retroauricolare, guance e pieghe del collo, distrofia  
 Linfadenomegalia ed epatomegalia



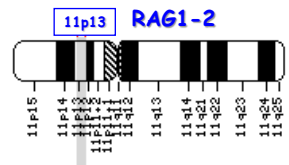
**ESAMI EMATOCHIMICI:**  
 GB: 10420 mmc (N 65, L 4, E 21, M 10%)  
**assenza** di linfociti B, linfociti T nella norma  
 IgA e IgM **assenti** IgE: 10450 UI/ml

**SINDROME DI OMENN**



**TMO**

**Eterozigote composto per la mutazione C2387T/C30166 del gene RAG1**



**LA SINDROME DI WISKOTT ALDRICH**

(Xp11.22-p11.23)

X-Linked  
 1:250.000 M

- Alterazioni linfo B: pazienti WAS sono capaci di produrre anticorpi contro certi microrganismi (come il tetano) ma sono incapaci di produrne contro altri germi, come l'Hemophilus influenzae o lo pneumococco, che presentano sulla loro membrana antigeni polisaccaridici
- Alterazioni linfo T: candida; Pneumocistis carinii, Herpes virus
- Alterazioni piastrine: piccole e ridotte (15.000-35.000)→ emorragie
- > Malattie autoimmuni

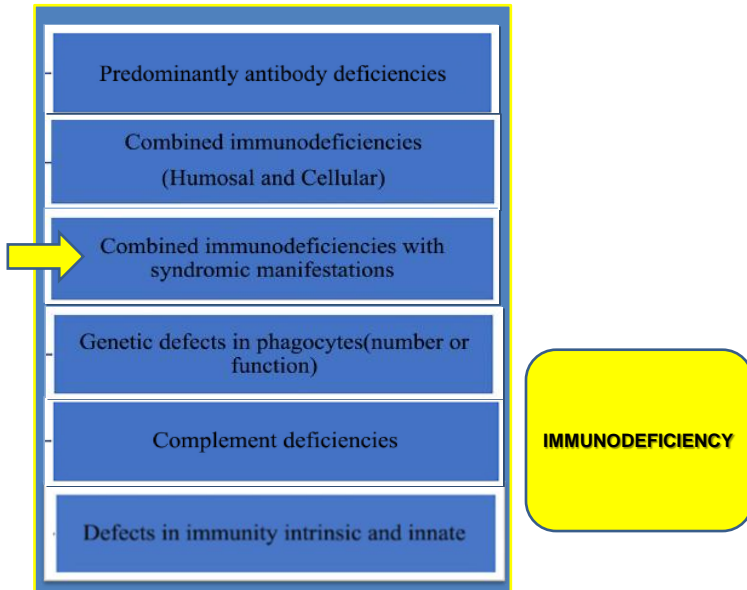
La WAS è classificata come "immunodeficienza combinata", poiché il deficit immunitario colpisce il sistema di entrambi i linfociti B e T, i principali produttori di anticorpi, e come "sindrome", poiché presenta alcuni altri problemi clinici



Disease and OMIM number for disease entry (examples)	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)
Wiskott-Aldrich syndrome (XLT/WAS) <a href="#">301000, 614493</a>	At least one of the following: <ul style="list-style-type: none"> <li>• eczema</li> <li>• recurrent bacterial or viral infections</li> <li>• autoimmune diseases (incl. vasculitis)</li> <li>• malignancy</li> <li>• reduced WASP expression in a fresh blood sample</li> <li>• abnormal antibody response to polysaccharide antigens and/or low isohemagglutinins</li> <li>• positive maternal family history of XLT/WAS</li> </ul> AND male patient with thrombocytopenia (less than 100,000 platelets/mm3) (measured at least twice) AND small platelets (platelet volume < 7,5 fl)

ESID Registry - Working definitions for clinical diagnosis of I/EI

## DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE



Library Journal Vol.06 No.05(2019)

## SINDROME 18q-: CORRELAZIONE GENOTIPO/FENOTIPO

<p>Bassa statura Ritardo mentale grave Microcefalia Ipertelorismo, Epicanto, Ptosi palpebrale, Nistagmo Strabismo, Orecchie a basso impianto Prominenza dell' elice e dell' antielice, bocca a carpa, dita lunghe, affusolate</p> <p style="text-align: right;"><b>ELENA</b></p>	
<p>severe / moderate MR</p>	
<p>Bassa statura Ritardo mentale lieve Microcefalia IRR, deficit IgA Epicanto, Nistagmo Strabismo, Orecchie a basso impianto Radice nasale appiattita, labbro superiore corto, mandibola sporgente, cardiopatia congenita</p> <p style="text-align: right;"><b>ALICE</b></p>	
<p>mild MR or normal development</p>	
<p>70   short stature   GH insufficiency &amp; delayed myelination   CAA   CP/CL  </p> <p>76  </p> <p><b>DEFICIT IgA</b></p>	<p>foot deformities</p>

*Int J Immunogenet.* 2007 Jun;34(3):143-7. Mapping susceptibility gene locus for IgA deficiency at **del(18)(q22.3-q23)**: report of familial cryptic chromosome t(18q; 10p) translocations. Dostal A et al.



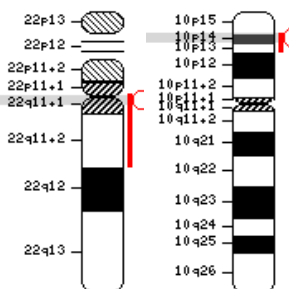
- Alla nascita Tetania ipocalcémica
- ipertelorismo, micrognatia, basso impianto delle orecchie e labbro superiore ipoplasico
- IRR
- Ipoplasia dell'arco aortico e del cuore

Alessia 6mesi



## SINDROME DI DI GEORGE

- cromosoma 22q11
- cromosoma 10p14-p13



Wilson et al. (1991); Shaikh et al. (2000)  
Jawad et al. (2001) Kawame et al. (2001)

## SDR DI NETHERTON

JAMA Dermatology February 10, 2016



"I bamboo hair", come vengono anche definiti, sono caratterizzati dall'invaginazione dell'estremità distale dello stelo del capello nell'estremità prossimale. I capelli sono radi, corti, si spezzano facilmente.

### Eritrodermia ittiosiforme AR

➤ Costituzione **atopica** (elevate IgE totali, manifestazioni atopiche, frequenti **sovrainfezioni** virali, fungine e batteriche, inclusa la "staphylococcal scalded skin syndrome (SSSS)" dalla nascita). Le manifestazioni allergiche più frequenti sono date da **orticaria**, **angioedema**, **dermatite atopica**, **asma**.





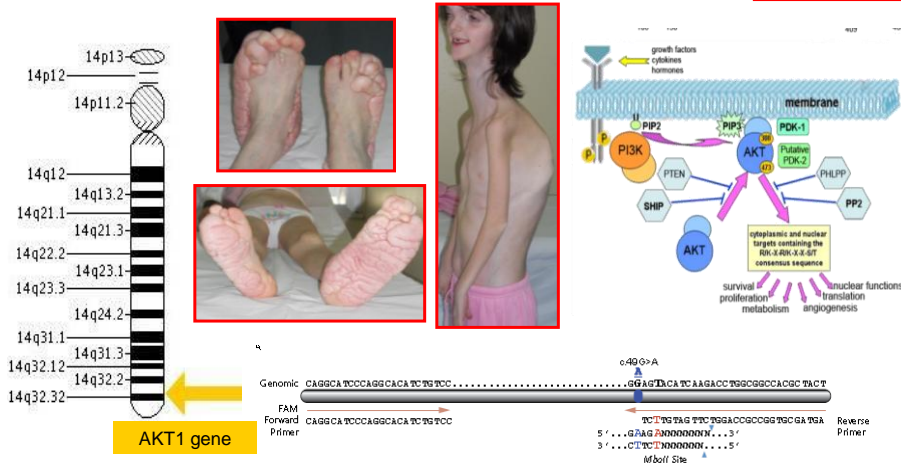
LETTER TO THE EDITOR

Open Access

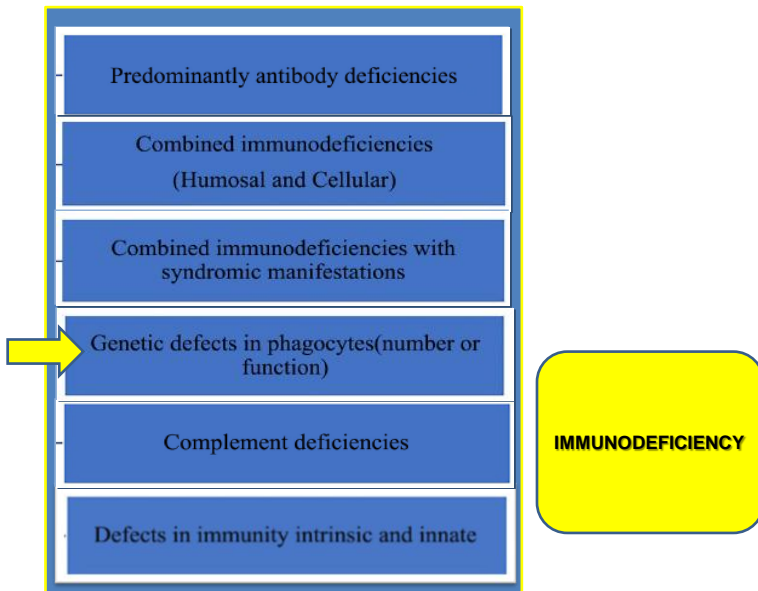


Proteus syndrome: evaluation of the immunological profile

Vassilios Lougaris<sup>1\*</sup>, Vincenzo Salpietro<sup>2</sup>, Maricia Cutrupi<sup>2</sup>, Manuela Baronio<sup>1</sup>, Daniele Moratto<sup>3</sup>, M. R. Pizzino<sup>2</sup>, Kshitiy Mankad<sup>4</sup>, Silvana Briuglia<sup>2</sup>, Carmelo Salpietro<sup>2</sup> and Alessandro Plebani<sup>1</sup>



**DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE**



## MALATTIA GRANULOMATOSA CRONICA

Proteina alterata	Locus genico	Ereditarietà	Sottotipo* (%)	Frequenza dei casi (%)
gp91phox	Xp21	XL	X91 <sup>0</sup> X91 <sup>-</sup> X91 <sup>+</sup>	55-60 5 1-3
p22phox	16p24	AR	A22 <sup>0</sup> A22 <sup>+</sup>	5 1
p47phox	7q11.23	AR	A47 <sup>0</sup>	25
p67phox	1q25	AR	A67 <sup>0</sup> A67 <sup>+/-</sup>	5 <1
p40phox	22q13.1	AR	A40 <sup>0/+</sup>	/

Tabella 1. \* La soprascritta indica che la proteina viene espressa in quantità normale (+), ridotta (-) o è assente (0).

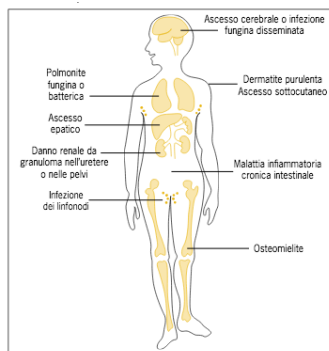
Infezione da Aspergillo a qualsiasi età
Infezione da Serratia a qualsiasi età
Osteomielite
Linfadenite da Stafilococco
Ascesso epatico
Colite granulomatosa
Ostruzione delle vie aeree e/o digestive e/o urinarie da flogosi granulomatosa

Tabella 4. Campanelli d'allarme che devono far pensare ad una Malattia Granulomatosa Cronica.

1:250.000  
M:F= 1:1

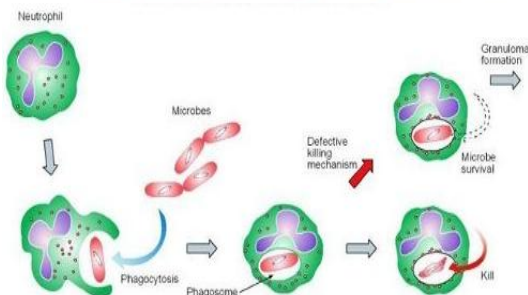
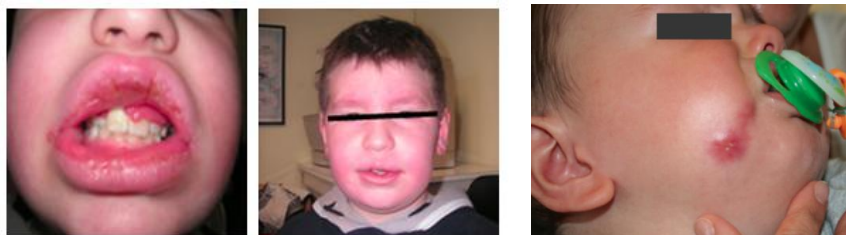
incapacità delle cellule fagocitiche (granulociti neutrofili, eosinofili, monociti e macrofagi) di uccidere i microorganismi fagocitati

Infezioni ricorrenti da: *Aspergillus fumigatus* e *Candida*, e batteri catalasi positivi *Staphylococcus aureus*, *Salmonella*, *Pseudomonas*, etc



ESID Registry - Working definitions for clinical diagnosis of IEG

## MALATTIA GRANULOMATOSA CRONICA

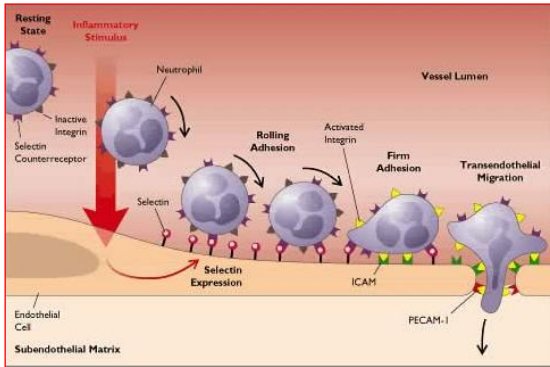


Infezione da <i>Aspergillus spp.</i> a qualsiasi età
Infezione da <i>Serratia marcescens</i> a qualsiasi età
Osteomielite
Linfadenite da Stafilococco
Ascesso epatico
Ostruzione delle vie digestive e/o urinarie da flogosi granulomatosa

AIEOP, 2015

**LEUKOCYTE ADHESION DEFICIENCY, TYPE 1 (LAD-1)**

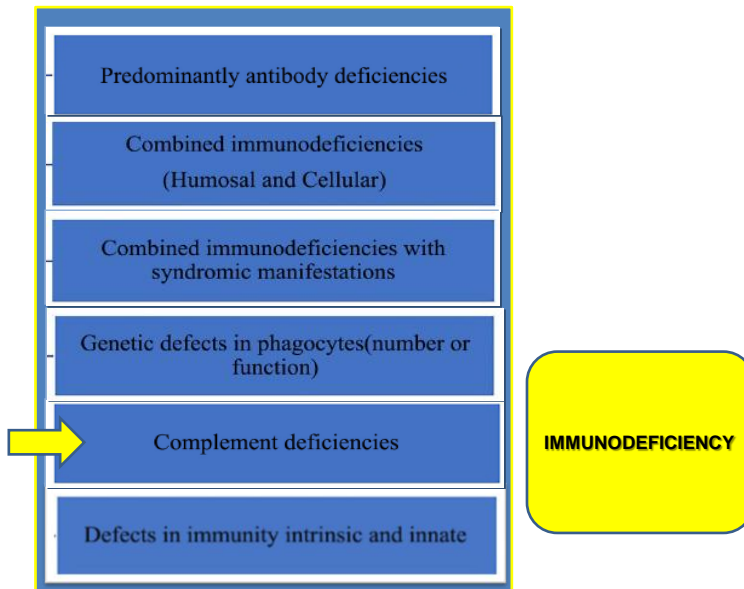
- Anomalia del processo di adesione dei leucociti
- Marcata leucocitosi
- Infezioni ricorrenti.



Prevalenza: ? > 300 casi AR

Seminars in Fetal & Neonatal Medicine xxx (2015) 1e9

**DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE**



Library Journal Vol.06 No.05(2019)



## CLINICAL SIGNIFICANCE OF COMPLEMENT DEFICIENCIES

**TABLE 1.** Hereditary Complement Deficiencies in Humans

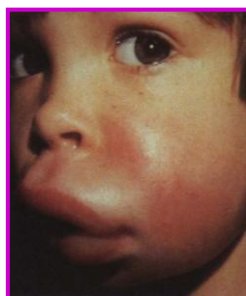
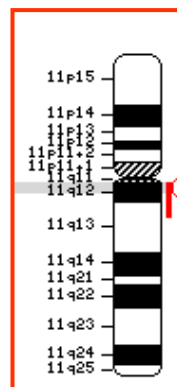
Deficiency	Reported Cases or Incidence	Primary Clinical Manifestations
C1q	41	SLE-like syndrome, encapsulated bacterial infections
C1r/s	19	SLE-like syndrome, encapsulated bacterial infections
C4	26	SLE-like syndrome, encapsulated bacterial infections
C2	1:10,000 to 1:20,000	SLE-like syndrome, encapsulated bacterial infections
C3	27	Bacterial infections, SLE-like syndrome
C1-INH	2–10:100,000	Angioedema
MBL	2–7% UK population	Increased susceptibility to bacterial infections
MASP-2	9 Caucasians	Unknown
Factor B	1	Meningococcal infection
Factor D	<10	Meningococcal and encapsulated bacterial infections
Properdin	>100	Meningococcal infection
Factor H	22 hemolytic uremic syndrome	Membranoproliferative glomerulonephritis;
Factor I	31	Encapsulated bacterial infections
C5	30 (0.0014% Japan)	Meningococcal infection
C6	80 (0.0027% Japan)	Meningococcal infection
C7	70 (0.0041% Japan)	Meningococcal infection
C8	70 (0.0027% Japan)	Meningococcal infection
C9	1:1000 and 0.0027% Japan	Meningococcal infection (less than C5-C8 deficiency)
CR3/CR4	1:1,000,000	Leukocyte adhesion deficiency
CD59	1–2:1,000,000	Paroxysmal nocturnal hemoglobinuria

Ann. N.Y. Acad. Sci. 1173: 108–123 (2005)

## EDEMA ANGIONEUROTICO EREDITARIO



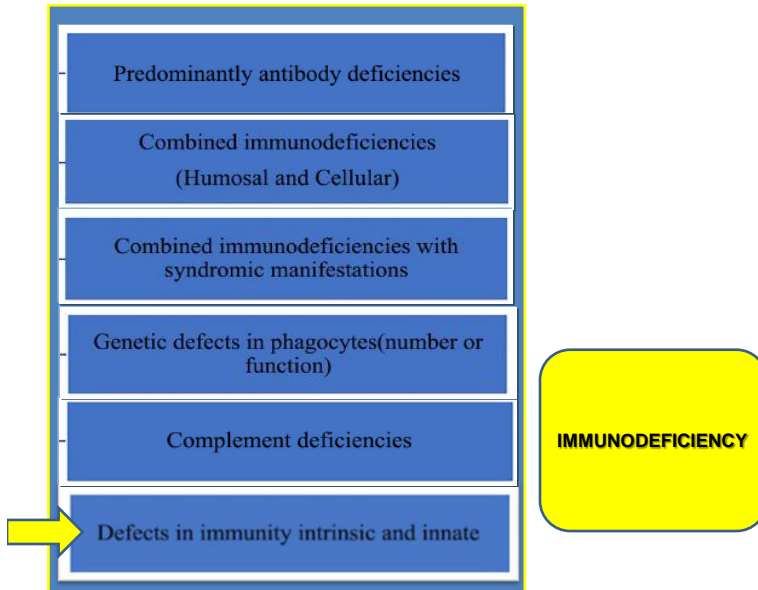
- 1: 150.000
- AD, 10% DI MUTAZIONI DE NOVO
- DIFETTO GENETICO:
- MUT. GENE 11q11-q13.1,
- 78% C1-INH ASSENTE (TIPO 1)
- 22% C1-INH INATTIVO (TIPO2)



- ATTACCHI RECIDIVANTI
- EDEMA DEL SOTTOCUTANEO
- EDEMA DELLA SOTTOMUCOSA GASTROENTERICA E RESPIRATORIA
- EDEMA LARINGEO
- NAUSEA, VOMITO
- DOLORI ADDOMINALI
- C1-INH <5 MG/DL (TIPO 1)
- C2 E C4 RIDOTTI

(Cicardi et al., 1982; Cicardi and Agostoni, 1996; Bowen et al., 2001).

## DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE



Library Journal Vol.06 No.05(2019)

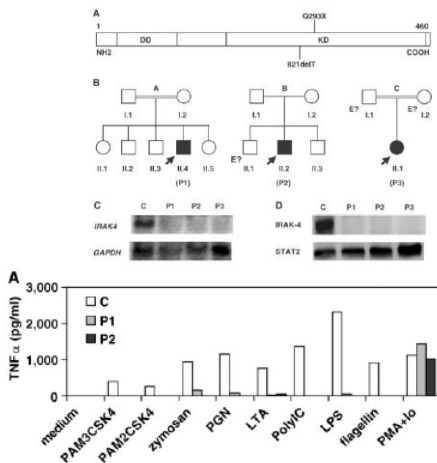
### DIFETTI DI IRAK4 E INFEZIONI DA PIOGENI

*Science* 299, 2076 (2003);  
DOI: 10.1126/science.1081902



### Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency

Capucine Picard,<sup>1</sup> Anne Puel,<sup>1</sup> Marion Bonnet,<sup>1</sup> Cheng-Lung Ku,<sup>1</sup>



3 bambini con infezioni invasive da Gram + (STR.P, S.aureus) e scarsa risposta infiammatoria in assenza di alterazioni fenotipiche dimostrabili



Deficit di produzione di citochine (TNFα, IL-6, IL-1, IFNγ)



Mutazione in omozigote di IRAK-4

Review Article

Innate Immune Recognition of *Mycobacterium tuberculosis*

Johanneke Kleinnijenhuis, Marije Oosting, Leo A. B. Joosten, Mihai G. Netea, and Reinout Van Crevel

Novel mutations in TLR genes cause hyporesponsiveness to *Mycobacterium avium* subsp. *paratuberculosis* infection

Mangesh R Bhide\*<sup>1,2</sup>, Rastislav Mucha<sup>2</sup>, Ivan Mikula Jr<sup>1</sup>, Lucia Kisova<sup>1</sup>, Rostislav Skrabana<sup>2</sup>, Michal Novak<sup>2</sup> and Ivan Mikula sr<sup>1,2</sup>

Deficit di produzione di citochine (TNFα, IL-4, IL-8, IL-12, IFNγ)

TABLE 1. SNPs associated with susceptibility to tuberculosis.

Receptor/signaling pathway	Gene	Amino acid	Association
TLR1	1905T>G	Lle60>Ser	[94]
	816T>C	Asn199>Asn	
	2258G>A	Arg753>Ile	[86]
TLR2	196 to 174 I/D*	—	[96]
	1384A>G	Asp299>Gly	[97, 98]
TLR4	1196C>T	Thr399>Ile	[100]
	1083G>C	Thr361>Thr	[100]
TLR6	785C>T	Ser349>Pro	[40]
	4959C>G	—	[40]
TLR8	2921A>G	—	[40]
	3943A>G	—	[40]
	5088A>G	Met1>Val	[40]
	588A>G	Lys196>Iys	[96]
TLR9	411C>T	His137>His	[96]
	539C>T	Ser180>Leu	[101]
TIRAP	336A>G	—	[103, 104]
	601C>T	—	
	871G>C	—	[103]
	939C>T	—	
DC-SIGN	—	—	
	—	—	[103, 105, 106]

\* I/D insertion/deletion.



BMC Genetics 2009, 10:21

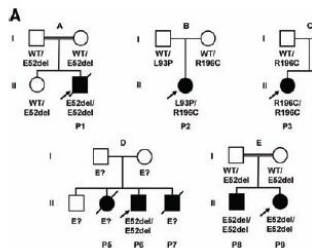
Clinical and Developmental Immunology Volume 2011, Article ID 405510, 12 pages

DIFETTI DI MyD88 E INFEZIONI DA PIOGENI

Pyogenic Bacterial Infections in Humans with MyD88 Deficiency



Horst von Bernuth, et al. Science 321, 691 (2008);



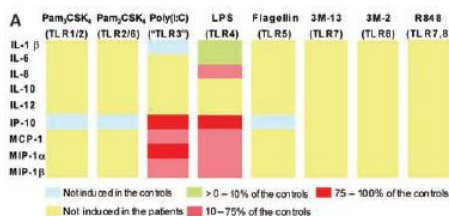
9 bambini con infezioni invasive da Pneumococco negativi per mutazione IRAK-4.



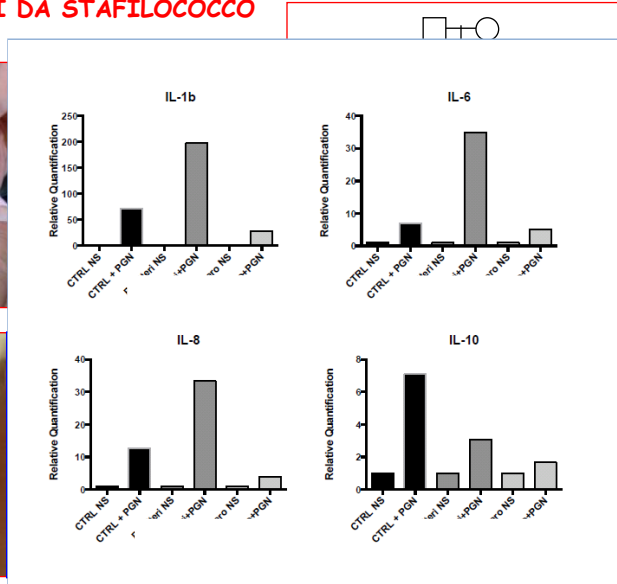
Deficit di produzione di TNFα, IL-6, IL-8, INFβ



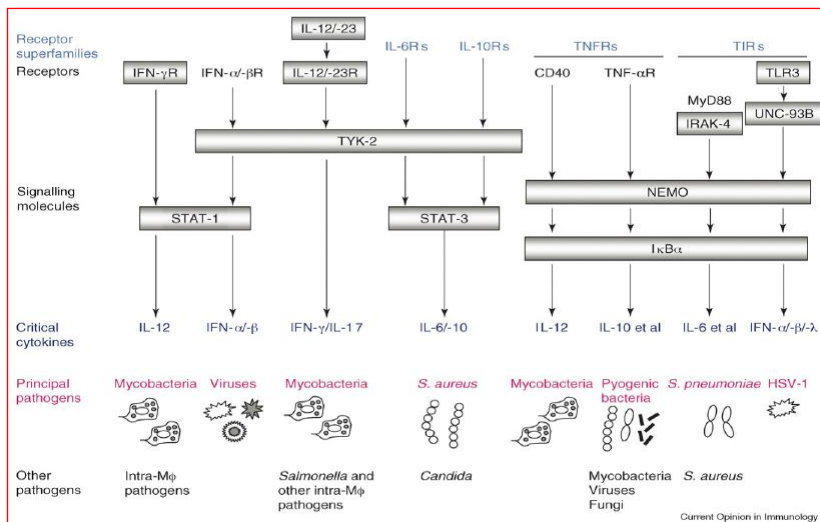
Mutazioni in omo- o eteroz. composta in 9/9 a carico di Myd88



**INFEZIONI RECIDIVANTI DA STAFILOCOCCO**



**ALTERAZIONI DEL SEGNALE INTRACELLULARE A VARI LIVELLI, IN RAPPORTO ALLA MOLECOLA INTERESSATA E AL PATHWAY CITOCHINICO ALTERATO, DETERMINEREBBERO UN'AUMENTATA PREDISPOSIZIONE A SVILUPPARE UNO SPETTRO PIU' O MENO AMPIO DI MALATTIE INFETTIVE**

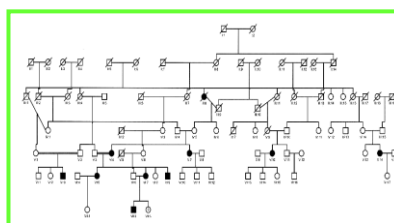


## CANDIDIASI MUCOCUTANEA CRONICA



**FAMILIAL CHRONIC NAIL CANDIDIASIS WITH ICAM-1 DEFICIENCY:  
A NEW FORM OF CHRONIC MUCOCUTANEOUS CANDIDIASIS**  
Zuccarello D, Salpietro DC, Gangemi S, Toscano V, Merlino MV, Briuglia S, Bisignano G, Mangino M, Mingarelli R, Dallapiccola B *J Medical Genetics*, 39(9): 671-75, 2002

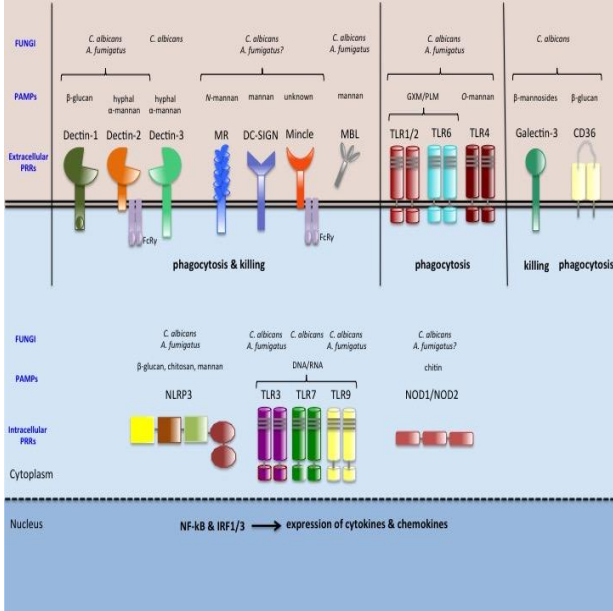
**A GENE FOR FAMILIAL ISOLATED CHRONIC NAIL CANDIDIASIS  
(CMC) MAPS TO CHROMOSOME 11p13-q12**  
Mangino M, Salpietro DC, Zuccarello D, Gangemi S, Rigoli L, Merlino MV, Briuglia S, Bisignano G, Mingarelli R, Dallapiccola B. *European Journal of Human Genetics*, 21,622-9,2003



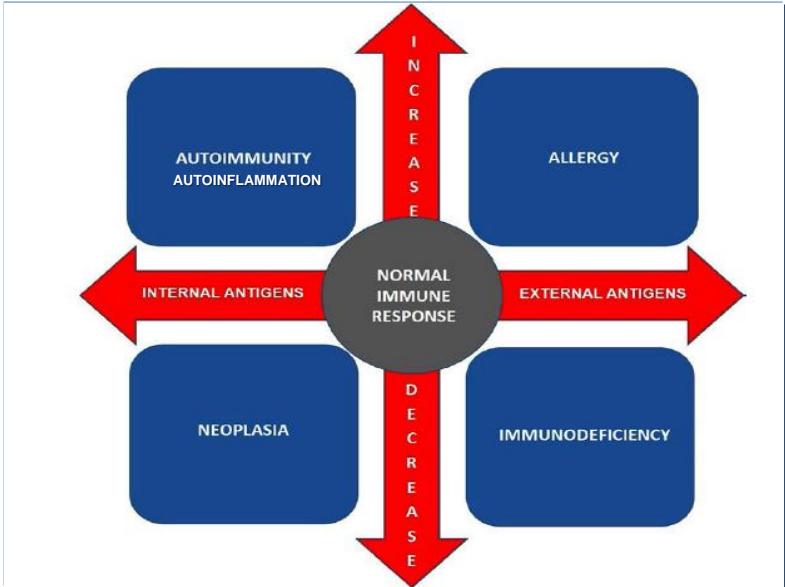
- CANDIDIASIS, FAMILIAL, 6; CANDF6 Cytogenetic locations: 6p12.2 OMIM: 613956
- CANDIDIASIS, FAMILIAL, 5; CANDF5 Cytogenetic locations: 22q11.1 OMIM: 613953
- CANDIDIASIS, FAMILIAL, 4; CANDF4 Cytogenetic locations: 12p13.2 OMIM: 613108
- CANDIDIASIS, FAMILIAL, 8; CANDF8 Cytogenetic locations: 6q21 OMIM: 615527
- CANDIDIASIS, FAMILIAL, 1; CANDF1 Cytogenetic locations: 2p22.3-p21 OMIM: 114580
- CANDIDIASIS, FAMILIAL, 2; CANDF2 Cytogenetic locations: 9q34.3 OMIM: 212050
- CANDIDIASIS, FAMILIAL, 3; CANDF3 Cytogenetic locations: 11p13-q12 OMIM: 607644
- CANDIDIASIS, FAMILIAL, 9; CANDF9 OMIM: 616445



# CMC: MECCANISMI MOLECOLARI

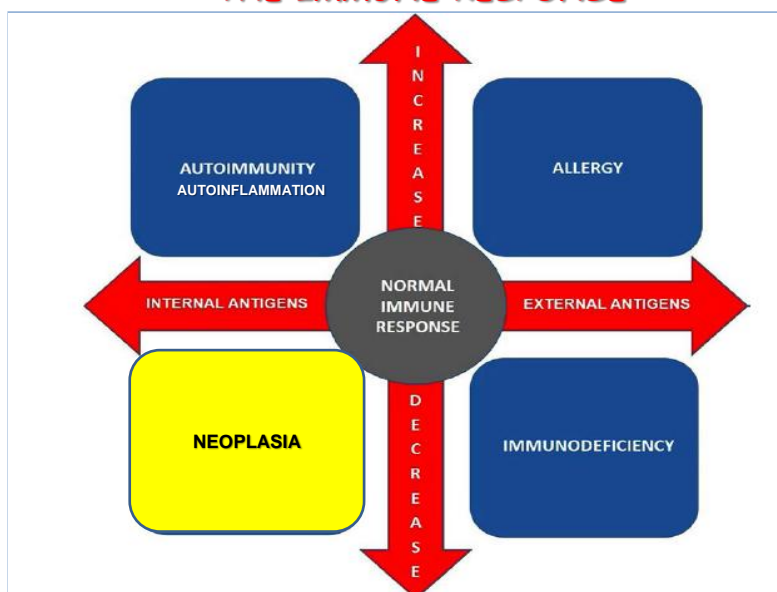


## DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE



Library Journal Vol.06 No.05(2019)

## DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE



Library Journal Vol.06 No.05(2019)

### Eline, 2 anni e 10/12



- Nazionalità tunisina
- Genitori deceduti per patologie neoplastiche
- Da 3 mesi comparsa di **tumefazione sottomentoniera, di circa 4x4 cm, di consistenza duro-lignea, poco mobile, indolente, ricoperta da cute indenne**
- Mesoadenia sottoangolomandibolare bilaterale (dx>sn)
- Nessun sintomo sistemico associato

## Eline, 2 anni e 10/12

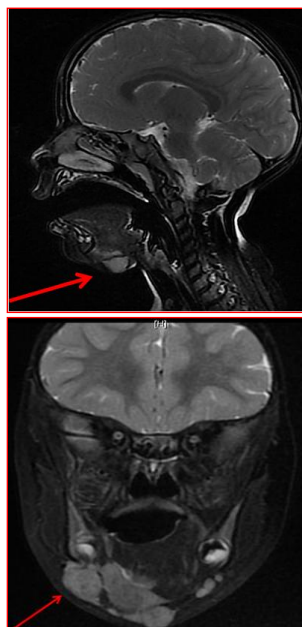
### INDAGINI EMATOCHIMICHE e STRUMENTALI:

- emocromo, indici di flogosi, funzionalità d'organo (nella norma)
- striscio periferico e tipizzazione linfocitaria (nella norma)
- sierologia ed RT-PCR per **CMV**, **EBV**, **toxoplasma**, **bartonella** (negativi)
- **Quantiferon + Mantoux** (negativi)
- **M. non tubercolari** (assenti)
- Rx torace (negativo)

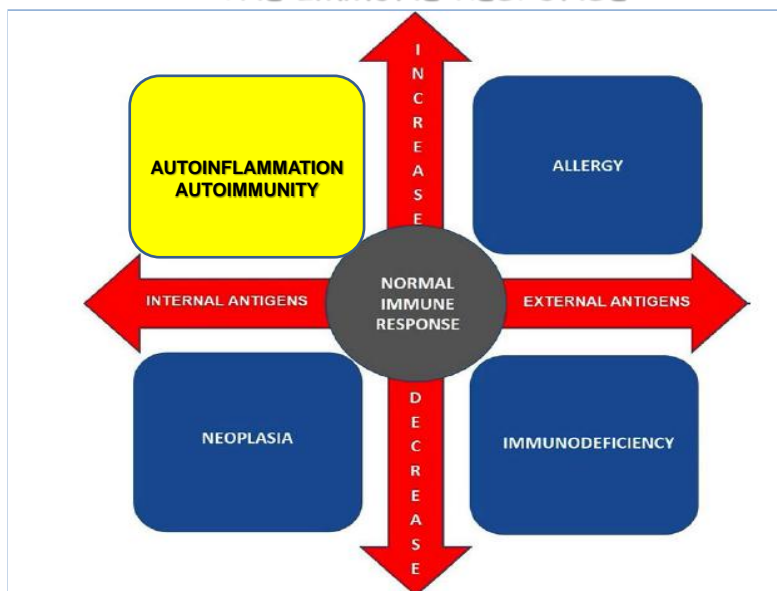
**ECOGRAFIA COLLO:** «in corrispondenza della tumefazione palpabile in sede sottomentoniera si apprezza disomogenea formazione espansiva, iso-ipoecogena con **calcificazioni contestuali**, delimitata da capsula fibrosa e da limitrofi linfonodi di aspetto reattivo..»

**RMN collo:** «...i reperti sono compatibili in prima ipotesi con **linfadenopatia sottomentoniera in fase di colliquazione** che interessa anche la cute con linfadenopatie satelliti...utile follow up ecografico e correlazione clinico-laboratoristica»

**CMV DNA:**  
3.200.000 copie/ml

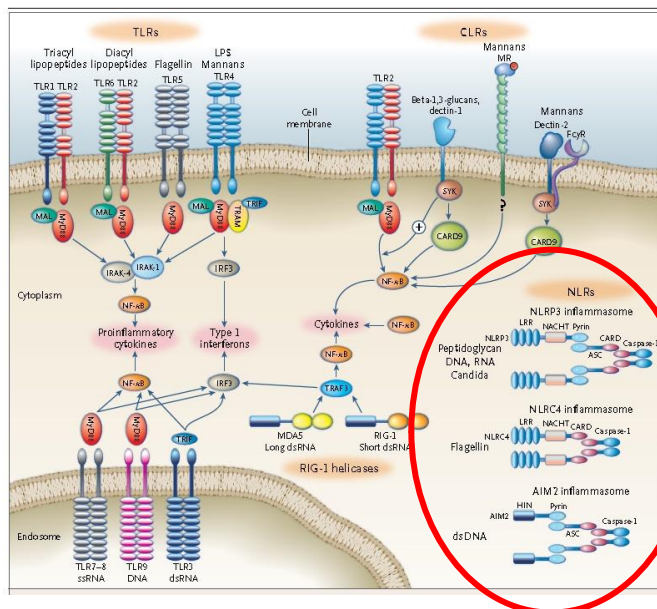


## DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE



Library Journal Vol.06 No.05(2019)

## MALATTIE AUTOINFIAMMATORIE



### Mattia 12 anni

Tiroidite (madre), ipertensione arteriosa (nonna paterna).

Dal 6° mese di vita, nei mesi invernali, ricorrenti episodi di febbre e manifestazioni orticarioidi pruriginose non responsive ad antistaminici



10 a. e 9/12 : ricovero nostra UOC "2 giorni prima comparsa di temperatura febbrile ( TC 38°C) e manifestazioni cutanee eritemato-pomfoidi agli arti inferiori".

PCR 1.30 mg/dl (v.n. 0-0,5), VES 17 (0-15), TAS 431 IU/ml



Biopsia cutanea: " infiltrati di mononucleati, prevalentemente linfociti con qualche granulocita neutrofilo; tali elementi si dispongono attorno ai vasi".

### CIAS1-PATIE

(CIAS1-Associated Periodic Syndrome, CAPS)

Indagine molecolare CIAS-1: I313V

TERAPIA: Canakinumab ?  
2 mg/kg (max 150 mg) ogni 8 settimane

Alessandro, 5 anni

**Anamnesi familiare**

IBD (RCU: padre; MC: zio paterno)

**Anamnesi fisiologica**

Fenomeni neonatali riferiti nella norma. SVPM nella norma.

**Anamnesi patologica remota**

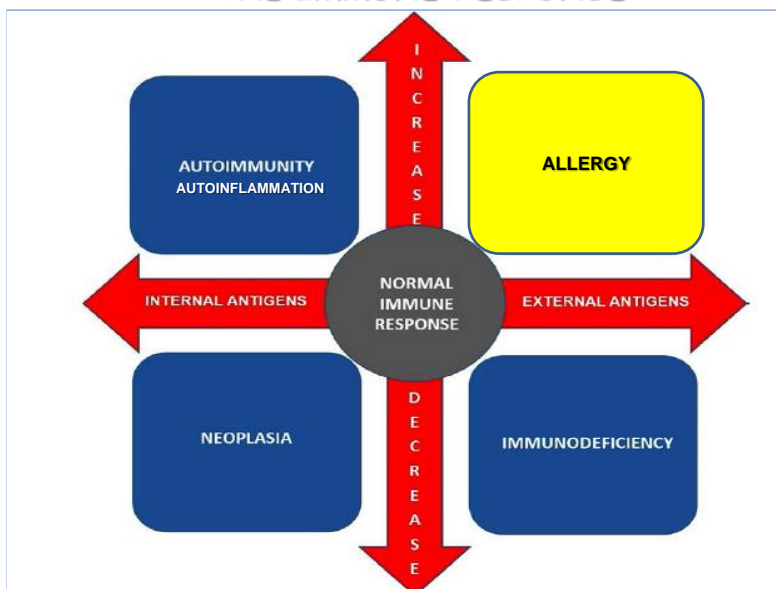
Da Marzo 2013, per comparsa di riferiti episodi di broncospasma, seguito presso il nostro ambulatorio di allergologia.

**Anamnesi patologica prossima**

Da settembre 2013 riferiti episodi febbrili a cadenza mensile della durata di 24-48h (TC max 38°C) sempre associati a marcati dolori addominali (senza vomito), talvolta diarrea. Aftosi cavo orale. Gli episodi erano responsivi a terapia corticosteroidica.

**Esame obiettivo**Parametri auxologici: peso Kg 13,900 (<3°C); statura cm 93 (<3°C).  
Tumefazione palpebrale e, talvolta, tumefazione grandi articolazioni arti inferiori associate a lesioni purpuriche agli arti inferiori.

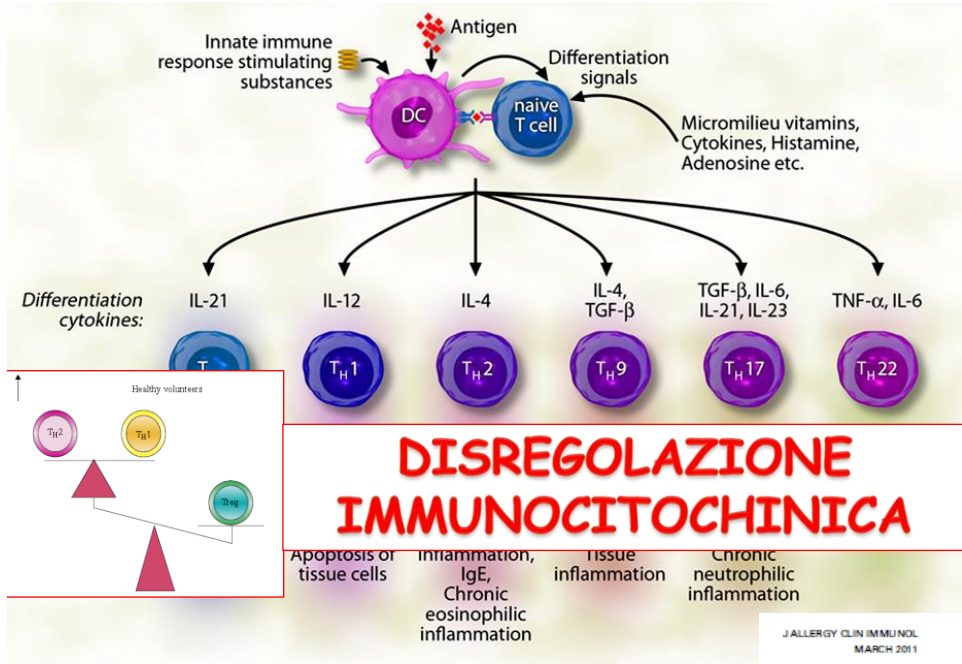
## DISEASES RESULTING FROM ALTERATIONS IN THE IMMUNE RESPONSE



Library Journal Vol.06 No.05(2019)

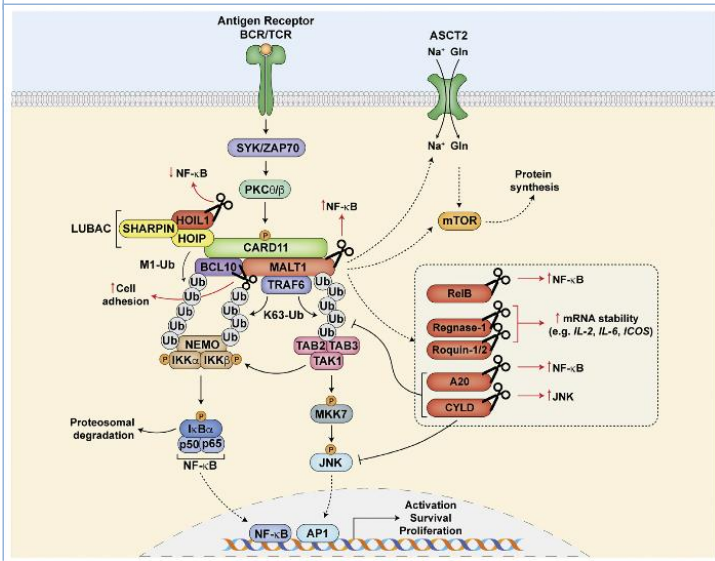


**INTERAZIONE GERME/OSPITE**



**Clinical reviews in allergy and immunology**

**Germline CBM-opathies: From immunodeficiency to atopy**



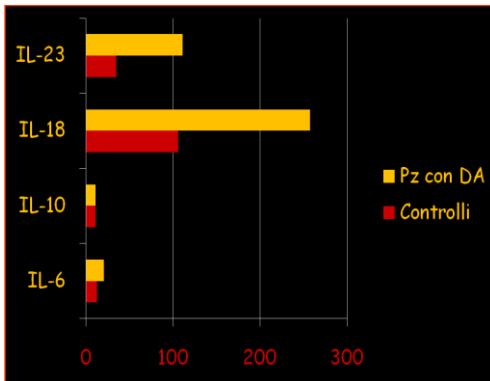
**CARD**  
**BCL10**  
**MALT1**

## AD PHENOTYPES AND RELATED ENDOTYPES

	European American AD	Asian AD	African American AD	Pediatric AD	Psoriasis
Clinical Phenotype					
Immune Polarization	Th2 (Int>Ext, C>A) ↑↑↑ Th22 (Int>>Ext, C>A) ↑↑↑ Th17 (Int>>Ext, C=A) ↑↑↑ Th1 (C>>A) ↑↑	Th2 ↑↑↑ Th22 ↑↑↑ Th17 ↑↑↑ Th1 ↔	Th2 ↑↑↑ Th22 ↑↑↑ Th17 X (Absent) Th1 X (Absent)	Th2 ↑↑↑ Th22 ↑↑↑ Th17 X (Absent) Th1 X (Absent)	Th2 X (Absent) Th22 ↑↑↑ Th17 ↑↑↑ Th1 ↑↑↑
Epidermal Barrier	Epidermal thickness ↑↑ KRT16 ↑ Int=Ext, C>A Ki67 ↑ FLG, LOR, PPL ↓↓	Epidermal thickness ↑↑↑ KRT16 ↑↑ Ki67 ↑↑ FLG ↓ LOR ↔	Epidermal thickness ↑↑ KRT16 ↑ Ki67 ↑ FLG ↔ LOR ↓↓	Epidermal thickness ↑↑ KRT16 ↑↑ Ki67 ↑↑ FLG, LOR, PPL ↔	Epidermal thickness ↑↑↑ KRT16 ↑↑ Ki67 ↑↑ FLG, LOR, PPL ↔

J ALLERGY CLIN IMMUNOL  
JANUARY 2019

## LE CITOCINE DI GIULIA



### TEST I:

- IL-6: significativo per  $P < 0,005$
- IL-10: non significativo
- IL-18: significativo per  $P < 0,001$
- IL-23: significativo per  $P < 0,001$

45 pz. con DA  
25F e 20M  
21 pz. Ctrl.  
13F e 8M

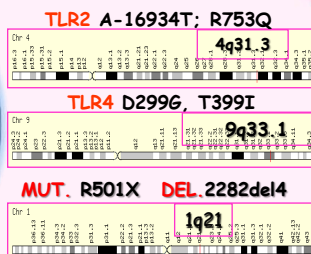
# GIULIA

## TRA

### FENOTIPO



### GENOTIPO



↑ IL-23, IL-18    ↑ IgE



Int Rev Immunol. 2019;38(2):70-78. doi: 10.1080/08830185.2019.1588267. Epub 2019 Apr 2.

### Asthma: An Undermined State of Immunodeficiency.

Christou FAA<sup>1</sup>, Giardino G<sup>2</sup>, Stefanaki E<sup>3</sup>, Ladomenou F<sup>3</sup>.

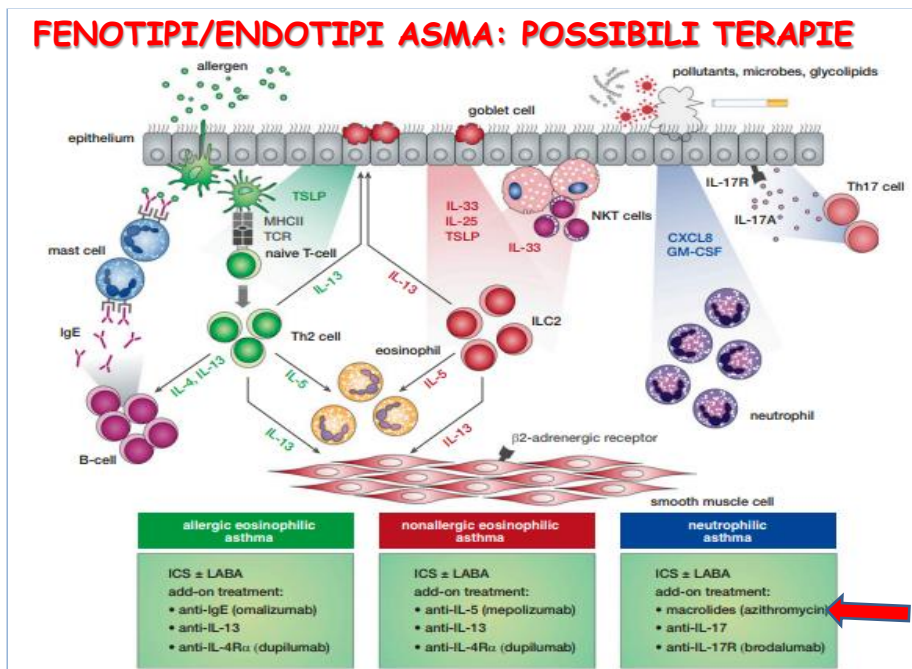
#### Author information

- a Medical School , University of Ioannina , Ioannina , Greece.
- b Department of Translational Medical Sciences , University of Naples Federico II , Naples , Italy.
- c Department of Pediatrics , Venizeleion General Hospital , Heraklion , Greece.

#### Abstract

Asthma is a heterogeneous chronic respiratory disease characterized by an increased burden of infections. Respiratory tract infections associated with an increased risk for asthma especially when occurring in the first months of life, also represent the most common cause of asthma exacerbations. The association between asthma and the increased frequency of infections and microbiota dysbiosis might be explained by a common mechanism, such as an underlying immune system defect. Apart from the well-established association between primary immunodeficiencies and asthma, several alterations in the immune response following infection have also been observed in asthmatic patients. An impairment in lung epithelial barrier integrity exists and is associated with both an increased susceptibility to infections and the development of asthma. Asthmatic patients are also found to have a deficient interferon (IFN) response upon infection. Additionally, defects in Toll-like receptor (TLR) signaling are observed in asthma and are correlated with both recurrent infections and asthma development. In this review, we summarize the common pathophysiological background of asthma and infections, highlighting the importance of an underlying immune system defect that predispose individuals to recurrent infections and asthma.

**KEYWORDS:** Asthma; Toll-like receptors; infection; interferons; microbiota



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Tabella 5. Bambino con sospetta IDP. Interpretazione degli esami immunologici di I livello.

Elettroforesi Siero	↓	$\gamma$ globuline	→	perdita, ritardata o mancata produzione
Immunoglobuline Sieriche	↓	IgG	→	XLA
	↓	IgA	→	CVID
	↓	IgM	→	Ipgammaglobulinemia transitoria
	↓	IgG	→	HIGM ( $\uparrow$ IgM)
	↓	IgA	→	CVID
			→	Ipgammaglobulinemia transitoria
Immunoglobuline Sieriche	↓	IgA	→	Deficit selettivo IgA
Emocromo				
	↓		→	Shwachman-Diamond
			→	Kostmann
			→	Granulocitopenia ciclica cronica benigna
Neutrofili				
	↑		→	LAD
Linfociti	↓		→	SCID
Piastrine	↓		→	WAS

Lymphocytes	RN	1 s - 2 m	2 - 5 m	5 - 9 m	9 - 15 m	15 - 24 m	2 - 5 a	5 - 10 a	10 - 16 a	>16 a
<b>Absolutes</b>	700 - 7300	3500 - 13,100	3700 - 9600	3800 - 9900	2600 - 10,400	2700 - 11,900	1700 - 6900	1100 - 5900	1000 - 5300	1000 - 2800
CD3 + T	600 - 5000	2300 - 7000)	2300 - 6500	2400 - 6900	1600 - 6700	1400 - 8000	900 - 4500	700 - 4200	800 - 3500	700 - 2100
CD4 + T	400 - 3500	1700 - 5300	1500 - 5000	1400 - 5100	1000 - 4600	900 - 5500	500 - 2400	300 - 2000	400 - 2100	300 - 1400
CD8 + T	200 - 1900	400 - 1700	500 - 1600	600 - 2200	400 - 2100	400 - 2300	300 - 1600	300 - 1800	200 - 1200	200 - 900
16/56 NK	100 - 1900	200 - 1400	100 - 1300	100 - 1000	200 - 1200	100 - 1400	100 - 1000	90 - 900	70 - 1200	90 - 600
CD19 + B	40 - 1100	600 - 1900	600 - 3000	700 - 2500	600 - 2700	600 - 3100	200 - 2100	200 - 1600	200 - 600	100 - 500

Library Journal Vol.06 No.05(2019)

Age	RN	1 m	2 m	3 m	4 m	5 m	6 m	7 - 9 m	10 - 12 m	2a	3a	4 - 5 a	6 - 8 a
IgG mg/dL	636 - 1606	251 - 906	206 - 601	176 - 581	196 - 558	172 - 814	215 - 704	217 - 904	294 - 1069	424 - 1051	441 - 1135	463 - 1236	633 - 1280
IgM mg/dL	6.3 - 25	20 - 87	17 - 105	24 - 89	27 - 101	33 - 108	35 - 102	34 - 126	41 - 149	48 - 168	47 - 200	43 - 196	48 - 207
IgA mg/dL	1.4 - 3.6	1.3 - 53	2.8 - 47	4.6 - 49	4.4 - 73	8.1 - 84	8.1 - 68	11 - 90	16 - 84	14 - 123	22 - 159	25 - 154	33 - 202

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## PERCORSI PEDIATRICI DELLO STRETTO 2020



SABATO 15 FEBBRAIO 2020

SABATO 18 APRILE 2020

SABATO 14 MARZO 2020

SABATO 9 MAGGIO 2020

SABATO 6 GIUGNO 2020