Università degli Studi di Napoli "Federico II"

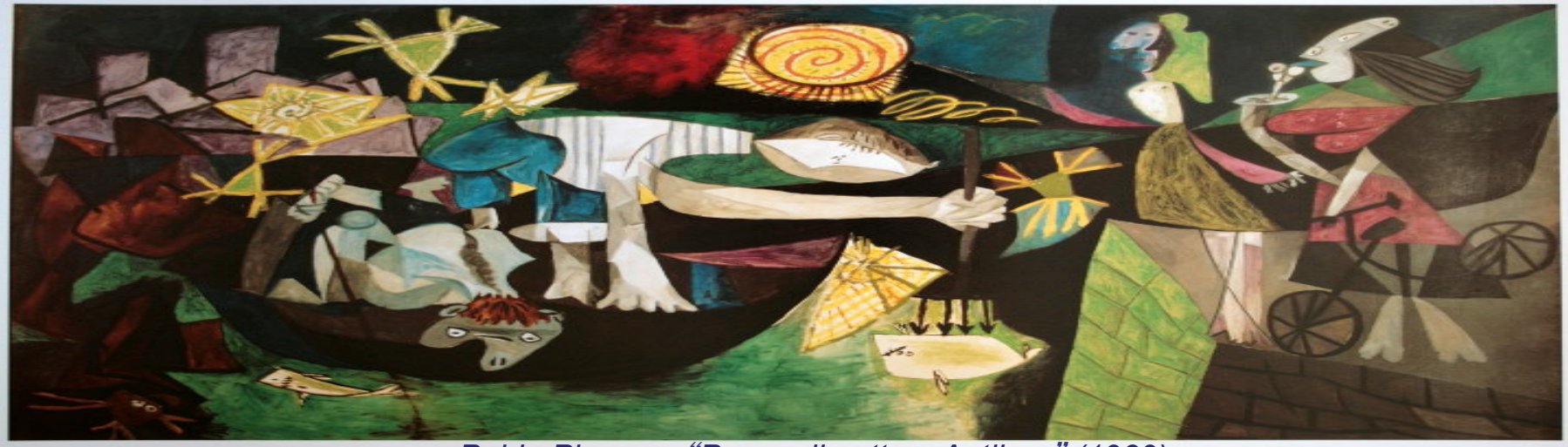
Scuola di Specializzazione in Pediatria

Direttore: Prof. Riccardo Troncone

GLI INCONTRI DEL MERCOLEDI'

9 Gennaio 2013

Quando la febbre ricorre…



Pablo Picasso, "Pesca di notte a Antibes" (1939)

Relatore: G. Ranucci

Esperto: Prof. C. Pignata

AMBULATORIO IMMUNOLOGIA PEDIATRICA

Alessandro, 2 aa e 3 mesi

- Dall'età di 8 mesi riferiti episodi di febbre della durata di 2-3 gg ricorrenti, intervallati da periodi di completo benessere clinico (responsivi al paracetamolo e trattati con antibiotici e betametasone)
- Linfoadenopatia laterocervicale
- Eritema perianale
- Rifiuto dell'alimentazione
- Madre HBV positiva

Epidemiologia della febbre

- 1/3 delle visite pediatriche
- >20% delle chiamate telefoniche del pediatra
- < 3 aa: 1^ causa di accesso in PS (10-15% degli accessi totali).

Baraff et al. Ann Emerg Med. 2003;41:644-52

Febbre ricorrente

Recurrent fever in children

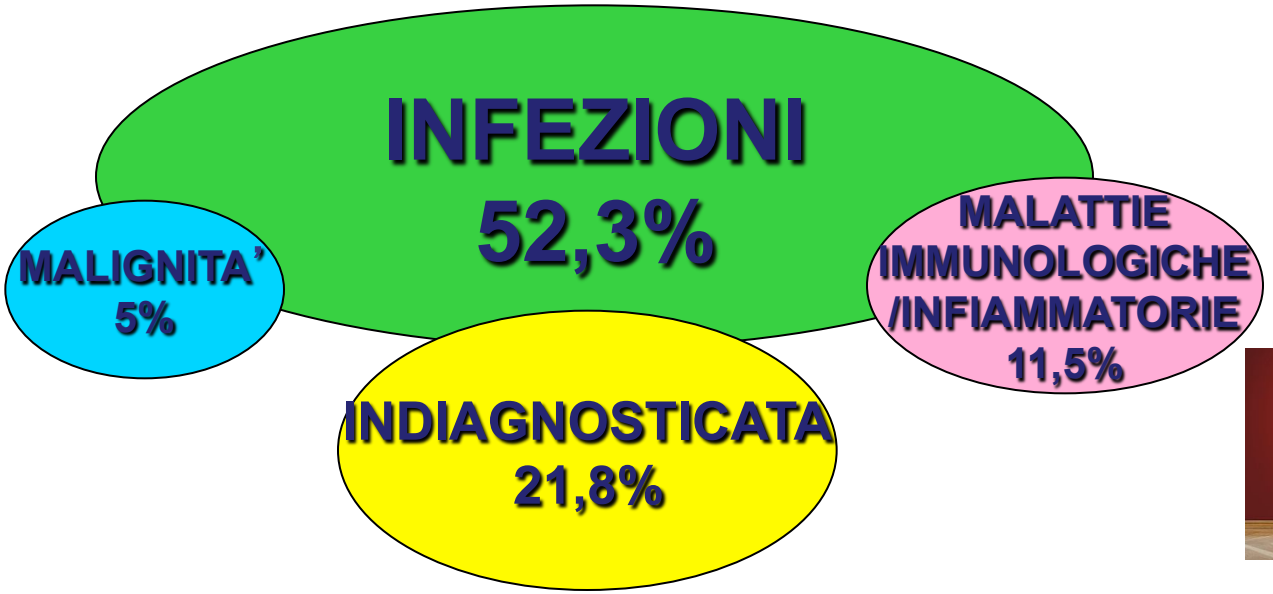
CHANDY C. JOHN, MD, MS AND JANET R. GILSDORF, MD

Pediatr Infect Dis J, 2002;21:1071–80

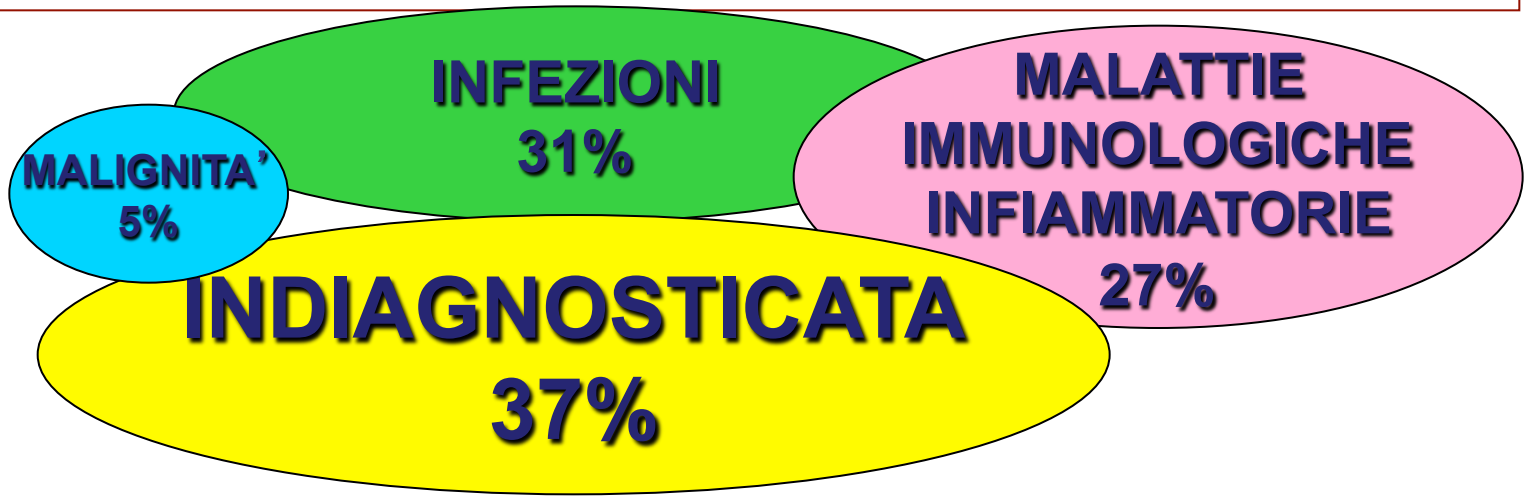
We arbitrarily define recurrent or periodic fever as three or more episodes of fever in a 6-month period, with no defined medical illness explaining the fevers and with an interval of at least 7 days between febrile episodes.

The etiologies of fever of unknown origin are far more diverse than those of recurrent fever, so defining a fever as recurrent rather than persistent is an important differentiating factor.

FUO IN ETA' PEDIATRICA



FEBBRE RICORRENTE IN ETA' PEDIATRICA



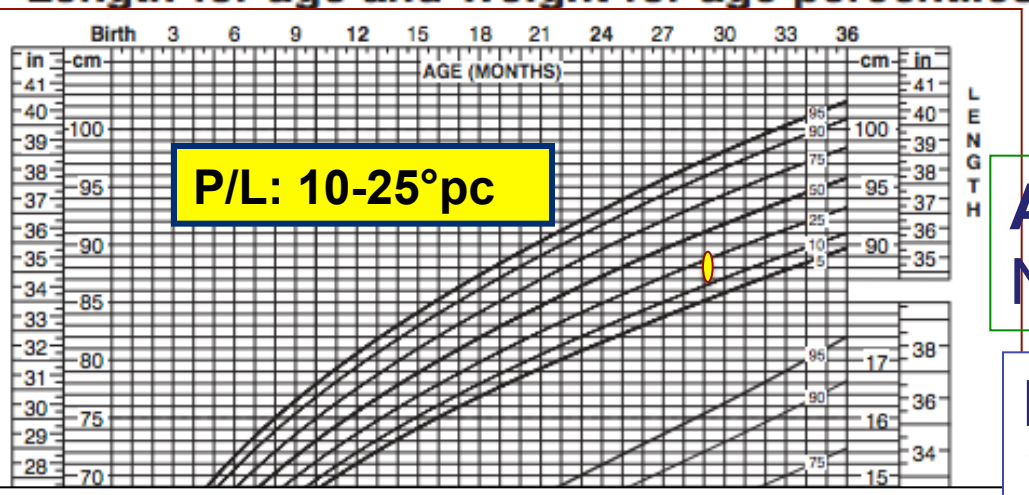
Gartner 1992, Steele 1991, Feigin 1976

3. *Identify important history and physical examination findings that must be ascertained in all children with recurrent fever.*

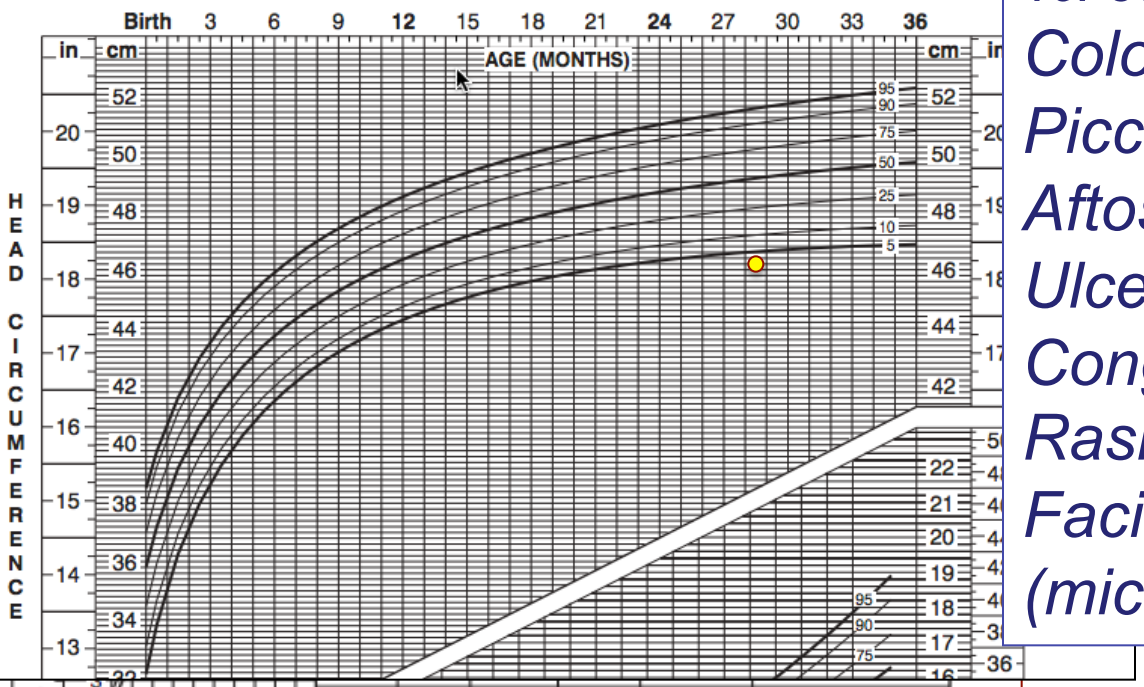
Birth to 36 months: Boys
Length-for-age and Weight-for-age percentiles

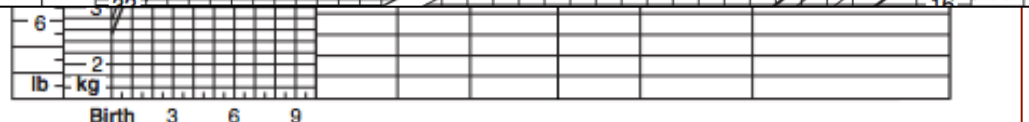
NAME GIULIANO ALESSANDRO

RECORD 2 anni e 3 mesi



P/L: 10-25°pc





ANAMNESI: Dati discordanti. Non attendibile.

E.O.

Tc: 37.5 °C; SO2 100%; FC 90 bpm
Colorito pallido
Piccolo vigile ma irritabile
Aftosi orale
Ulcere perianali
Congiuntivite bilaterale
Rash maculo-papulare
Facies dismorfica (microcefalia)

Yale University SCORE per il bambino con febbre

McCarthy et al. Pediatrics 2006

Criteri clinici	**1 (normale)**	**2 (poco compromesso)**	**3 (molto compromesso)**
Qualità del pianto	Vivace, di tonalità normale	Pianto lamentoso o con singhiozzi	Pianto debole o di tonalità alta
Reazione agli stimoli dolorosi	Piange per breve tempo, poi smette	Piange a intermittenza	Continua a piangere o reagisce violentemente
Stato di veglia	Normale stato di veglia. Se dorme, stimolato si sveglia prontamente	Chiude gli occhi. Si sveglia brevemente o solo se stimolato a lungo	Sonno profondo o insonnia
Colorito della cute	Roseo	Estremità pallide o cianotiche	Pallido o cianotico o marezzato o grigiastro
Idratazione	Cute e mucose normoidratate	Mucosa orale un po' asciutta	Cute e mucose aride. Occhi cerchiati
Reazione a sollecitazioni sociali	Sorride. Presta attenzione	Brevi sorrisi. Attenzione breve	Non sorride. Espressione ansiosa del volto. Inespressività. Non presta attenzione

E’ INDICATO IL RICOVERO?

- Situazione familiare
- Altre malattie dei familiari
- Ansia dei genitori
- Contatti con persone che hanno sviluppato malattie infettive gravi
- Viaggi recenti in zone tropicali/subtropicali, o aree con un alto rischio di infezioni endemiche
- Quando una febbre non ha segni di localizzazione, ha una durata maggiore di quanto ci si aspetta da una patologia autolimitante.

Br J Gen Pract. 2007 Oct;57(543):835.

NICE guidelines on fever in children.

Havinga W.

ESAMI DI PRIMO LIVELLO

- **Esame emocromocitometrico con formula: GB 24.000/mcl (N 15.000); Hb 10 mg/dl; MCV 63 fl; Plt 400.000/mcL**
- **VES: 49 mm; PCR 73 mg/L; fibrinogeno 600 ng**
- Esame urine con sedimento, urinocoltura con conta colonie: negativo
- Emocoltura: negativa
- Funzionalità epatica, renale, LDH, ferritina, CPK, gammaGT: nella norma

Nelson, Trattato di Pediatria Ed. XVII

r in children

ET R. GILSDORF, MD

GNOSIS

ion described above, the child s no further evaluation other than continued clinical follow-up if he or she meets the following criteria: (1) no signs and symptoms suggestive of a specific disease in the differential diagnosis for recurrent fever; (2) no anemia or neutropenia, (3) no growth on bacterial urine culture; and (4) a normal ESR and CRP with fever or normalization of ESR and CRP between episodes of fever.

…INQUADRAMENTO DI ALESSANDRO

INFETTIVOLOGICO
- Urinocultura: negativa
- Emocultura: negativa
- Tampone faringeo e nasale: negativi
- Coprocoltura: negativi
- Intradermoreazione di Mantoux: negativa
- HIV: negativa
- HBsAg: negativo
- Sierologia per EBV, CMV, Toxo, Bartonella, Vidal Wright: negativo
- TPHA

IMMUNOLOGICO/ INFIAMMATORIO
- QPE, Ig: nella norma
- FT3, FT4, TSH: nella norma
- ANA, C3, C4, auto-Ab: nella norma
- NBT test: negativo
- Risposta anticorpale : buona
- **IgE 143**

h

IMAGING
- Rx torace: interstiziopatia
- TAC TORACE: formazione bollosa 22 mm LIS polmone dx
- Eco Addome: nella norma
- Eco collo: linfonodi ovalari tendenti alla confluenza

GASTRO
- Calpro
- Sangue occulto fecale: neg
- **EGDS+Colonoscopia: infiammazione cronica minima a carico di tutti i segmenti intestinali**

- Visita oculistica: nella norma

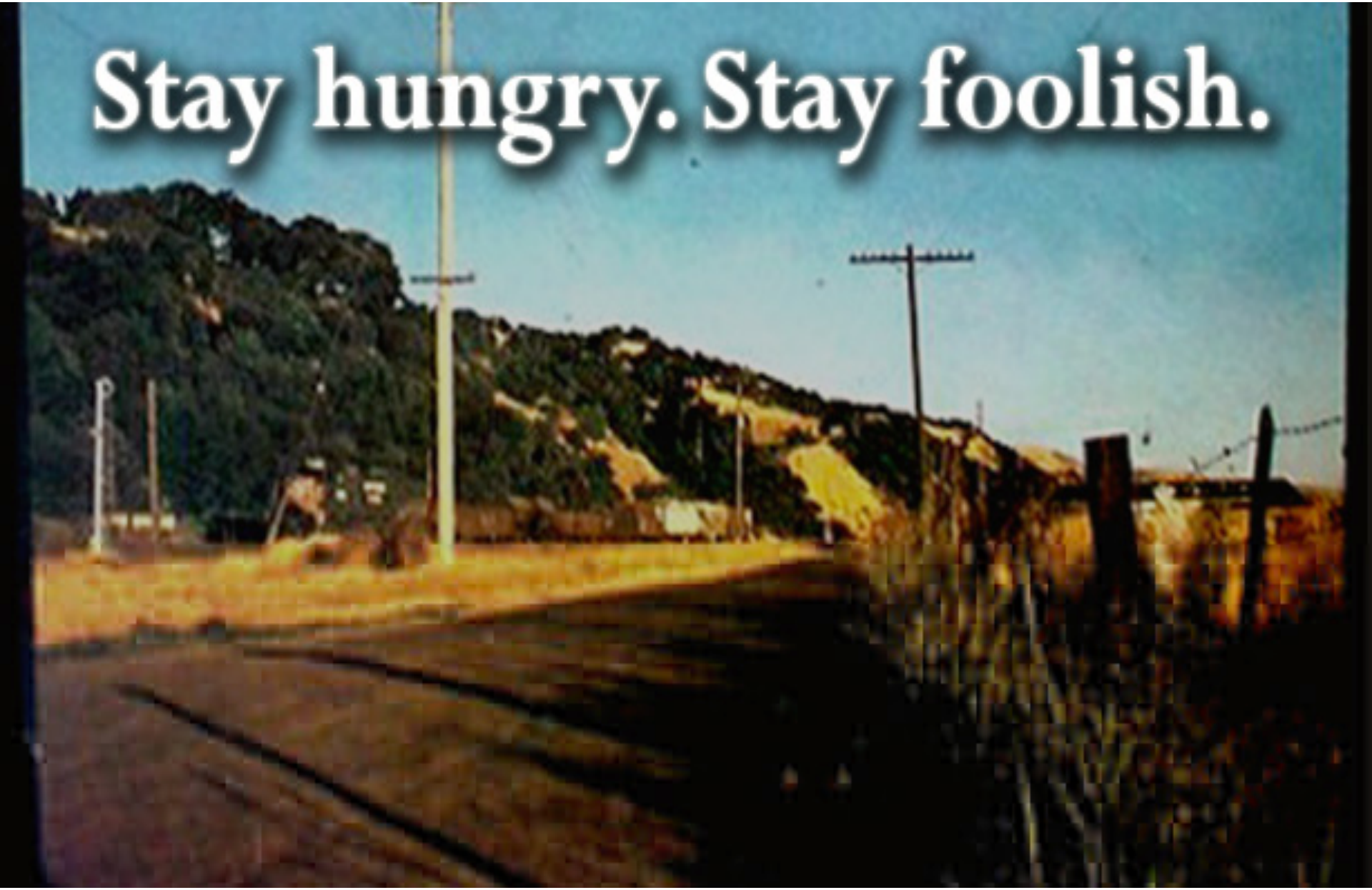
EMATONCOLOGICO
- Striscio periferico: nella norma
- VMA e OMA: negativi
- Aspirato midollare: nella norma

…EPISODI FEBBRILI A RICOVERO

	12.01.2012	05.03.2012	27.03.2012	07.05.2012
FEBBRE (durata)	+ (5 gg)	+ (7 gg)	+ (4 gg)	+ (6 gg)
LINFOADENOPATIA	+	+	+++	++
AFTE	++	+	-	+
ULCERE PERIANALI	++	-	-	+ (diarrea)
COINVOLGIMENTO OCULARE	+ (congiuntiv.)	++ (dacriocis.)	++ (dacriocis.)	-
RASH ORTICARIOIDE	++	+	+	+
GB	24.000	25.000	27.000	18.000
N	16.000	15.000	15.000	9.000
Plt	600.000	900.000	650.000	700.000
Hb	10	9	9.5	10.5
VES	49	100	65	30
PCR	73	90	70	10
Autolimitazione	+	+	+	+

THE SYSTEMIC AUTOINFLAMMATORY DISEASE

Syndromes	OMIM*	Inheritance	Genes or Risk Factors
Hereditary periodic fever syndromes			
Familial Mediterranean fever (FMF)	249100	Autosomal recessive	*MEFV*
TNF receptor–associated periodic syndrome (TRAPS)	142680	Autosomal dominant	*TNFRSF1A*
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)	260920	Autosomal recessive	*MVK*
Familial cold autoinflammatory syndrome (FCAS)	120100	Autosomal dominant	*CIAS1/NALP3/PYPAF1*
Muckle-Wells syndrome (MWS)	191100	Autosomal dominant	*CIAS1/NALP3/PYPAF1*
Neonatal-onset multisystem inflammatory disease (NOMID)/ chronic infantile neurologic cutaneous and articular (CINCA) syndrome	607115	Sporadic, autosomal dominant	*CIAS1/NALP3/PYPAF1*
Idiopathic febrile syndromes			
Syndrome of periodic fever with aphthous stomatitis, pharyngitits, and cervical adenopathy (PFAPA)	—-	Not usually familial	—
Systemic-onset juvenile idiopathic arthritis (SOJIA)	604302	Complex	IL-6, MIF polymorphisms
Adult-onset Still's disease	—	Not usually familial	—
Granulomatous disorders			
Crohn's disease	266600	Complex	*NOD2/CARD15, ABCB1* (Ala893), *MEFV (?)*
[illegible] neuropathy (Blau syndrome)	186580	Autosomal dominant	*NOD2/CARD15*
Early onset sarcoidosis	609464	Sporadic, autosomal dominant	*NOD2/CARD15*
Pyogenic disorders			
Syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA)	604416	Autosomal d	
Chronic recurrent multifocal osteomyelits (CRMO)	259680	Sporadic, autosomal re	
Synovitis, acne, pustulosis, hyerostosis, and osteitis syndrome (SAPHO)	—	Not usually f	
Hemophagocytic disorders			
Primary hemophagocytic lymphohistiocytosis	603553, 607624	Autosomal r	
Macrophage activation syndrome (MAS)	—	Not usually f	
Complement disorders			
Hereditary angioedema	106100	Autosomal d	
Vasculitic syndromes			
Behçet's disease	109650	Complex	


Stay hungry. Stay foolish.

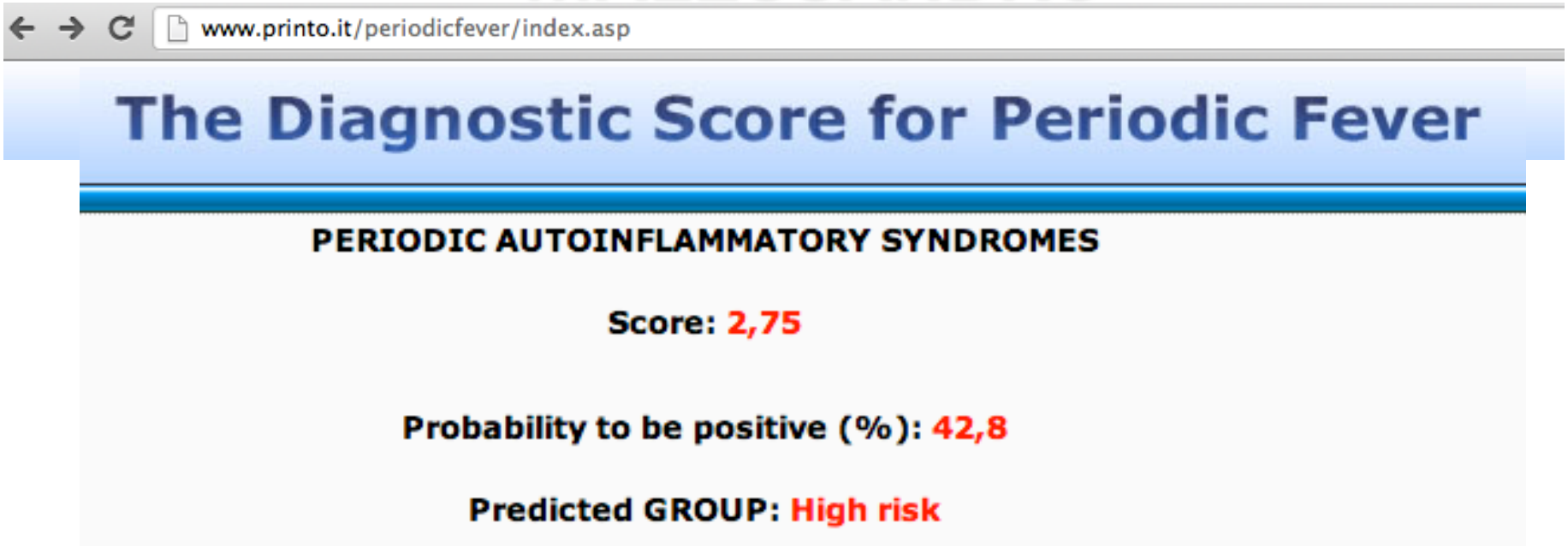
Best Pract Res Clin Rheumatol. 2012 Aug;26(4):505-33.

Table 2. Clinical features of the hereditary periodic fever syndromes.

Clinical Feature	FMF	TRAPS	HIDS	FCAS	MWS	NOMID/CINCA
Usual ethnicity	Turkish, Armenian, Arab, Jewish, Italian	Any ethnicity	Dutch, other Northern European	Mostly European	Mostly European	Any ethnicity
Duration of attacks	12-72 hours	Days to weeks	3-7 days	12-24 hours	2-3 days	Continuous, with flares
Abdominal	Sterile peritonitis,	Peritonitis, diarrhea	Severe pain, vomiting,	Nausea	Abdominal pain	Not common
Pleural	Common	Common	Rare	Not seen	Rare	Rare
Arthropathy	Monoarthritis, rarely protracted arthritis in knee or hip	Arthritis in large joints, arthralgia	Arthralgia, symmetric polyarthritis			
Polyarthralgia	Polyarthralgia, oligoarthritis, clubbing	Epiphyseal overgrowth, contractures, intermittent or chronic arthritis, clubbing				
Cutaneous	Erysipeloid erythema on lower leg, ankle, foot	Migratory rash, underlying myalgia	Diffuse maculopapular rash, urticaria	Cold-induced urticarial rash	Urticaria-like rash	Urticaria-like rash
Ocular	Rare	Conjunctivitis, periorbital edema	Uncommon	Conjunctivitis	Conjunctivitis, episcleritis	Uveitis, conjunctivitis, progressive vision loss
Neurologic	Rarely aseptic meningitis	Controversial	Headache	Headache	Sensorineural deafness	Sensorineural deafness, chronic aseptic meningitis, mental retardation, headache
Lymphatic	Splenomegaly, occasional lymphadenopathy	Splenomegaly, occasional lympadenopathy	Cervical adenopathy in children	Not seen	Rare	Hepatosplenomegaly, adenopathy
Vasculitis	Henoch-Schönlein purpura (HSP), polyarteritis nodosa	HSP, lymphocytic vasculitis	Cutaneous vasculitis common, rarely HSP	Not seen	Not seen	Occasional
Systemic amyloidosis	Risk depends on *MEFV* and *SAA* genotypes; more common in Middle East	Occurs in ~10%; risk increased with cysteine mutations	Rare	Rare	Occurs in ~25%	May develop in some patients, usually in adulthood

Abbreviations: FMF, familial Mediterranean fever; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; FCAS, familial cold

…ALESSANDRO



MVK: nessuna variante
TRAPS: nessuna variante

CIAS1/NLP3: eterozigosi per p. Q703K

Monogenic IL-1 mediated autoinflammatory and immunodeficiency syndromes: Finding the right balance in response to danger signals

Cailin Henderson [1], Raphaela Goldbach-Mansky *

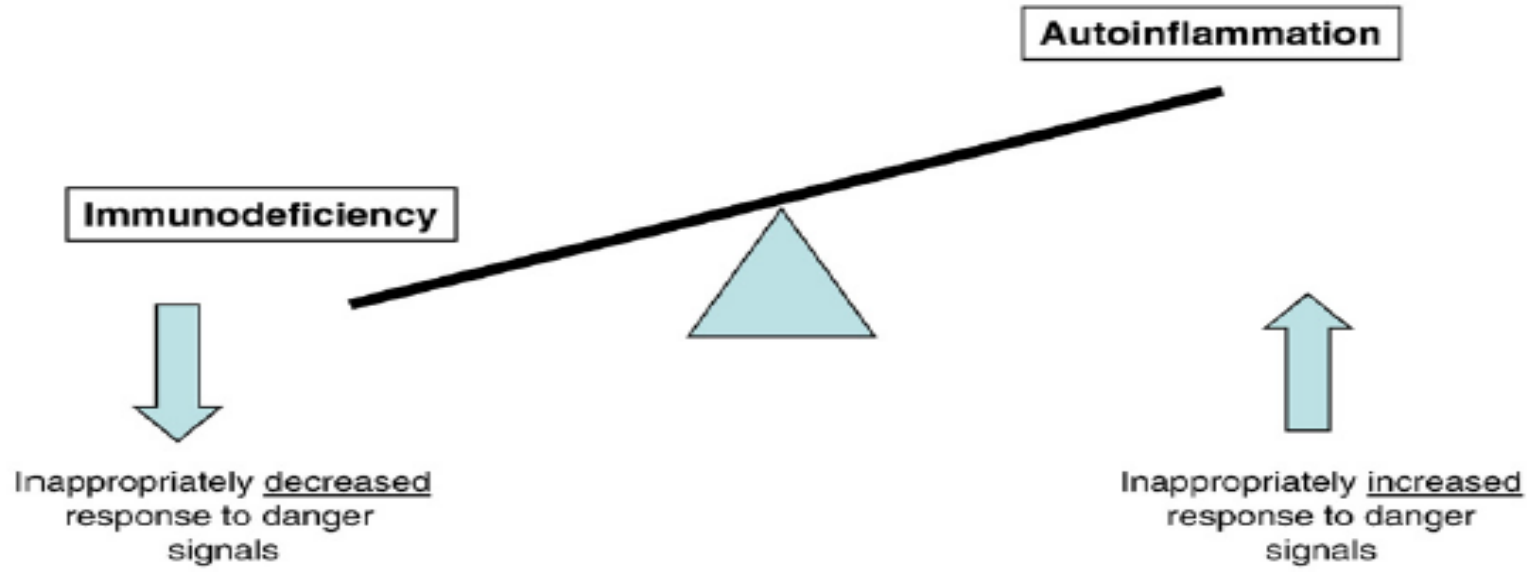


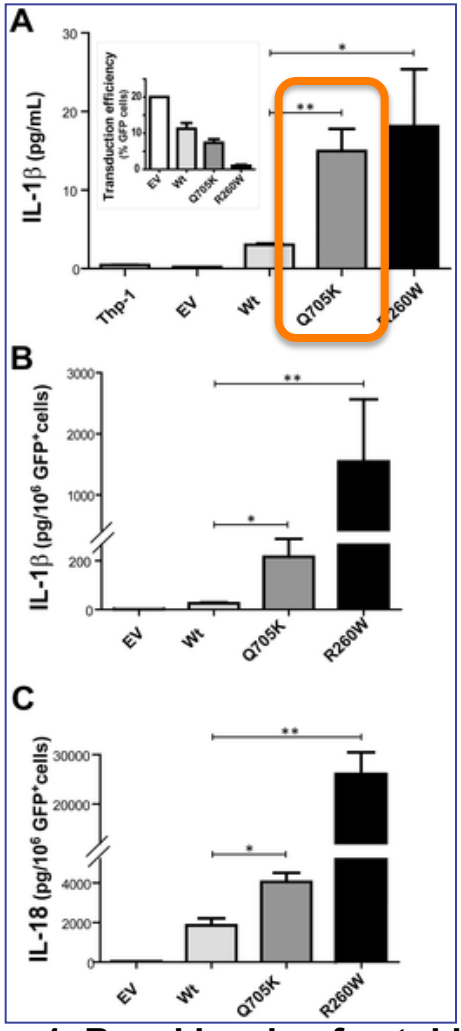
Figure 3 Dysregulated balance of immune response to danger signals.

The concept of autoinflammation as excessive inflammation and immunodeficiencies as insufficient inflammation in response to danger sensing

The Q705K Polymorphism in NLRP3 Is a Gain-of-Function Alteration Leading to Excessive Interleukin-1β and IL-18 Production

Deepti Verma[1]*, Eva Särndahl[2], Henrik Andersson[3], Per Eriksson[4], Mats Fredrikson[5], Jan-Ingvar Jönsson[3], Maria Lerm[3☯], Peter Söderkvist[1☯]

PLoS ONE | www.plosone.org 1 April 2012 | Volume 7 | Issue 4 | e34977



Monogenic and genetically complex diseases of increased TLR/IL-1 signaling

Cryopyrin-associated periodic syndrome (CAPS)

Figure 1. Basal levels of cytokine production by NLRP3-tranduced THP-1 cells.

blood

2008 111: 2132-2141
Prepublished online December 6, 2007;
doi:10.1182/blood-2007-06-094201

Disease-associated *CIAS1* mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients

Megumu Saito, Ryuta Nishikomori, Naotomo Kambe, Akihiro Fujisawa, Hideaki Tanizaki, Kyoko Takeichi, Tomoyuki Imagawa, Tomoko Iehara, Hidetoshi Takada, Tadashi Matsubayashi, Hiroshi Tanaka, Hisashi Kawashima, Kiyoshi Kawakami, Shinji Kagami, Ikuo Okafuji, Takakazu Yoshioka, Souichi Adachi, Toshio Heike, Yoshiki Miyachi and Tatsutoshi Nakahata

Table 1. Clinical profiles and *CIAS1* mutations identified in 11 patients with cryopyrin-associated periodic syndrome

Patient number	Diagnosis	Age, y*	Sex	Initial classification	Site of mutation	Biologics therapy	Central nervous system		Skin	Articular		Reference number
							Mental retardation	Meningitis	Urticarial rash†	Arthritis	Contracture	
1	CINCA	2	Female	Mutation-positive	N477K (1431C>A)	None	–	+	+	–	–	(28)
2	CINCA	3	Female	Mutation-positive	G755R (2263G>C)	Anakinra	+	+	+	+	–	(29)
3	CINCA	12	Male	Mutation-positive	M662T (1985T>C)	None	–	+	+	+	–	—
4‡	CINCA	12	Male	Mutation-positive	R260W (778C>T)	None	–	+	+	+	–	—
5	CINCA	13	Male	Mutation-positive	D303N (907G>A)	None	–	+	+	+	–	—
6	CINCA	14	Male	Mutation-positive	Y441H (1321C>T)	Tocilizumab	+	+	+	+	–	—
7	CINCA	15	Male	Mosaic	Y570C (1709A>G)	Anakinra§	–	+	+	+	+	(12)
8	CINCA	18	Female	Mutation-negative	L264F (790C>T)	None	–	+	+	–	–	(30)
9	CINCA	11	Male	Mutation-negative	G307S (919G>A)	None	–	–	+	+	+	—
				Mutation-negative	E567K			Not assessed				
11	CINCA	11	Male	Mutation-negative	Unknown	None	+	+	+	+	–	(32)

E PER ALESSANDRO….ABBIAMO LA DIAGNOSI!?!

….ALESSANDRO ERA DISMORFICO…

CARIOTIPO:

Mosaico costituito ***cui la prima (66%) pres*** ***arker sovrannumerario*** ***le*** e la seconda (34%) con

FISH:

due linee cellulari ale e l'altra con un **mark** **vante da un cromosoma 7**

Può spiegare i sintomi che si discostano dalla CAPS? Dismorfismi, malformazione polmonare….

CHROMOSOME 7 (microdel 7q 11.23) SINDROME DI WILLIAMS

Cosa ha Alessandro?

Microcefalia

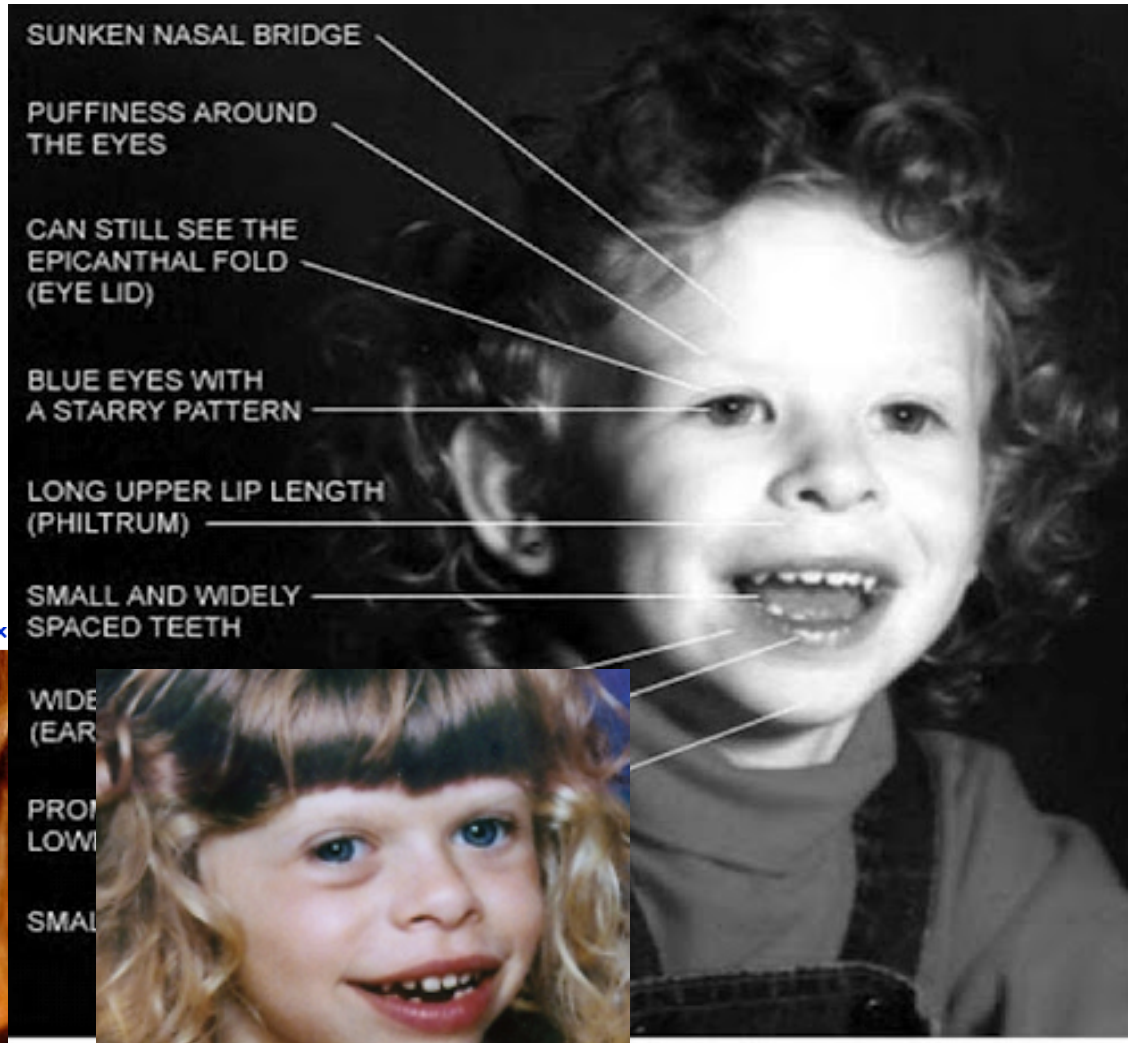
Faccia felina

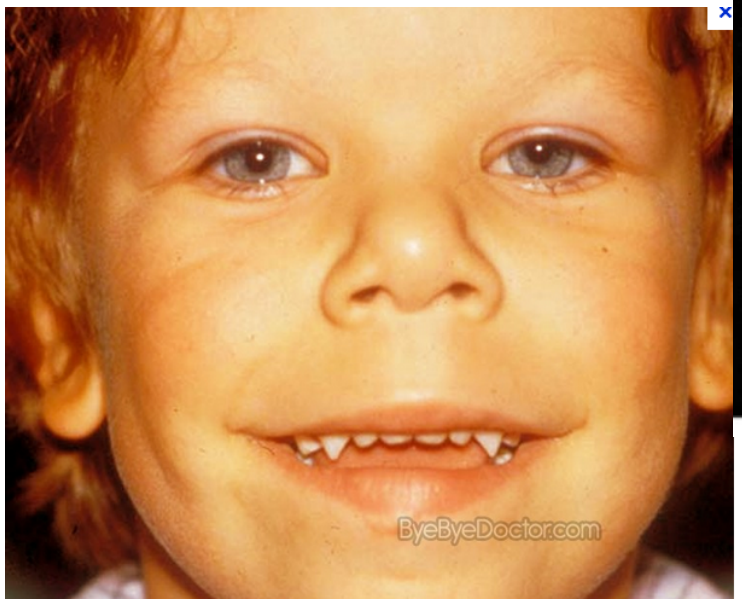
Labbra carnose

Bocca larga

Ponte nasale piatto

Fronte ampia





ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 1; EEC1

Alternative titles; symbols

EEC
EEC SYNDROME 1

HGNC Approved Gene Symbol: EEC1

Anomalie anatomiche che determinano infezioni ricorrenti:
-Dacriocistite ricorrente
-Infezioni respiratorie
-IVU

Cytogenetic location: 7q11.2-q21.3 ***Genomic coordinates (GRCh37): 7:61,700,000 - 98,000,000*** (from NCBI)

Ann Rheum Dis. 2012 Sep;71(9):1577-81. doi: 10.1136/annrheumdis-2012-201340. Epub 2012 Jun 29.

Deficient production of IL-1 receptor antagonist and IL-6 coupled to oxidative stress in cryopyrin-associated periodic syndrome monocytes.

Carta S, Tassi S, Delfino L, Omenetti A, Raffa S, Torrisi MR, Martini A, Gattorno M, Rubartelli A.

*147620

INTERLEUKIN 6; IL6

Alternative titles; symbols

INTERFERON, BETA-2; IFNB2
B-CELL DIFFERENTIATION FACTOR
B-CELL STIMULATORY FACTOR 2; BSF2
HEPATOCYTE STIMULATORY FACTOR; HSF
HYBRIDOMA GROWTH FACTOR; HGF

HGNC Approved Gene Symbol: IL6

cbm cluster in biomedicine · CRG Centre de Regulació Genòmica · UniTrap · igem

Tools for the biologist enabling optimized use of gene trap clones

Homepage | Blast Search | GO Search | Advanced Search | About

Gene **ENSMUSG00000078817** (Nlrp12)

Chromosomal location	Chr 7: 3235151 - 3249741 (-)
Description	NLR family, pyrin domain containing 12 Gene [Source:MGI Symbol;Acc:MGI:2676630]
UniGene	**Mm.277152**
MGI	**MGI:2676630**
Uniprot/SPTREMBL	**Q6UQE6 Q08EE9**
Human Ortholog	**ENSG000001424 5** (NALP12)
Omim	**611762 - FAMILI L COLD AUTOINFLA MATORY SYNDROME 2**

Cytogenetic location: 7p15.3 ***Genomic coordinates (GRCh37): 7:22,766,765 - 22,771,620*** (from NCBI)

Take home messages

Di fronte ad un bambino con febbre ricorrente…

- Fare un ***uso giudizioso delle risorse*** e del tempo!
- Evitare la ***parents fever phobia!***
- Accettare che la diagnosi di malattia autoinfiammatoria sistemica rappresenta una ***sfida diagnostica***!
- L'arma vincente per la definizione di una sindrome autoinfiammatoria è l'osservazione del paziente nel tempo: ***wait and see***!
- Credere nella clinica e valorizzare i sintomi nel loro insieme: è più probabile che un ***nesso*** ci sia!!