3) Search for a causal relationship

The evidence presented above demonstrates a correlation between the decrease of infections or factors predisposing to infections and immune disorders. A causal relationship remains to be established. Three lines of evidence argue in this direction.

a| A number of anti-infectious interventions have led to increased allergies. Thus, anti-helminthic treatment and the anti-pneumonia vaccine (just mentioned) were reported to increase incidence. There are also some data related to antibiotics, but they are more controversial, perhaps because of the difficulty in separating the effect of antibiotics and that of the infections at the origin of the antibiotics treatment. Note however that kanamycin treatment in mice increases the IgE level [8].

In the same vein, the prevention or even healing of atopic dermatitis by administration of non-pathogenic lactobacilli is very telling [9].

The best piece of evidence, though, has been derived from the prevention of a number of animal models of allergic or autoimmune diseases by infections in animal models. Even more striking is the observation, reminiscent of the Pakistani immigrants to the UK, that non-obese diabetic (NOD) mice which show a low incidence of IDDM in conventional facilities immediately show a jump to 100% disease incidence when bred in germ-free conditions [1].

4) Putative mechanisms

A number of mechanisms probably explain the protective role of infections discussed above.

Antigenic competition is the most obvious possibility. It has been known for several decades that a given ongoing immune response may compete with other immune responses. The underlying mechanisms are not clear but probably involve MHC peptide competition and cytokine consumption, notably of IL-7, a cytokine playing a major role in homeostatic-driven lymphocyte activation and proliferation.

Bystander suppression is another possibility. Immune responses generate the activation of various subsets of regulatory T cells, the effects of which are not limited to the immune response against the initial antigen.

Last but not least, infectious agents might influence immune responses after stimulation of various receptors independently from the evoked immune response. Toll-like receptors are major candidates in this respect, all the more so because several TLR agonists have proven capable of preventing IDDM in NOD mice. Virus receptors could also be instrumental as previously shown for the measles virus and more recently for the hepatitis A virus (HAV). Atopy is less frequent in HAV seropositive subjects.

Genetic predisposition to asthma involves a gene on chromosome 5 which has recently been shown to code for a protein, named TIM-1, expressed by Th2 cells [10]. TIM-1 polymorphism does not differ between atopic and non-atopic subjects, considered as a whole, but does it when one considers HAV seropositive subjects separately [11]?

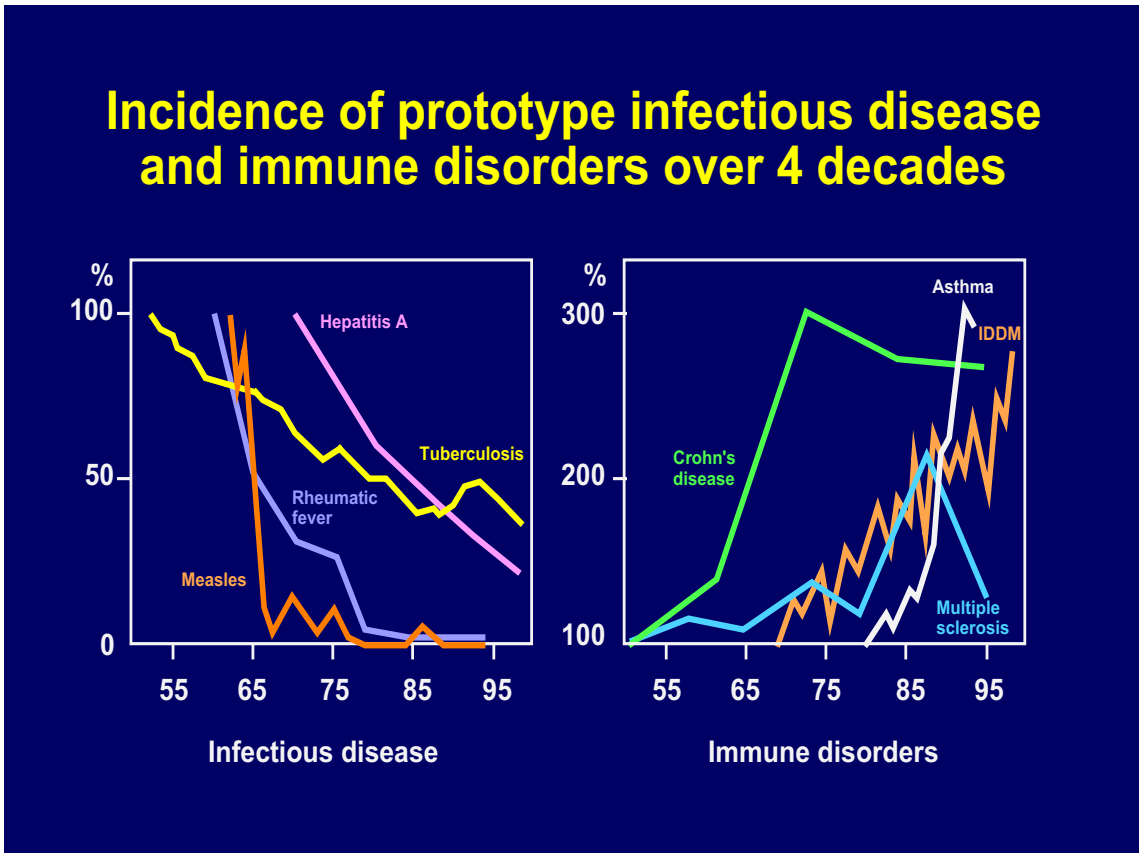
5) Practical implications and applications

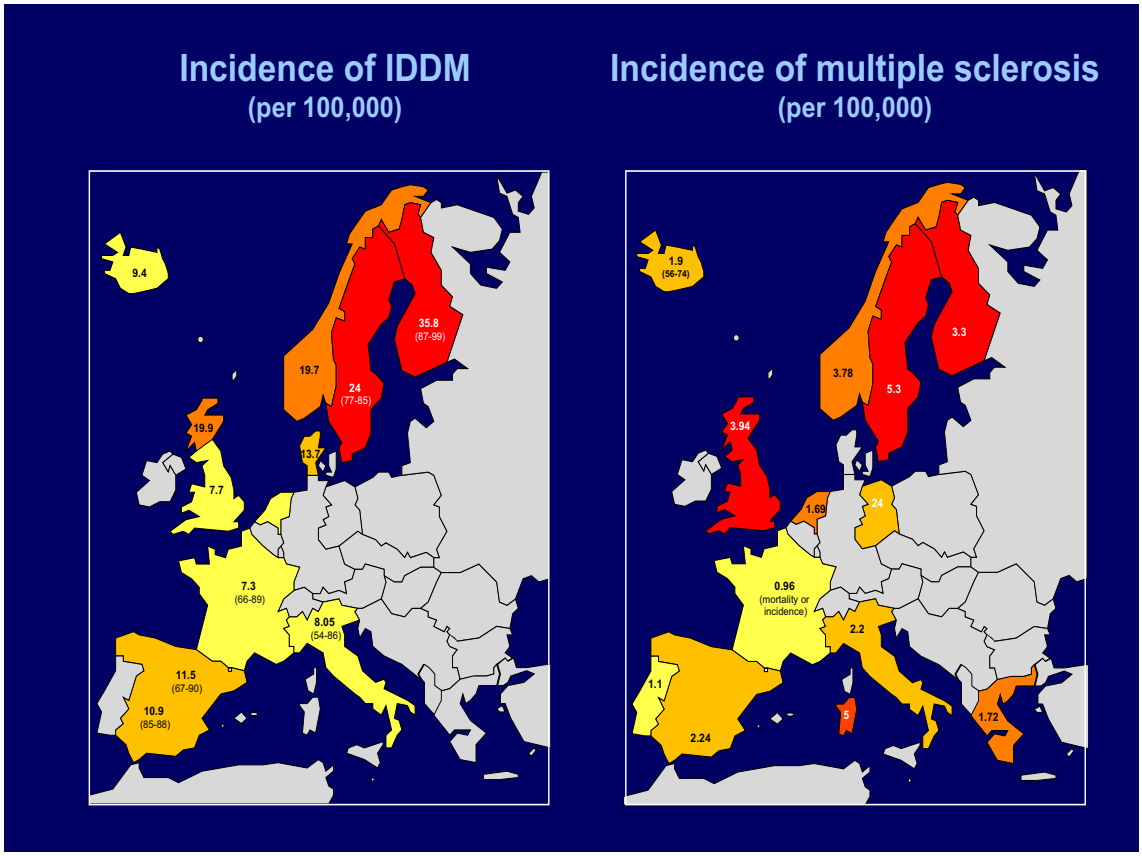
The data presented above clearly show that some of the infections primarily observed in Western countries had a favourable role which is missing today. What could the practical consequences be of such an observation? It is obviously out of question to reconsider hygiene measures which allowed the remarkable decrease of severe childhood infections or efficient modern vaccination programs. One may note, however, that extreme measures are probably not justified, as is sometimes observed in a somewhat obsessive fashion. One should be more critical about unnecessary measures, notably unjustified antibiotic treatment which, in addition to creating antibiotic resistance, may contribute to increased frequency of immune disorders.

Lastly, one should conduct active research for immunostimulatory therapies which could substitute for infections. One may think of bacterial extracts. There have been some interesting preliminary data with mycobacterium vaccae extracts in asthma, atopic dermatitis and psoriasis [12-14]. One may also explore the effect of probiotics as suggested by two very promising randomised trials [15, 16]. More generally, one should pay more attention to the maintenance of a physiological gut flora.

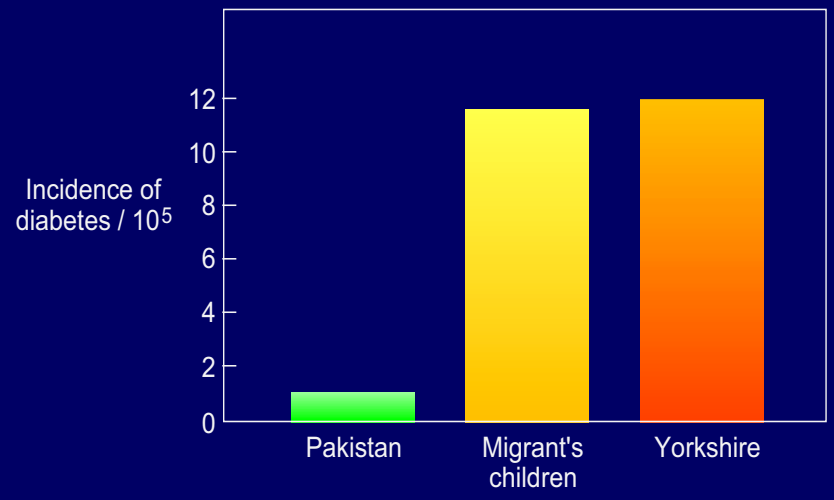
REFERENCES

1. Bach JF (2002). The effect of infections on susceptibility to autoimmune and allergic diseases. N. Engl. J. Med., 347(12):911-920.
2. Bach JF (1994). Predictive medicine in autoimmune diseases: from the identification of genetic predisposition and environmental influence to precocious immunotherapy. Clin. Immunol. Immunopathol., 72(2):156-161.
3. Staines A, Hanif S, Ahmed S, McKinney PA, Shera S, Bodansky HJ (1997). Incidence of insulin dependent diabetes mellitus in Karachi, Pakistan. Arch. Dis. Child., 76(2):121-123.
4. Patterson CC, Carson DJ, Hadden DR (1996). Epidemiology of childhood IDDM in Northern Ireland 1989-1994: Low incidence in areas with highest population density and most household crowding. Diabetologia, 39(9):1063-1069.
5. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL (2000). Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N. Engl. J. Med., 343(8):538-543.
6. Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, Bonini S (2000). Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. Brit. Med. J., 320(7232):412-417.
7. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N (2003). A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N. Engl. J. Med., 349(14):1341-1348.
8. Sudo N, Yu XN, Aiba Y, Oyama N, Sonoda J, Koga Y, Kubo C (2002). An oral introduction of intestinal bacteria prevents the development of a long-term Th2-skewed immunological memory induced by neonatal antibiotic treatment in mice. Clin. Exp. Allergy, 32(7):1112-1116.
9. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E (2001). Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet, 357(9262):1076-1079.
10. McIntire JJ, Umetsu SE, Akbari O, Potter M, Kuchroo VK, Barsh GS, Freeman GJ, Umetsu DT, Dekruyff RH (2001). Identification of Tapr (an airway hyperreactivity regulatory locus) and the linked Tim gene family. Nat. Immunol., 2(12):1109-1116.
11. McIntire JJ, Umetsu SE, MacAubas C, Hoyte EG, Cinnioglu C, Cavalli-Sforza LL, Barsh GS, Hallmayer JF, Underhill PA, Risch NJ, Freeman GJ, de Kruyff RH, Umetsu DT (2003). Hepatitis A virus link to atopic disease. Nature, 425(6958):576.
12. Camporota L, Corkhill A, Long H, Lordan J, Stanciu L, Tuckwell N, Cross A, Stanford JL, Rook GAW, Holgate ST, Djukanovic R (2003). The effects of Mycobacterium vaccae on allergen-induced airway responses in atopic asthma. Eur. Resp. J., 21(2):287-293.
13. Arkwright PD, David TJ (2001). Intradermal administration of a killed Mycobacterium vaccae suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease. J. Allergy Clin. Immunol., 107(3):531-534.
14. Balagon MV, Walsh DS, Tan PL, Cellona RV, Abalos RM, Tan EV, Fajardo TT, Watson JD, Walsh GP (2000). Improvement in psoriasis after intradermal administration of heat-killed Mycobacterium vaccae. Int. J. Dermatol., 39(1):51-8.
15. Rosenfeldt V, Benfeldt E, Nielsen SD, Michaelsen KF, Jeppesen DL, Valerius NH, Paerregaard A (2003). Effect of probiotic Lactobacillus strains in children with atopic dermatitis. J. Allergy Clin. Immunol., 111(2):389-395.
16. Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E (2003). Probiotics and prevention of atopic disease: 4-year follow- up of a randomised placebo-controlled trial. Lancet, 361(9372):1869-1871.


Incidence of prototype infectious disease and immune disorders over 4 decades
%
100
50
0
Hepatitis A
Tuberculosis
Rheumatic fever
Measles
55
65
75
85
95
Infectious disease
%
300
200
100
Asthma
IDDM
Crohn's disease
Multiple sclerosis
55
65
75
85
95
Immune disorders


Incidence of IDDM
(per 100,000)
9.4
35.8
(87-99)
19.7
24
(77-85)
19.9
13.7
7.7
7.3
(66-89)
8.05
(54-86)
11.5
(67-90)
10.9
(85-88)
Incidence of multiple sclerosis
(per 100,000)
1.9
(56-74)
3.3
3.78
5.3
3.94
1.69
.24
0.96
(mortality or incidence)
2.2
1.1
2.24
5
1.72

IDDM incidence in children of migrants from Pakistan to Yorkshire



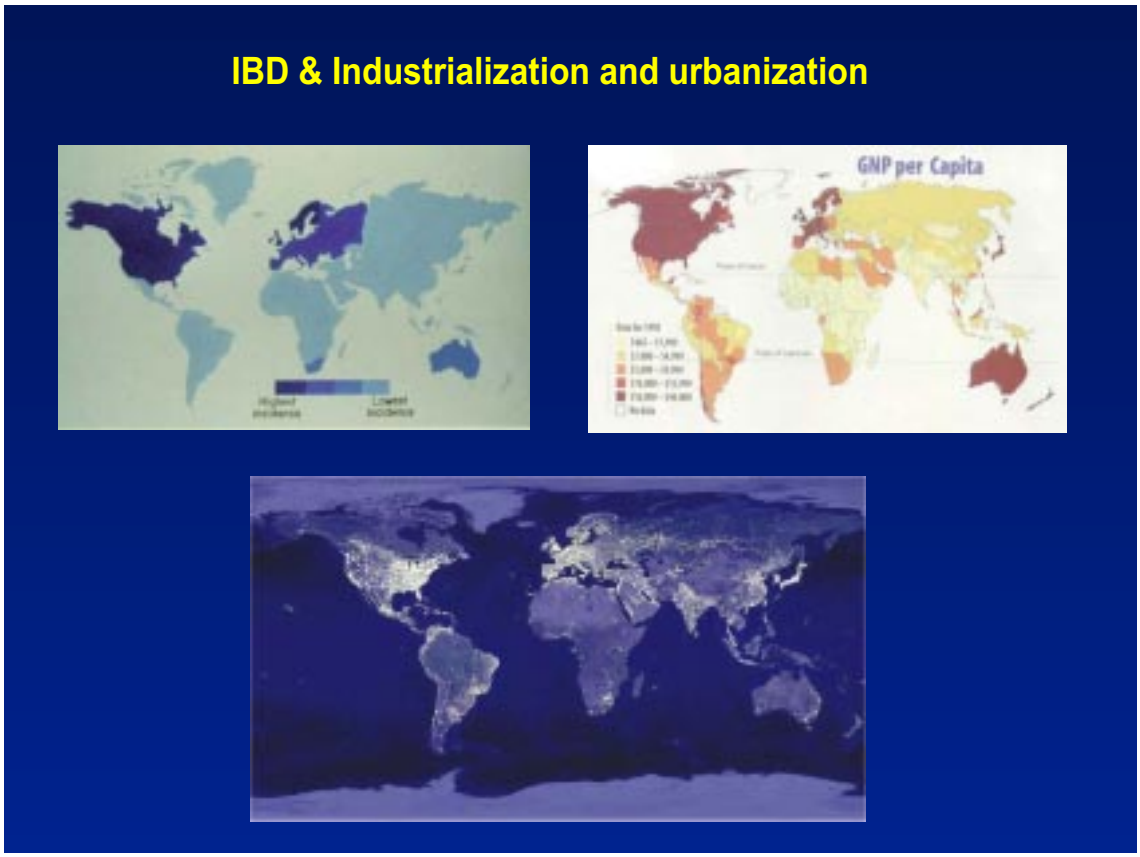
Staines A. (1997) and Bodansky H.J. (1992)

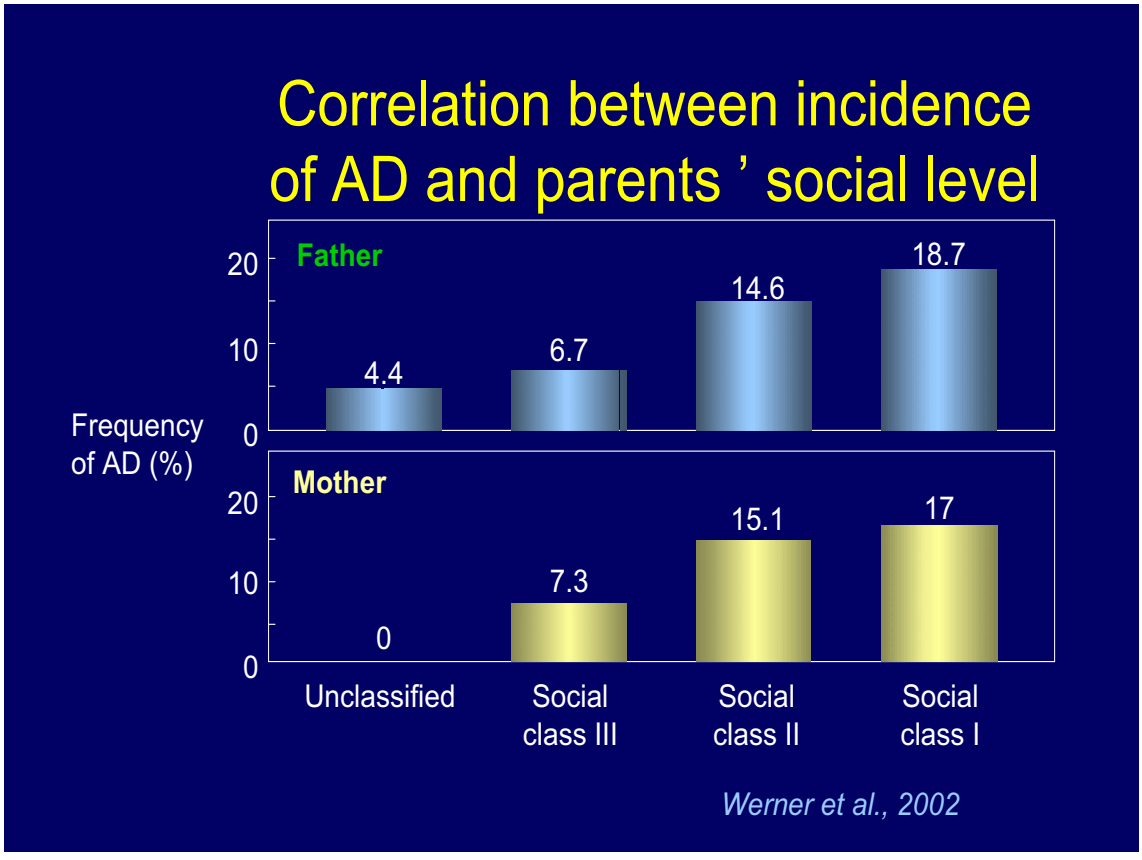
PREVALENCE OF ASTHMA AND ATOPY IN TWO AREAS OF WEST AND EAST GERMANY

	West	East
• ATOPIC SENSITIZATION	36.7%	18.2%
	OR 2.6	
	p<0.0001	
• CURRENT ASTHMA AND	5.9%	3.9%
HAY FEVER	8.6%	2.7%
	OR 1.5 p<0.0001	
	OR 3.4 p<0.0001	

N=5.030 West
N=2.623 East

E. Von Mutius, Am J Respir Crit Care Med. 1994


IBD & Industrialization and urbanization
GNP per Capita


Correlation between incidence of AD and parents ' social level
Father
Mother
Frequency of AD (%)
20
10
0
4.4
6.7
14.6
18.7
0
7.3
15.1
17
Unclassified
Social class III
Social class II
Social class I
Werner et al., 2002

CORRELATION BETWEEN HYGIENE INDICES AND IBD (ODDS RATIO)

RISK FACTORS	CROHN'S DISEASE	ULCERATIVE COLITIS
WATER TAP	1.8	0.9
HOT WATER TAP	5.0	1.3
SEPARATE BATHROM	3.3	1.3
FLUSH TOILET	1.1	1.4
MAINS DRAINAGE	2.6	1.2

(A.E. Gent et al., 1994)

DAY CARE ATTENDANCE IN EARLY LIFE AND RISK OF ASTHMA AT 6 YEARS

	O.R.
Atopic dermatitis	0.3
Asthma at 6 years	0.3
Recurrent wheezing	0.3

Celedon JC, Am. J. Respir. Crit. Care Med. 2003

FACTORS CONTRIBUTING TO THE APPEARANCE OF INFECTIONS

Sources of pathogenic agents

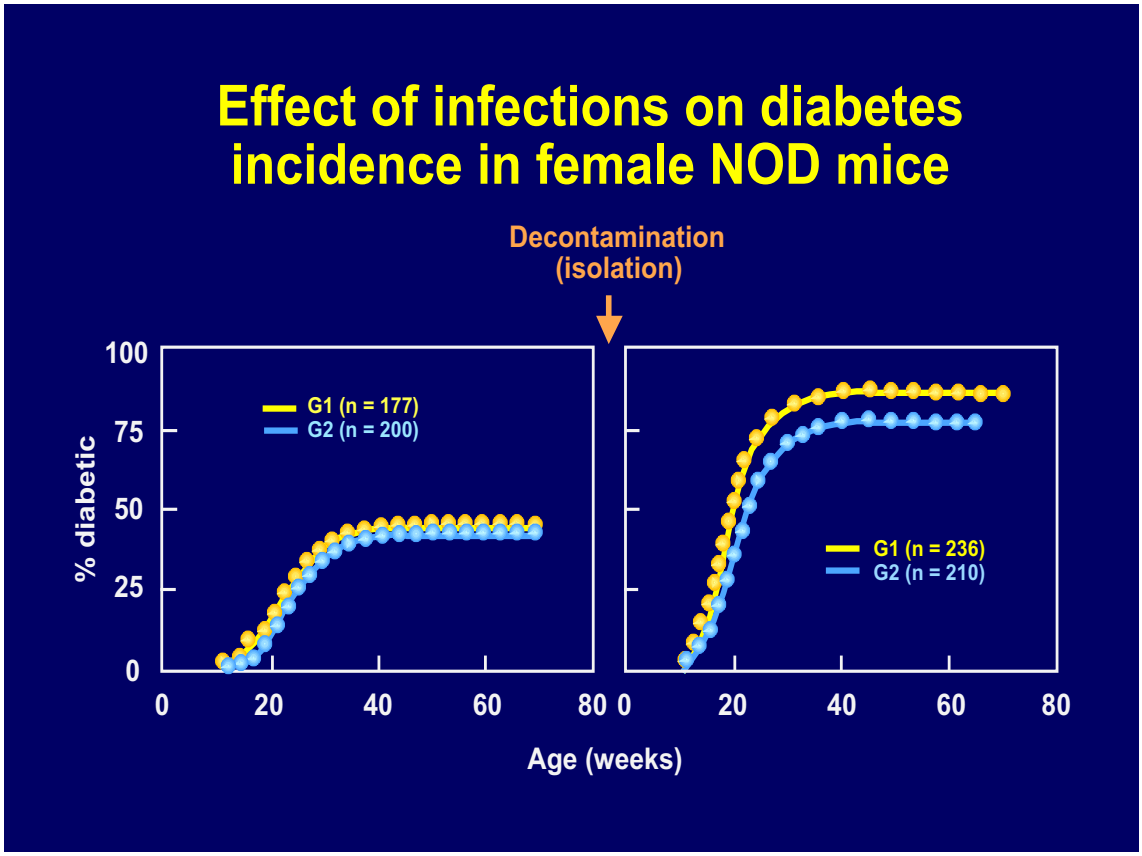
- drinking water
- food (cold storage)
- climate
- housing conditions

Anti-infectious defense

- genetic factors
- nutrition
- antibiotics
- vaccination

CAUSAL RELATIONSHIP

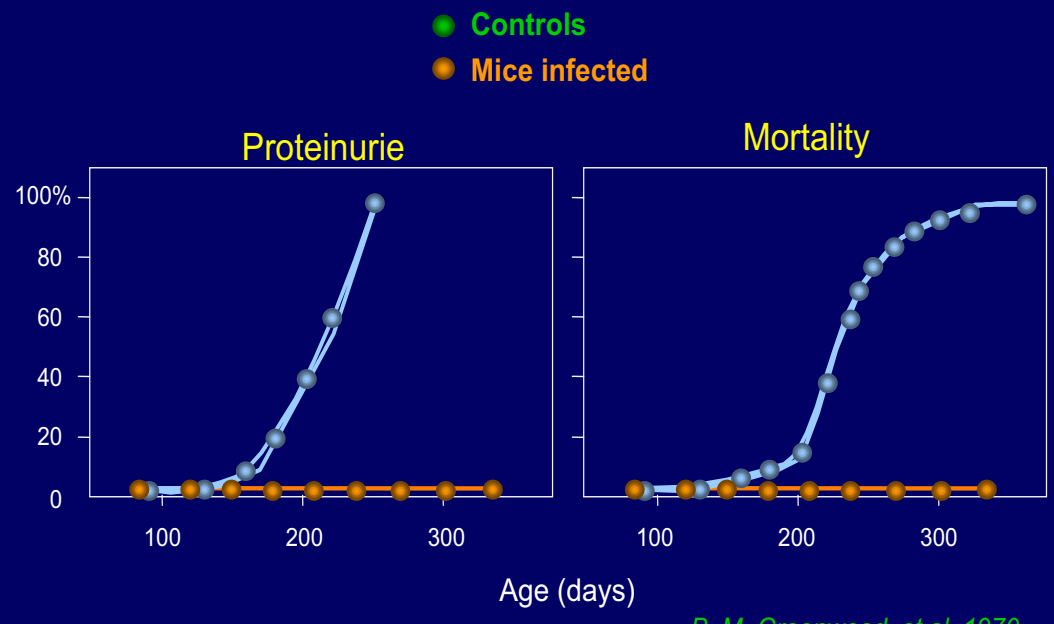
- ANIMAL MODELS
- CLINICAL TRIALS (THERAPEUTIC PROOF OF PRINCIPALE)


Effect of infections on diabetes incidence in female NOD mice
Decontamination (isolation)
% diabetic
100
75
50
25
0
G1 (n = 177)
G2 (n = 200)
G1 (n = 236)
G2 (n = 210)
0
20
40
60
80
Age (weeks)

PREVENTION OF IDDM IN NOD MICE BY INFECTIOUS AGENTS

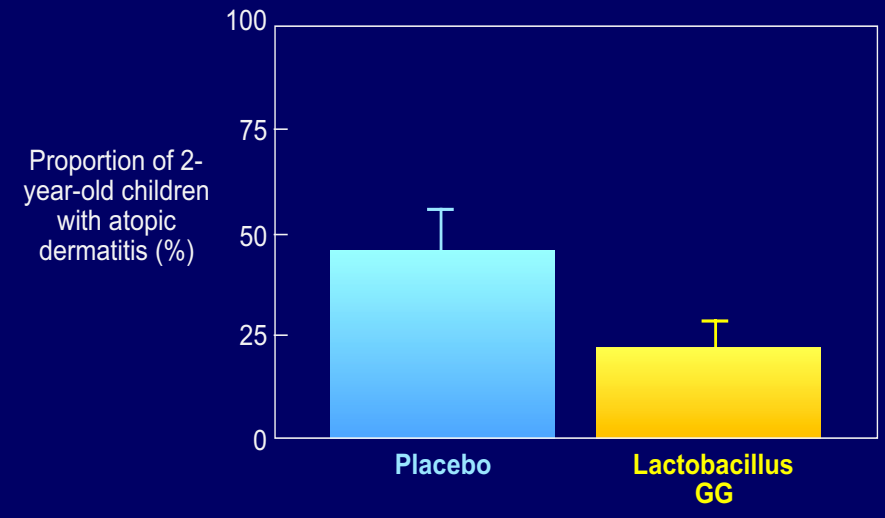
Bacteria	streptococci salmonella mycobacteria (CFA, BCG, …)
Viruses	LCMV MHV LDHV
Parasites	schistosoma oxyures

Effect of malaria in B / W mice



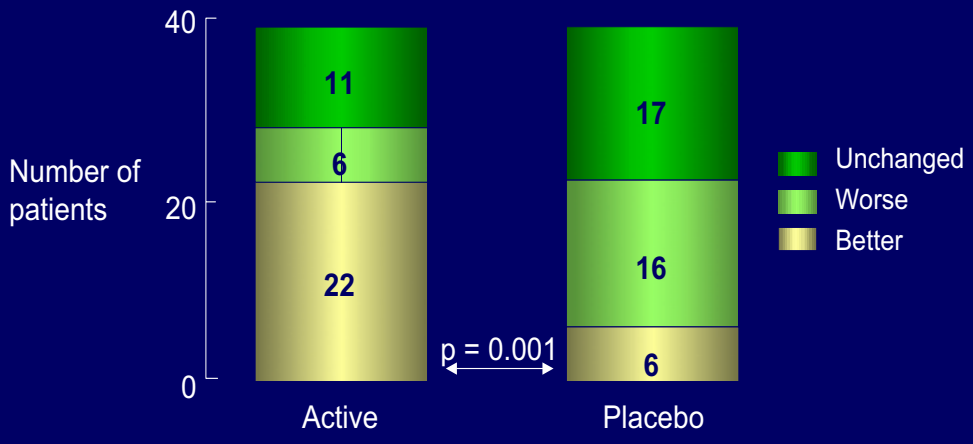
B. M. Greenwood et al, 1970

Treatment effect of Lactobacillus GG on atopic dermatitis



The Lancet, 2001

Effect of a 6-week treatment of atopic dermatitis in Danish children (aged 1-13) by probiotics (L rhamnosus and L reuteri)



Rosenfeldt et al., 2003

MECHANISMS

MECHANISMS OF THE PROTECTION FROM AUTOIMMUNE DISEASES AFFORDED BY INFECTIONS

1. Antigenic competition

Effect on antigen presentation

- preemption (phagocytosis)
- antigen processing
- antigen binding to MHC molecules

Competition for homeostatic signals

MECHANISMS OF THE PROTECTION FROM AUTOIMMUNE DISEASES AFFORDED BY INFECTIONS

2. Antigen-induced immunoregulation (by-stander suppression)

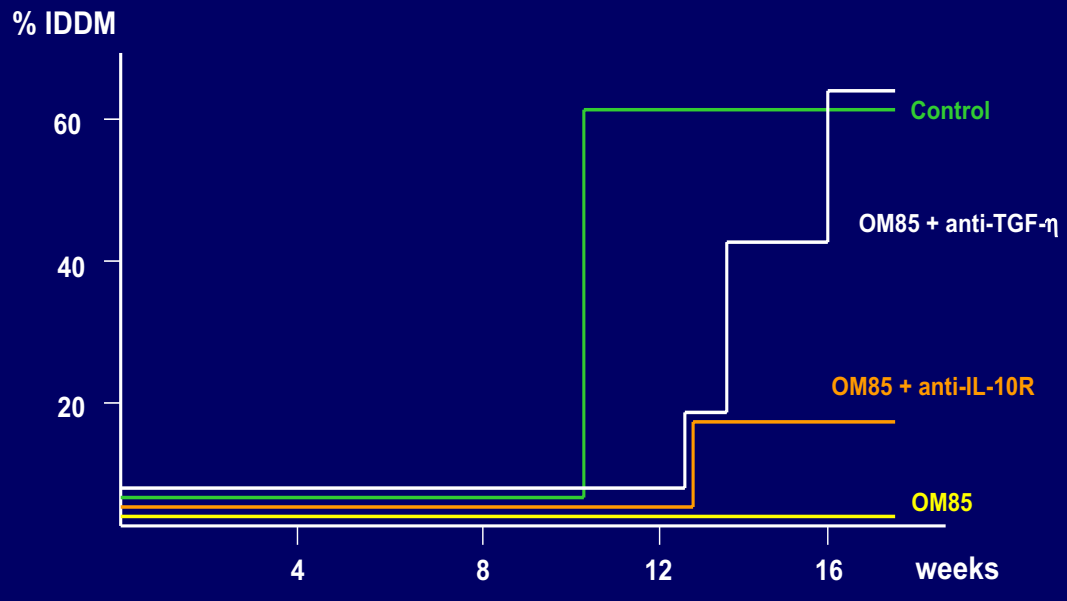
Th1/Th2 cells

Th3 cells

NKT cells

$CD25^+$ T cells

cytokine dependency of the OM85-induced diabetes protection



MECHANISMS OF THE PROTECTION FROM AUTOIMMUNE DISEASES AFFORDED BY INFECTIONS

3. Non-antigen-mediated effects

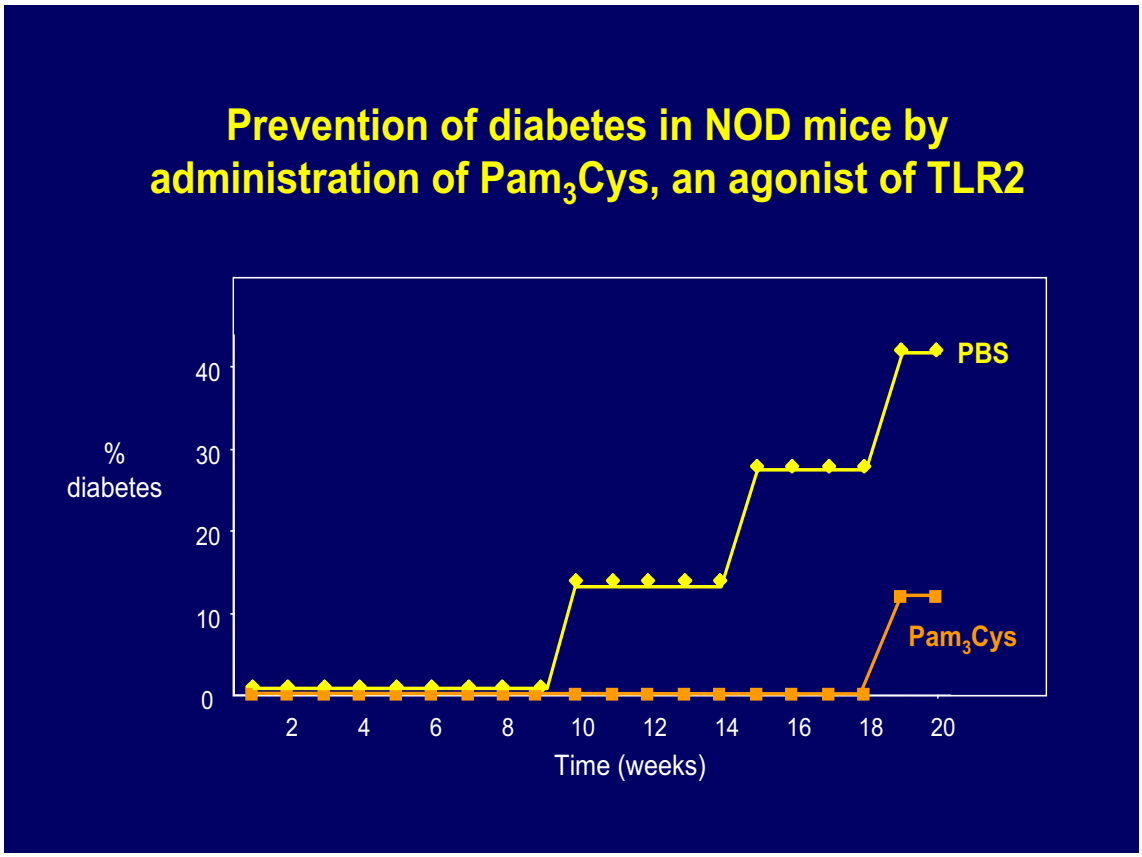
Toll-like receptors (regulatory cytokines)

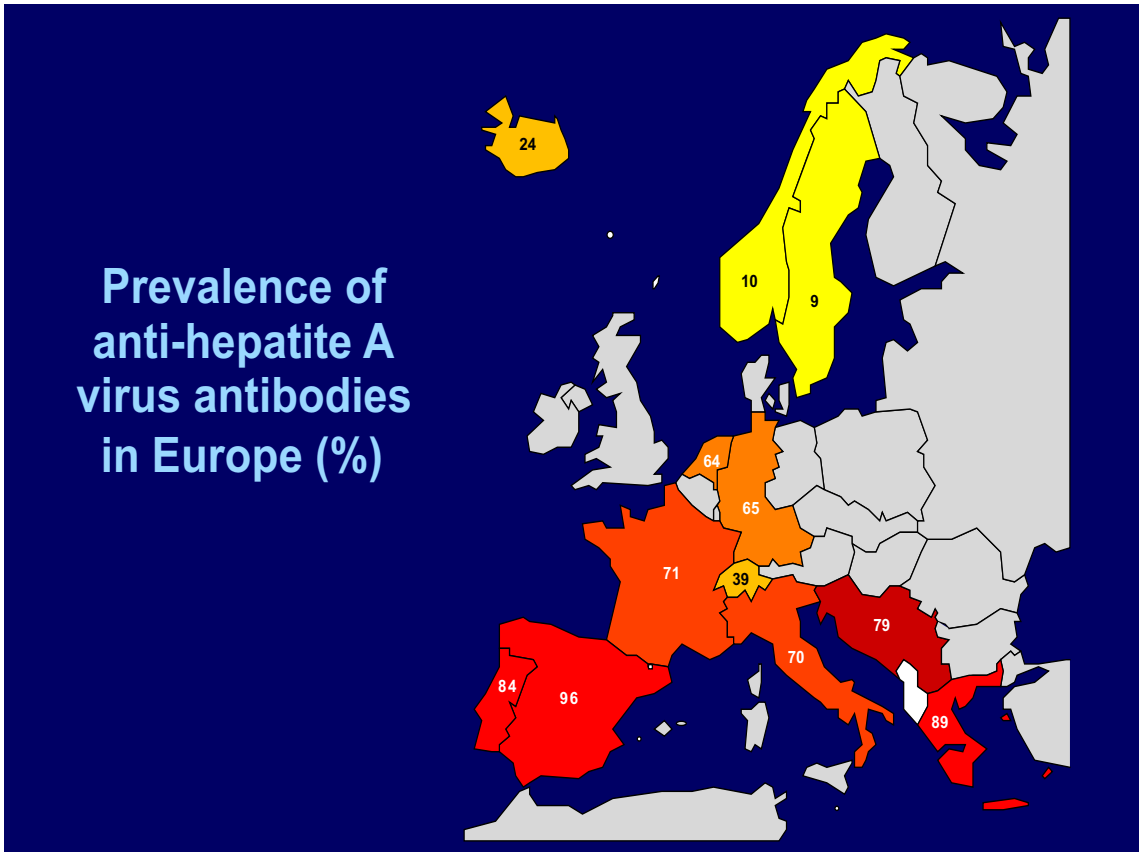
Superantigens (depletion of T cell subsets)

Immunosuppressive proteins

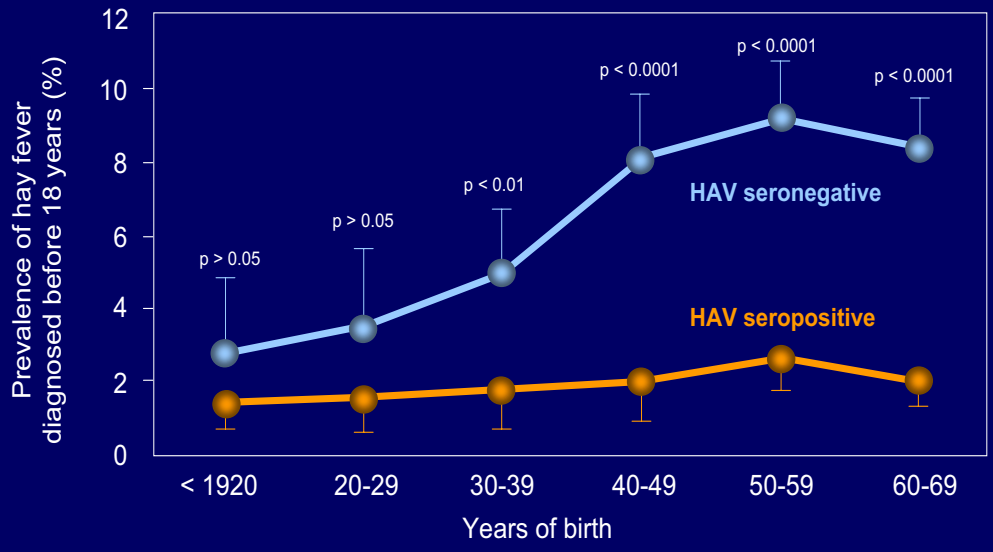
TOLL-LIKE RECEPTORS

TLR Family	Ligands (examples)
TLR1	Tri-acyl lipopeptides (bacteria, mycobacteria)
TLR2	Lipoprotein/lipopeptides (a variety of pathogens) Peptidoglycan and Lipoteichoic acid (Gram-positive bacteria) Glycoinositolphospholipids (Trypanosoma Cruzi) HSP70 (host)
TLR3	Double-stranded RNA (virus)
TLR4	LPS (Gram-negative bacteria) Taxol (plant) Fusion protein (RSV) HSP60 (host)
TLR5	Flagellin (bacteria)
TLR6	Di-acyl lipopeptides (mycoplasma)
TLR7	Imidazoquinoline (synthetic compounds)
TLR8	?
TLR9	CpG DNA (bacteria)
TLR10	?


Prevention of diabetes in NOD mice by administration of Pam3Cys, an agonist of TLR2
% diabetes
0
10
20
30
40
2
4
6
8
10
12
14
16
18
20
Time (weeks)
PBS
Pam3Cys


Prevalence of anti-hepatite A virus antibodies in Europe (%)
24
10
9
64
65
71
39
79
70
84
96
89

Hay fever at/or before 18 years in the USA general population according to serology for hepatitis A virus (NHANES-III)



HA-Ab⁻	442	549	663⁻	972	1626⁻	2006
HA-Ab⁺	1929	1591	1174	1227	1454	1292

S. Bonini et al. JACI, 2002

Asthma, HAV and TIM-1

- Major asthma susceptibility gene at human chromosome 5q23-35
- Production of congenic mice differing at the homologous chromosomal segment
- Identification of a Mendelian trait expressed by TH2 cells controlling airway hyperreactivity
- Positional cloning identified a gene family that encodes TIM proteins
- The human homologue of TIM-1 is Hepatitis A Virus (HAV) receptor

(JJ.McIntire et al., Nature Immunology, 2001)

CONCLUSIONS

- The decline of infectious diseases in developed countries parallels the increase of allergic and autoimmune disorders
- High socio-economic level is a risk factor for immune disorders

CONCLUSIONS (Continued)

- Collective and possibly also individual hygiene is a risk factor
- Underlying mechanisms are multiple including homeostasis, bystander suppression, Toll-like and HAV receptors

Familial Mediterranean Fever and the Expanding Spectrum of Hereditary Autoinflammatory Disorders

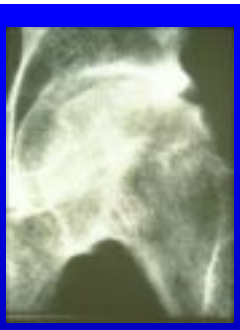
Dan Kastner, MD, PhD
Genetics and Genomics Branch
NIAMS, NIH, DHHS

FMF: Clinical Features

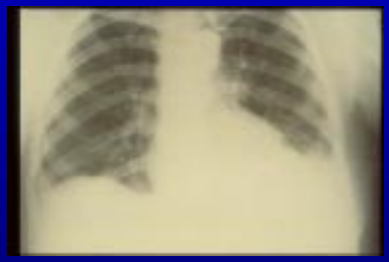
1-3 day episodes of fever with:

- Abdominal pain
- Chest pain
- Arthritis
- Rash

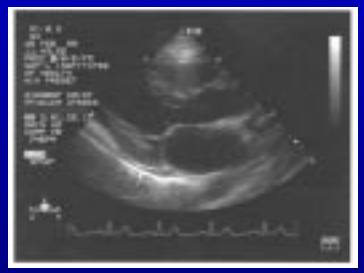
Peritonitis (air-fluid levels)



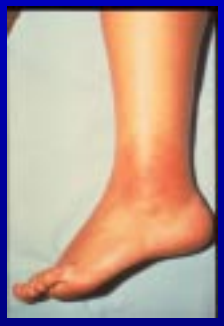
Chronic arthritis of the hip



Pleurisy (left pleural effusion)

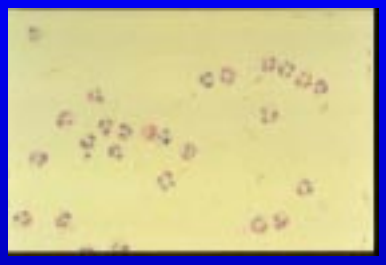


Posterior pericardial effusion

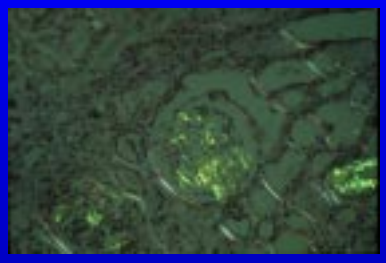


Erysipeloid erythema

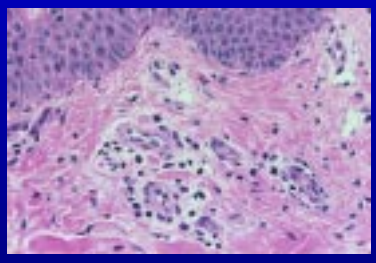
FMF: Histology



PMNs, synovial fluid



Renal amyloid, Congo red

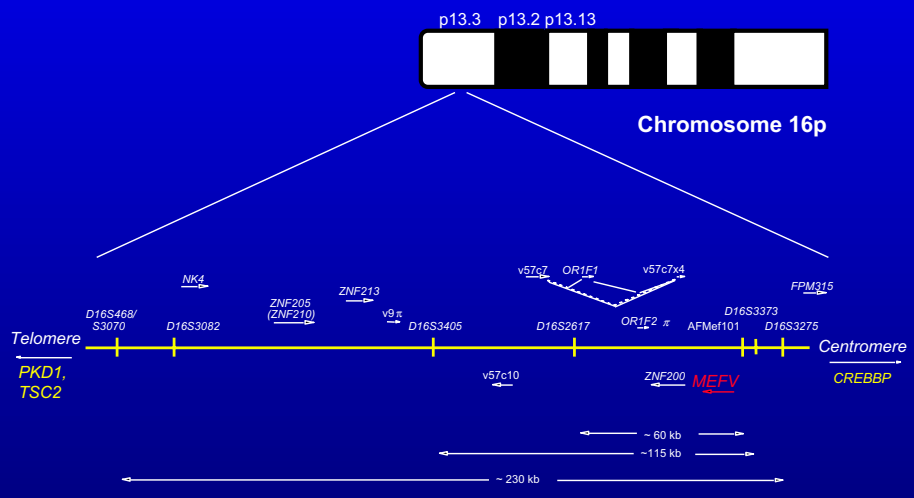


Erysipeloid erythema

Renal amyloid, EM

FMF Family Studies

Positional Cloning of *MEFV*, the FMF Gene

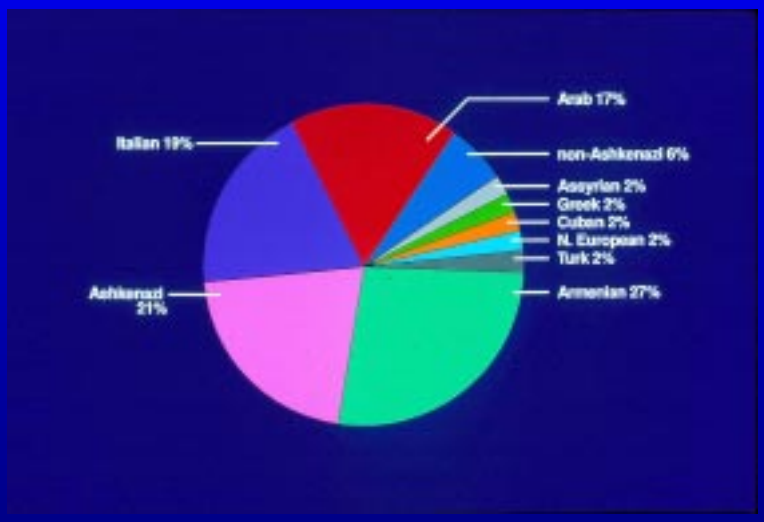


FMF Protein: Pyrin or Marenostrin

Spread of Ancient Ancestral Mutations in FMF

Hospital Practice 33:131, 1998

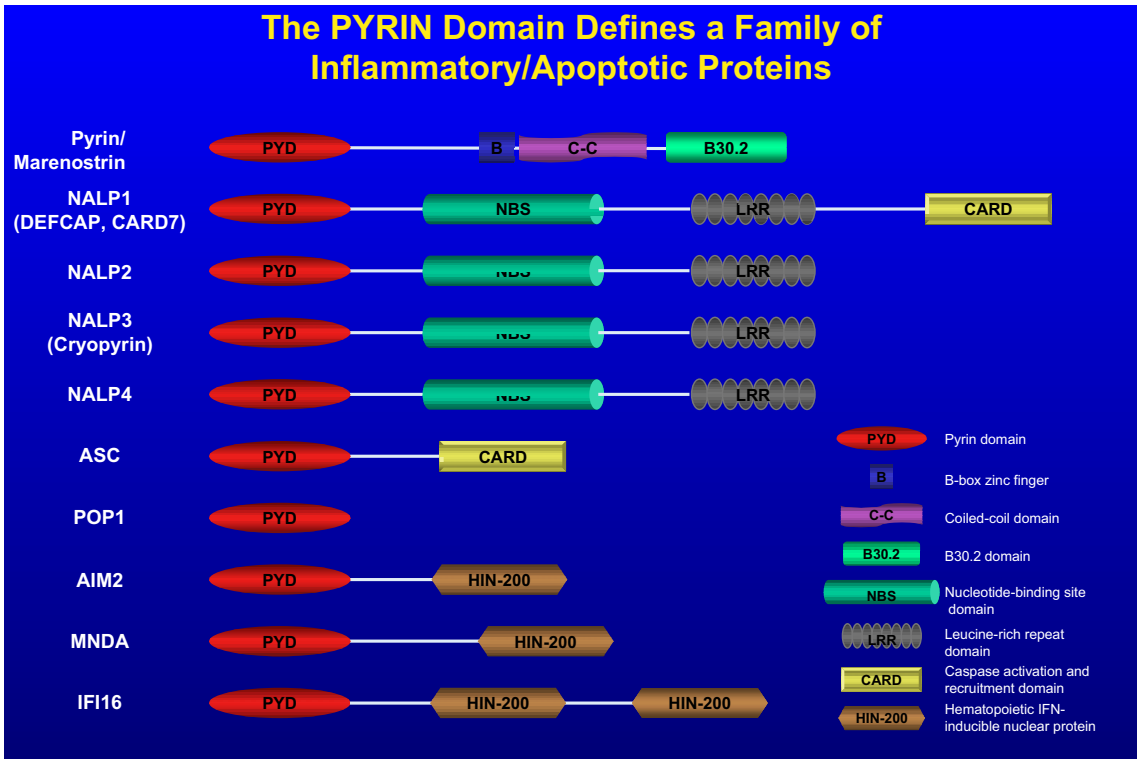
DNA Diagnosis Expands the Clinical Spectrum of FMF



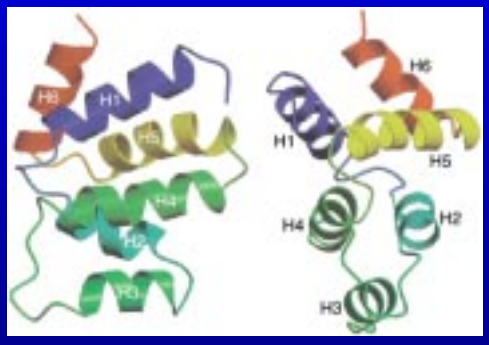
Medicine (Baltimore) 77:268, 1998

Genetic Testing In FMF

- 41 mutations currently known
- “Hot spots” in exon 10 and, to a lesser degree, exon 2
- Two mutations required for genetic diagnosis
- Only about 70% of patients with clinical FMF have two identifiable mutations
- Strong possibility of locus heterogeneity
- Clinical judgment still required to make the diagnosis



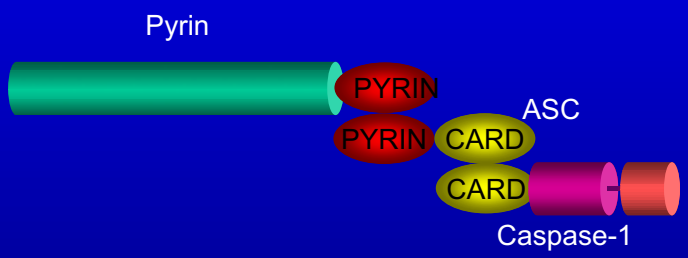
Structure of the Death Domain-Fold Motifs



- Adaptor domain architecture important in homotypic protein-protein interactions
- Death domains
- Death effector domains
- Caspase activation and recruitment domains (CARDs)
- Pyrin domains

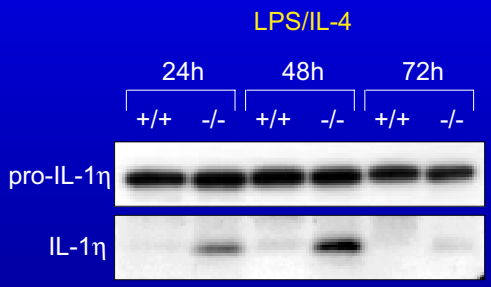
Protein Science 10:1911, 2001

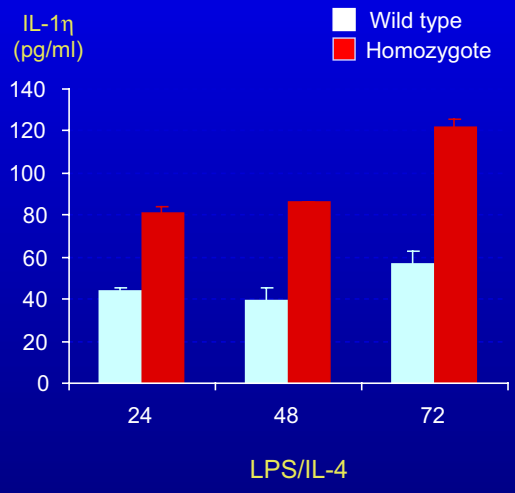
ASC Can Act as a Link between the PYRIN Domain and Apoptotic and Inflammatory Pathways



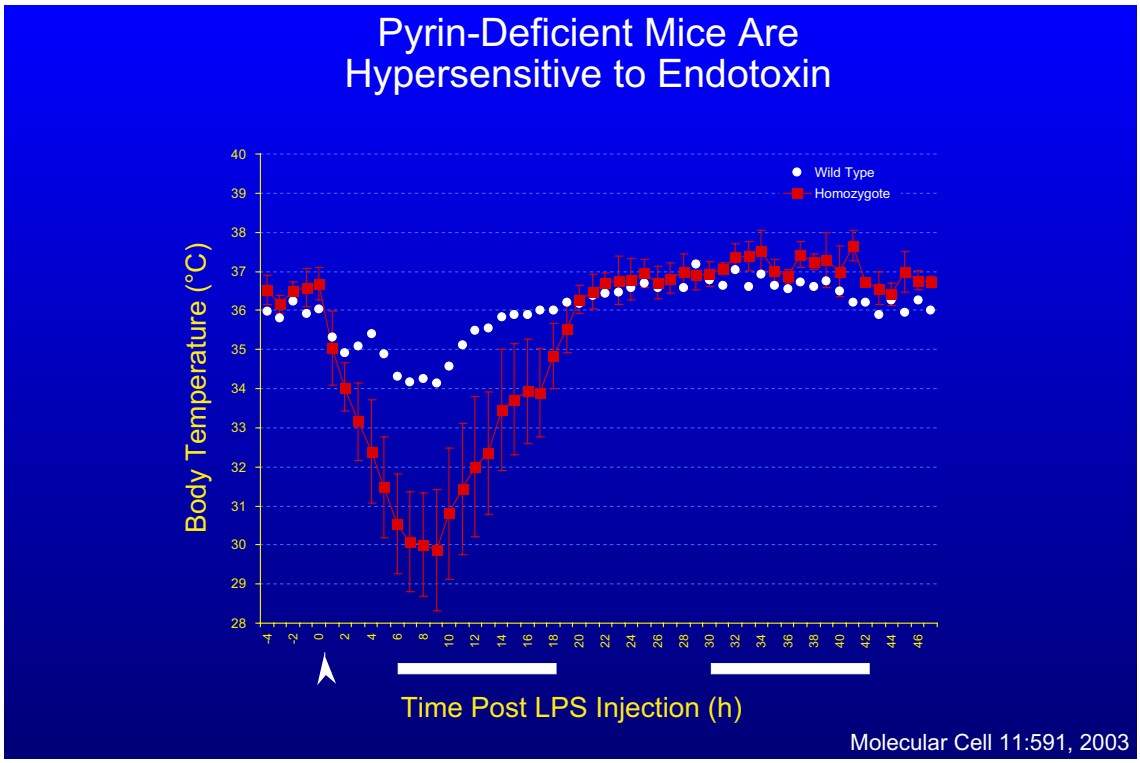
IL-1η Converting Enzyme (ICE)

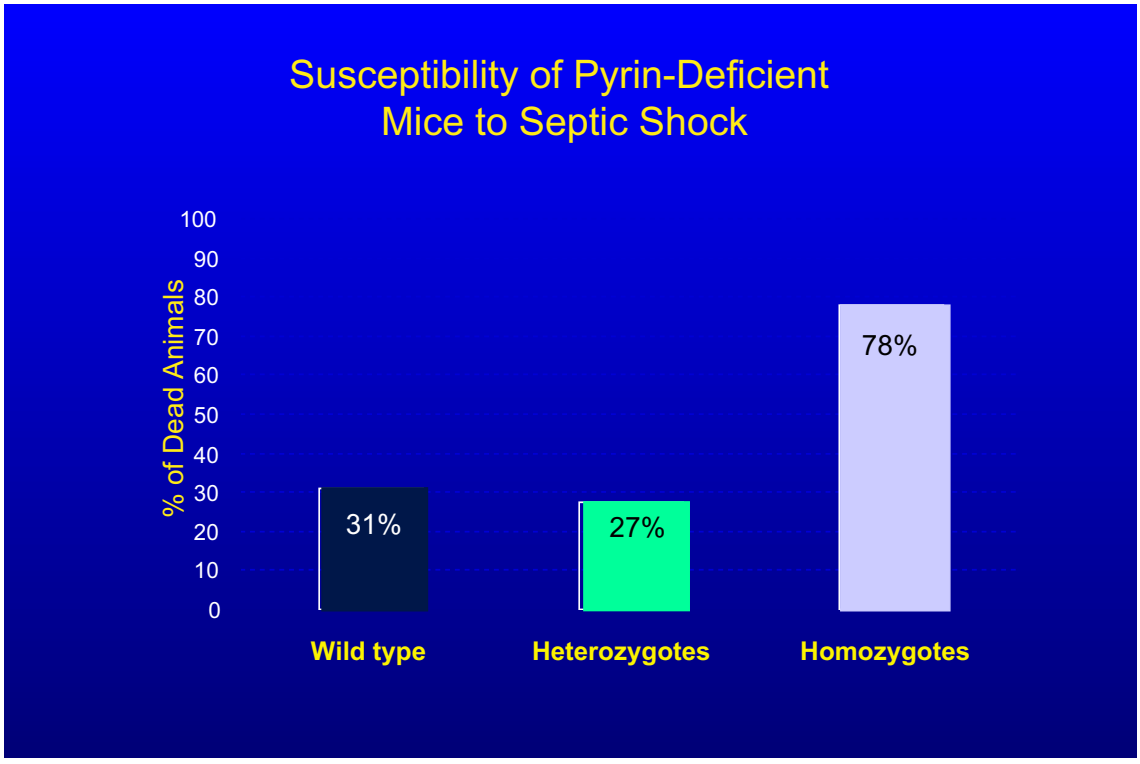
Pyrin-Deficient Mice Produce More IL-1η#Than Wild-Type

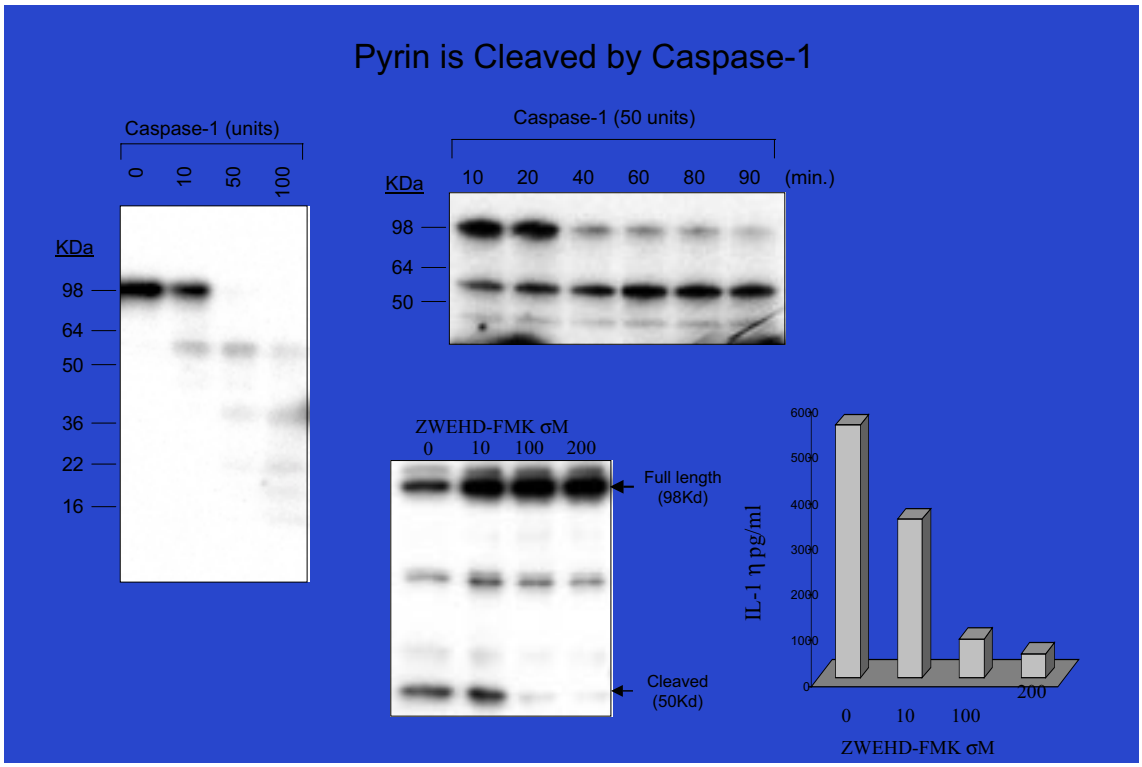


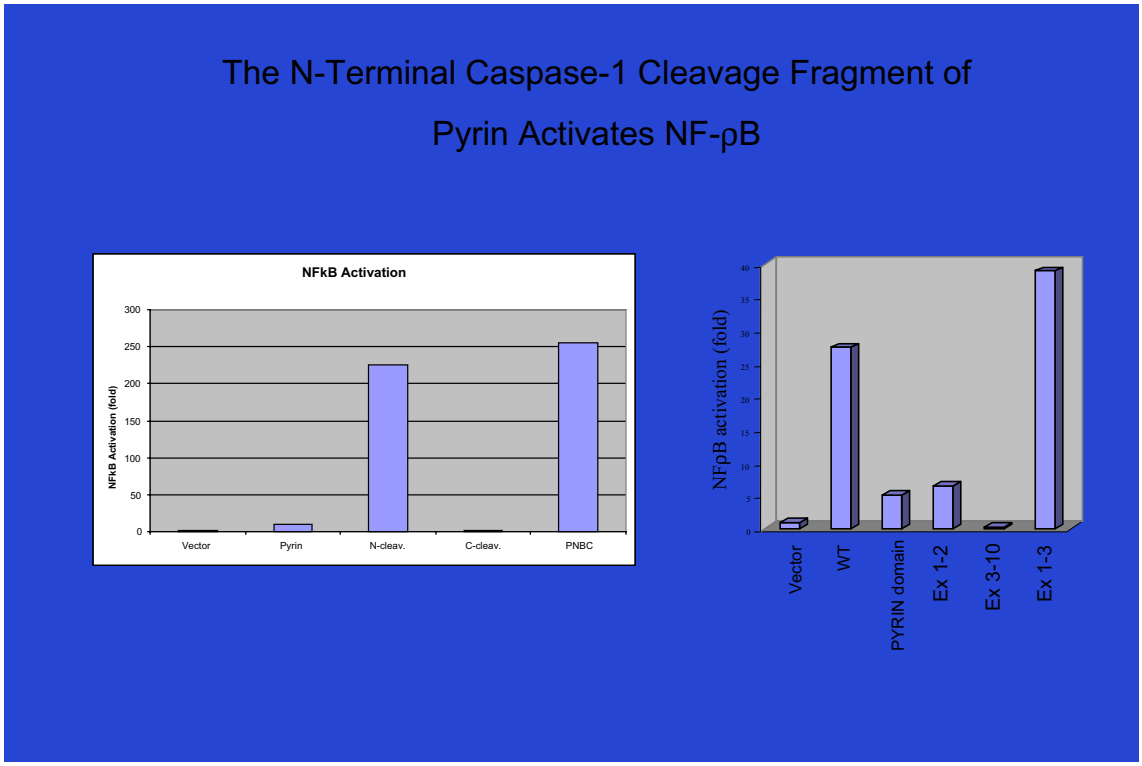


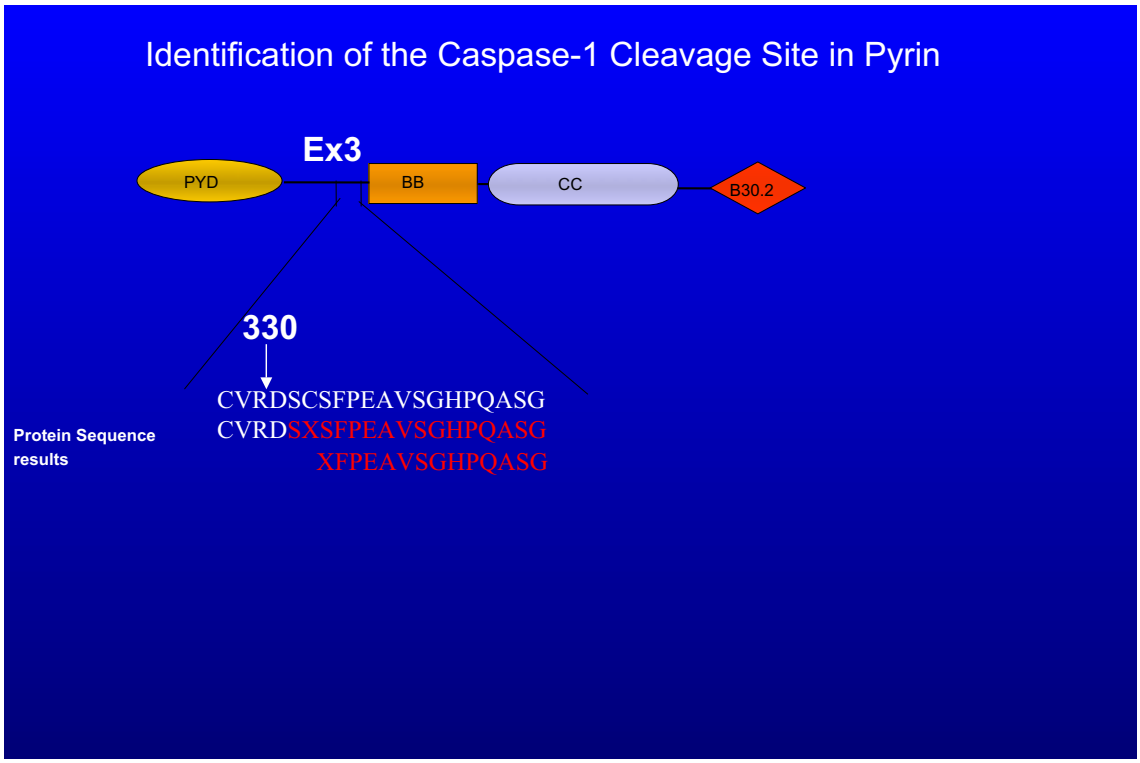
Molecular Cell 11:591, 2003


Pyrin-Deficient Mice Are Hypersensitive to Endotoxin
Wild Type
Homozygote
Body Temperature (°C)
Time Post LPS Injection (h)
Molecular Cell 11:591, 2003


Susceptibility of Pyrin-Deficient Mice to Septic Shock
% of Dead Animals
31%
27%
78%
Wild type
Heterozygotes
Homozygotes

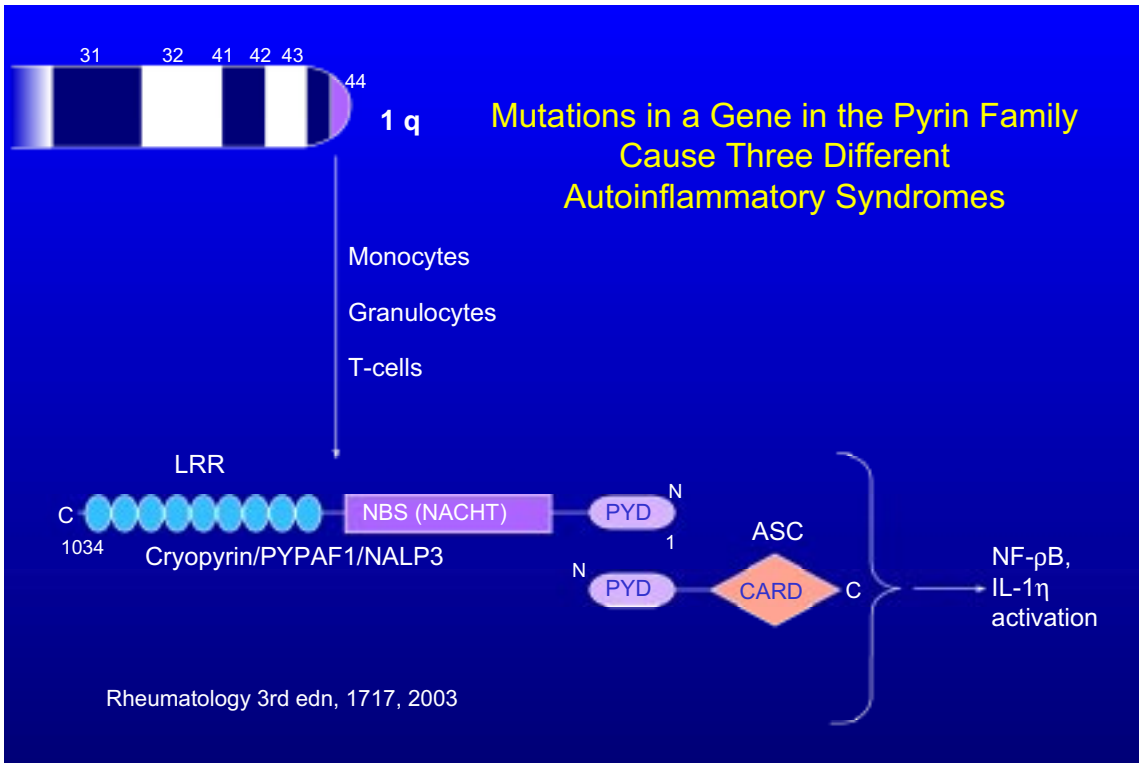

Pyrin is Cleaved by Caspase-1
Caspase-1 (units)
0
10
50
100
KDa
98
64
50
36
22
16
Caspase-1 (50 units)
KDa
10
20
40
60
80
90
(min.)
98
64
50
ZWEHD-FMK σM
0
10
100
200
Full length (98Kd)
Cleaved (50Kd)
IL-1 η pg/ml
6000
5000
4000
3000
2000
1000
0
200
0
10
100
ZWEHD-FMK σM

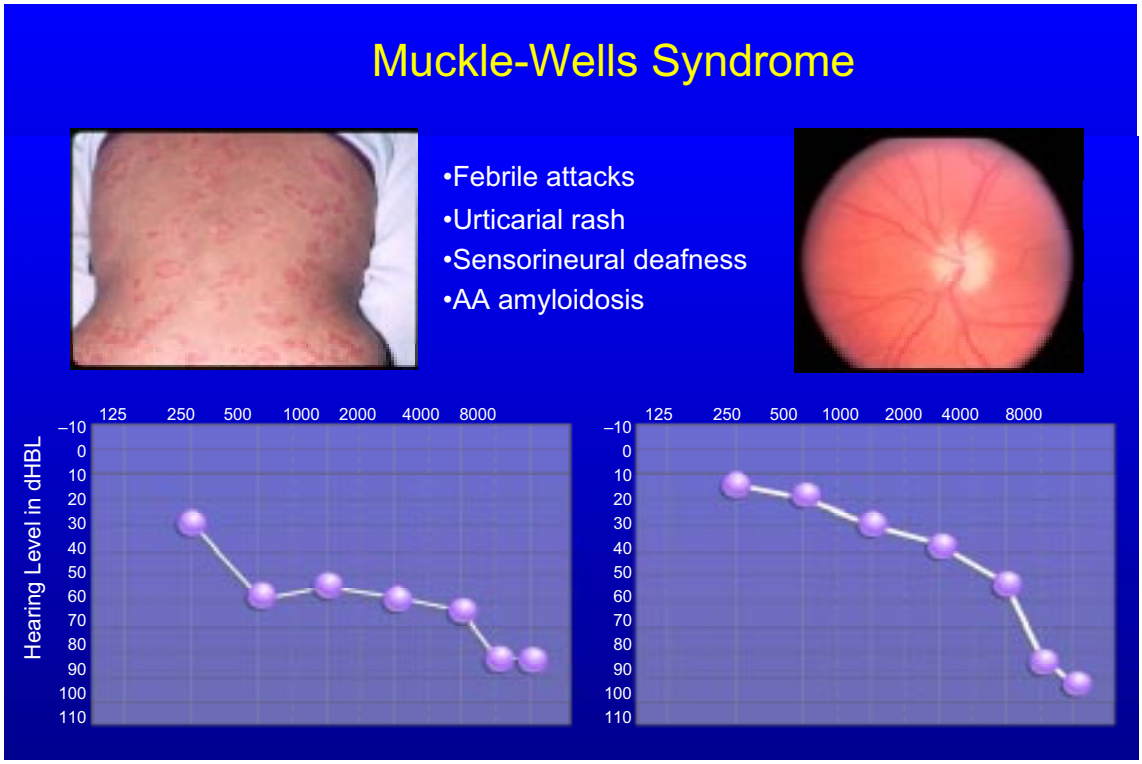

The N-Terminal Caspase-1 Cleavage Fragment of Pyrin Activates NF-ρB
NFkB Activation
NFkB Activation (fold)
300
250
200
150
100
50
0
Vector
Pyrin
N-cleav.
C-cleav.
PNBC
NFρB activation (fold)
40
35
30
25
20
15
10
5
0
Vector
WT
PYRIN domain
Ex 1-2
Ex 3-10
Ex 1-3

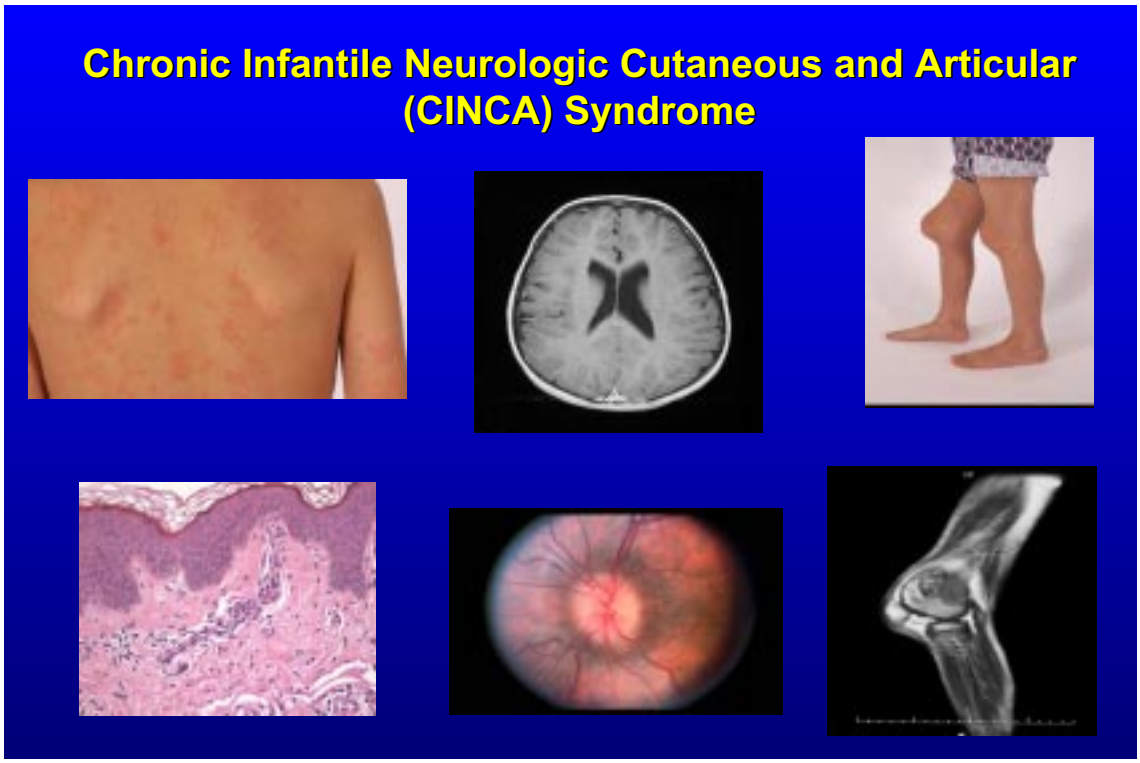


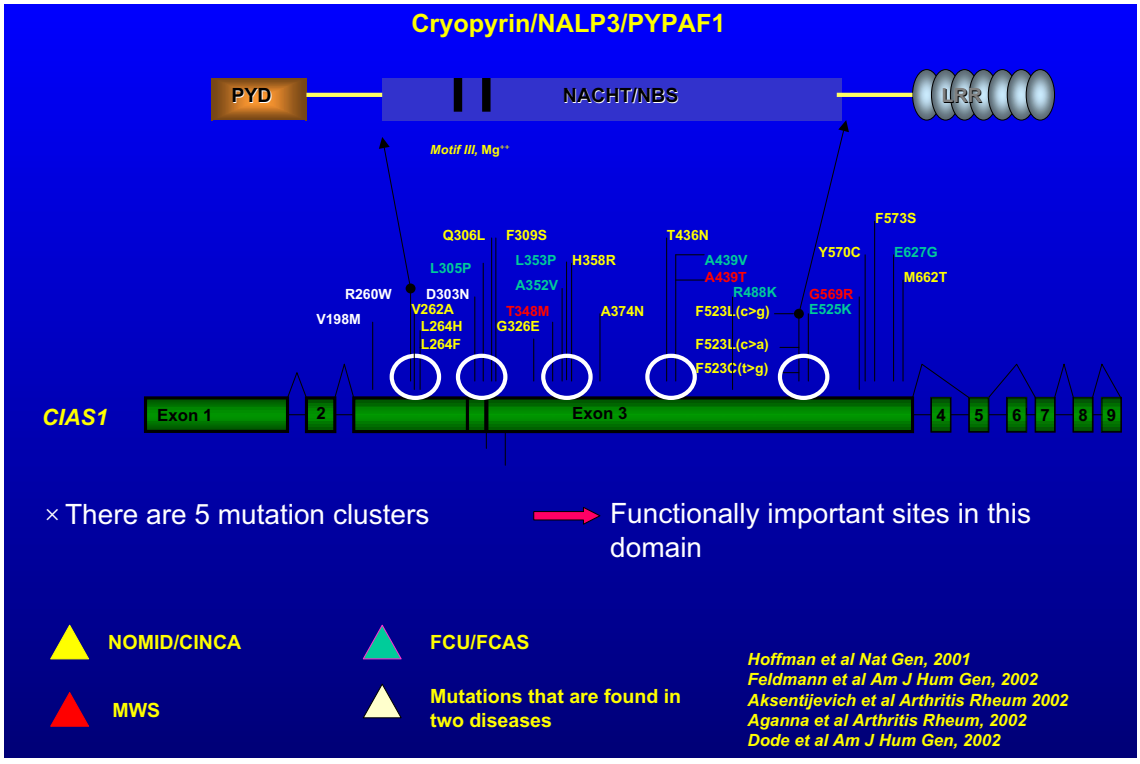
Molecular Pathogenesis of FMF

- Caused by mutations in pyrin/marenostrin
- Pyrin/marenostrin regulates:
  - IL-1η production
  - NF-ρB activation
  - Monocyte apoptosis
- The PYRIN domain defines a family of inflammatory regulators

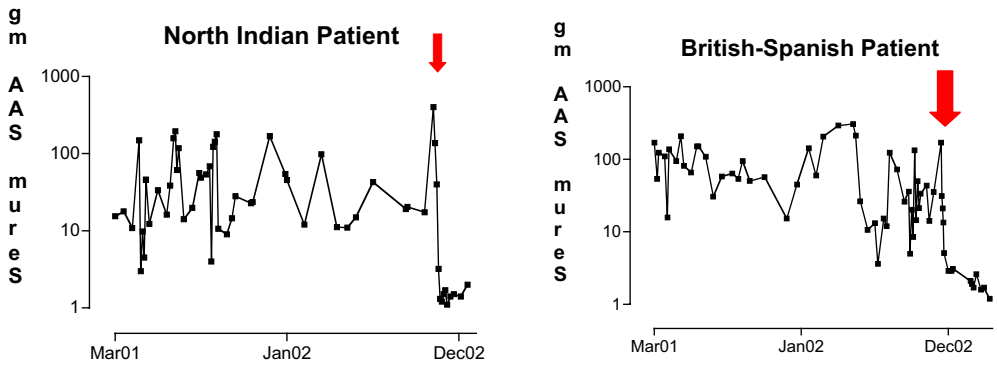

31 32 41 42 43 44
1 q
Mutations in a Gene in the Pyrin Family Cause Three Different Autoinflammatory Syndromes
Monocytes
Granulocytes
T-cells
LRR
C
1034
NBS (NACHT)
PYD
N
1
Cryopyrin/PYPAF1/NALP3
N
PYD
ASC
CARD
C
NF-ρB, IL-1η activation
Rheumatology 3rd edn, 1717, 2003


Muckle-Wells Syndrome
•Febrile attacks
•Urticarial rash
•Sensorineural deafness
•AA amyloidosis
Hearing Level in dHBL
125 250 500 1000 2000 4000 8000
–10 0 10 20 30 40 50 60 70 80 90 100 110
125 250 500 1000 2000 4000 8000
–10 0 10 20 30 40 50 60 70 80 90 100 110


Chronic Infantile Neurologic Cutaneous and Articular (CINCA) Syndrome

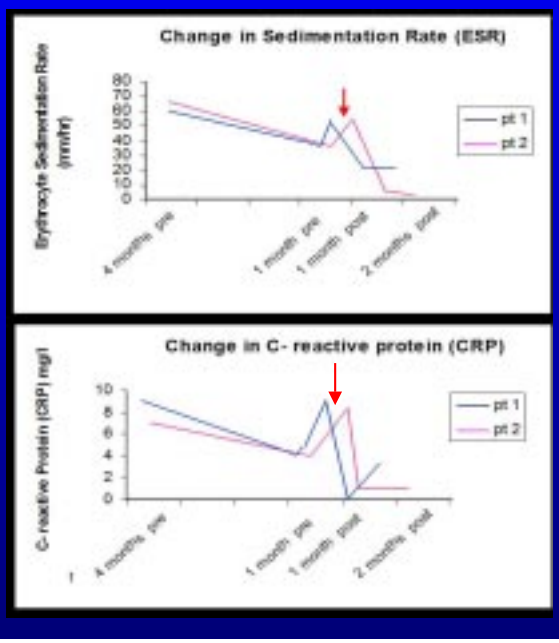

Cryopyrin/NALP3/PYPAF1
PYD
NACHT/NBS
LRR
Motif III, Mg++
Q306L
F309S
T436N
F573S
L305P
L353P
H358R
A439V
Y570C
E627G
A352V
A439T
M662T
R260W
D303N
R488K
G569R
V198M
V262A
T348M
A374N
F523L(c>g)
E525K
L264H
G326E
L264F
F523L(c>a)
F523C(t>g)
CIAS1
Exon 1
2
Exon 3
4
5
6
7
8
9
× There are 5 mutation clusters
Functionally important sites in this domain
NOMID/CINCA
FCU/FCAS
MWS
Mutations that are found in two diseases
Hoffman et al Nat Gen, 2001
Feldmann et al Am J Hum Gen, 2002
Aksentijevich et al Arthritis Rheum 2002
Aganna et al Arthritis Rheum, 2002
Dode et al Am J Hum Gen, 2002

Interleukin-1 Receptor Antagonist in Two Patients with R260W *CIAS1* Mutations



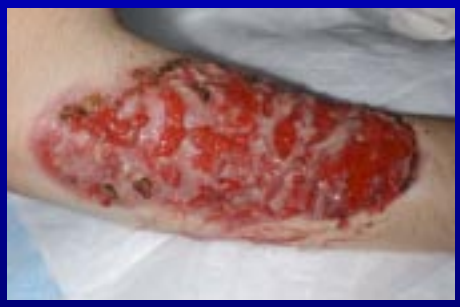
Hawkins et al., NEJM 348:2583, 2003.

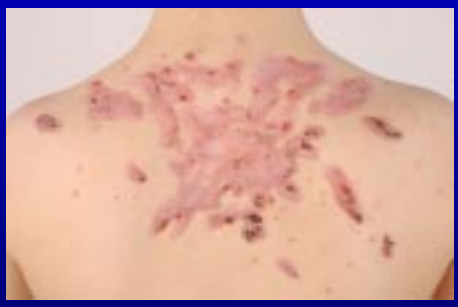
Response to the IL-1 Receptor Antagonist in Two Patients with NOMID/CINCA



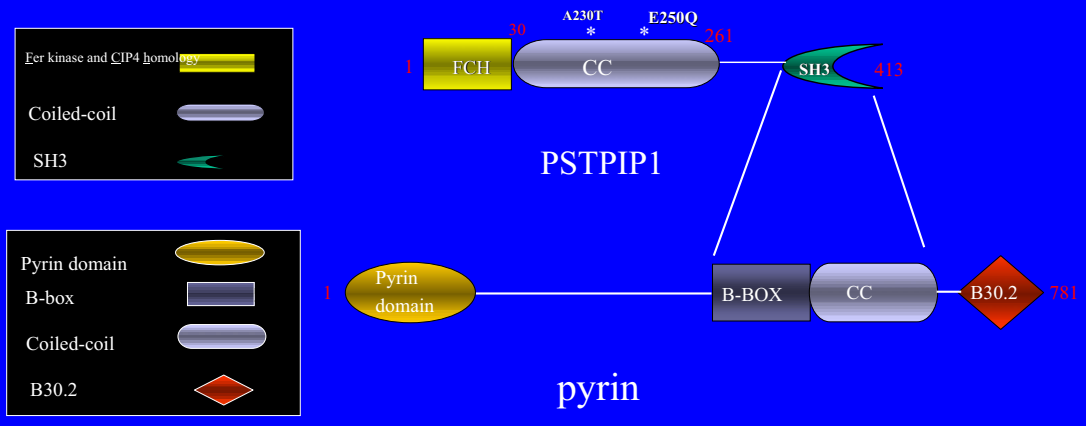
PAPA Syndrome

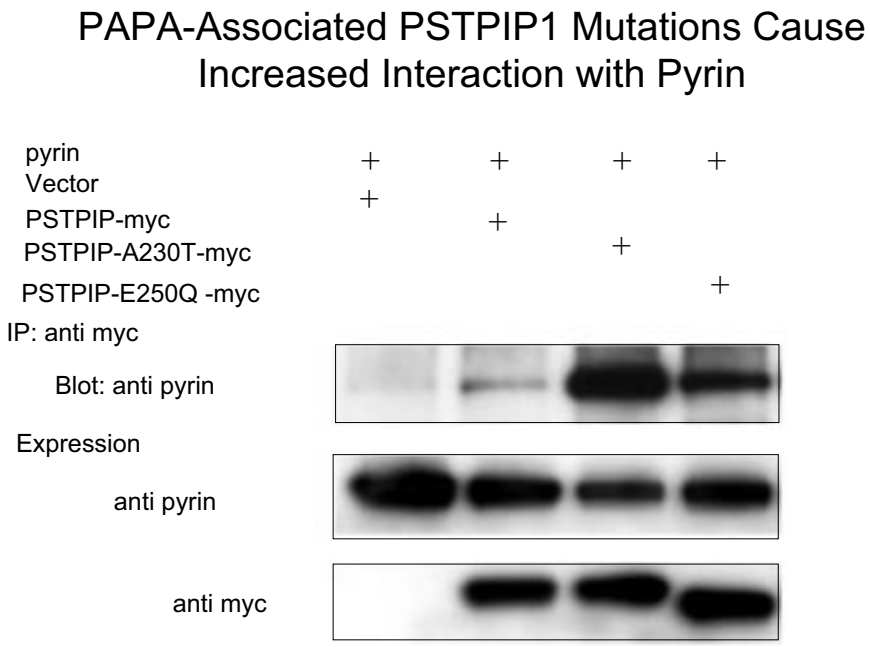
- Pyogenic arthritis
- Pyoderma grangrenosum
- Acne
- Autosomal dominant inheritance
- Caused by mutations in PSTPIP1

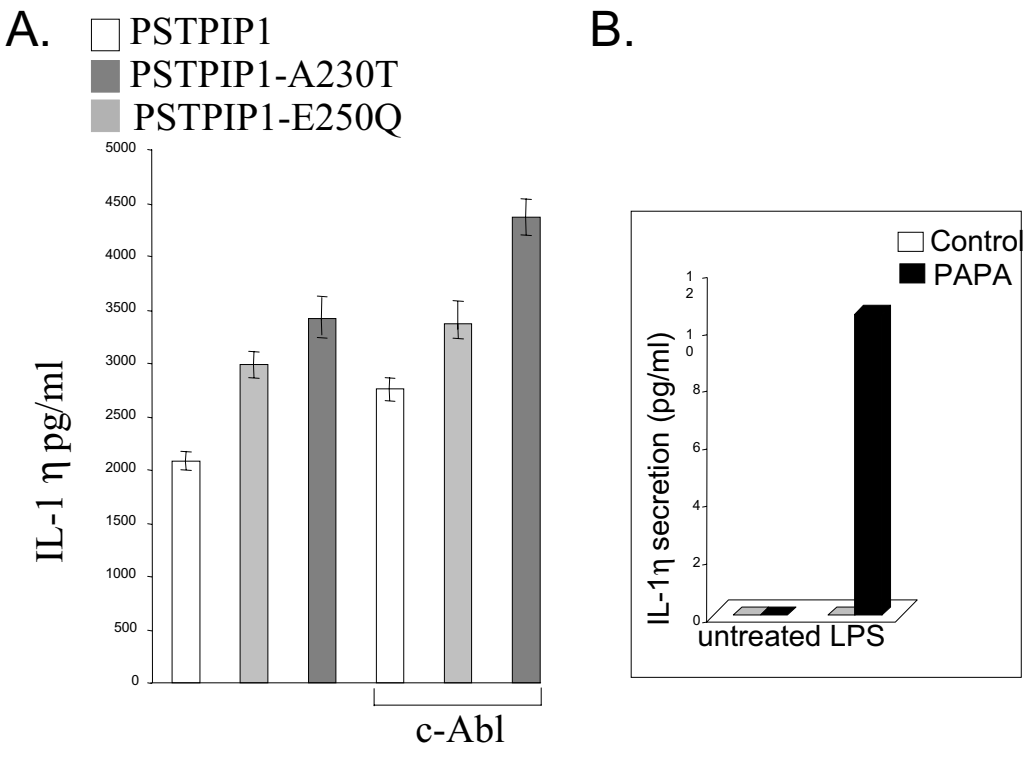




Extending the Pyrin Pathway:
Proline Serine Threonine Phosphatase Interacting Protein 1 (PSTPIP1/CD2BP1)

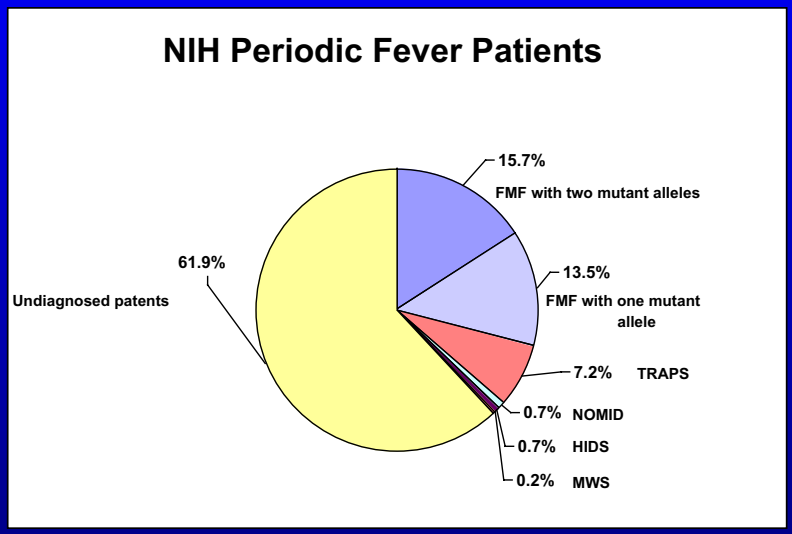



PAPA-Associated PSTPIP1 Mutations Cause Increased Interaction with Pyrin
pyrin
Vector
PSTPIP-myc
PSTPIP-A230T-myc
PSTPIP-E250Q -myc
IP: anti myc
Blot: anti pyrin
Expression
anti pyrin
anti myc


A.
PSTPIP1
PSTPIP1-A230T
PSTPIP1-E250Q
IL-1 η pg/ml
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
c-Abl
B.
Control
PAPA
IL-1η secretion (pg/ml)
untreated LPS

FMF and Family: Lessons on the Control of Inflammation

- Mutations in pyrin/marenostrin and related proteins have been found in FMF, FCAS (FCU), MWS, CINCA/NOMID, and PAPA syndrome
- The N-terminal PYRIN domain defines a new family of proteins involved in inflammation and apoptosis
- The proteins encoded by these genes may prove to be important targets for therapeutic intervention



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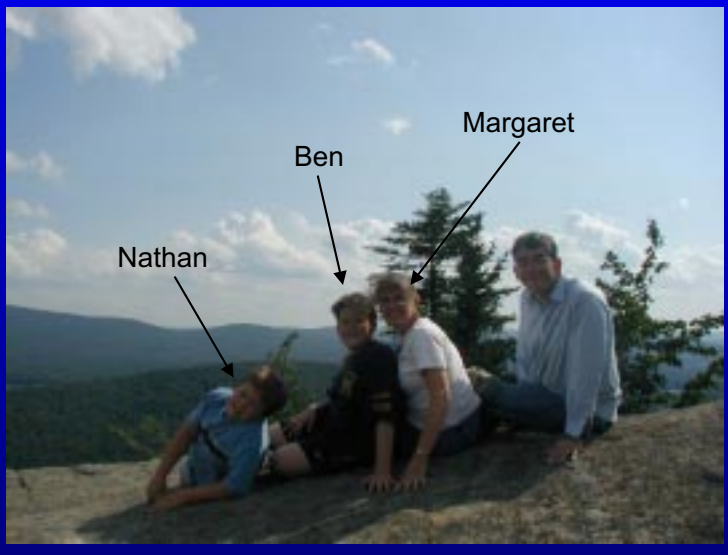
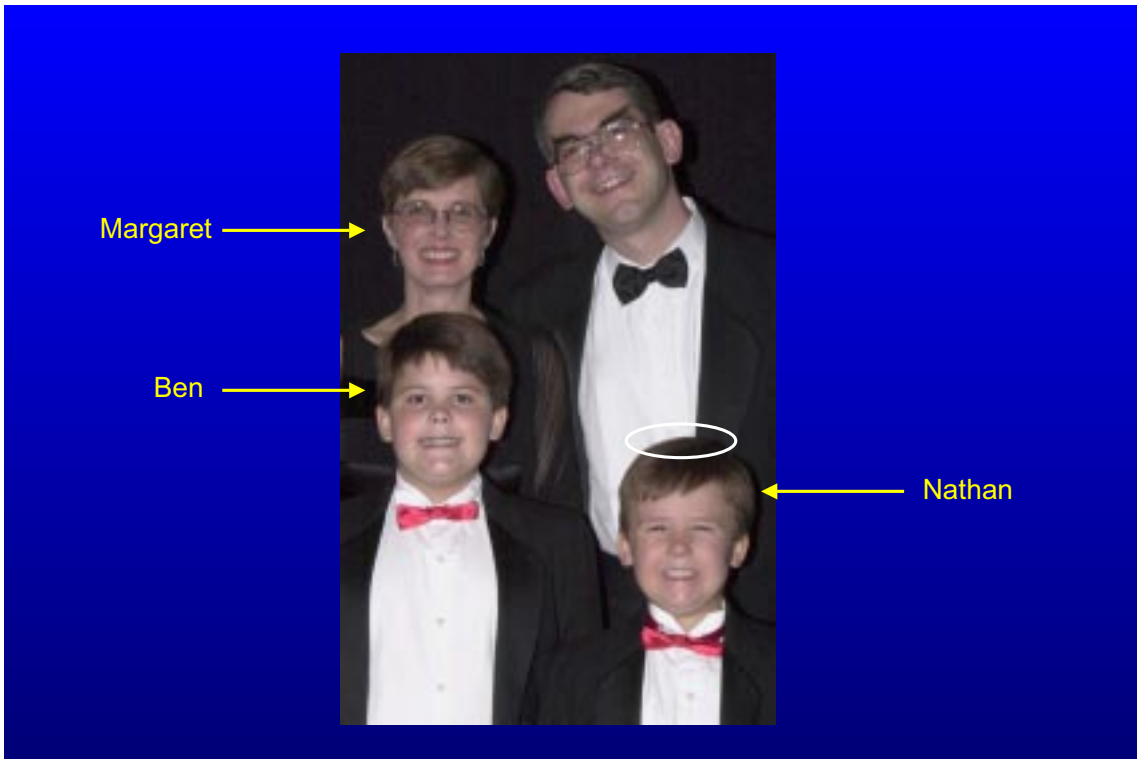
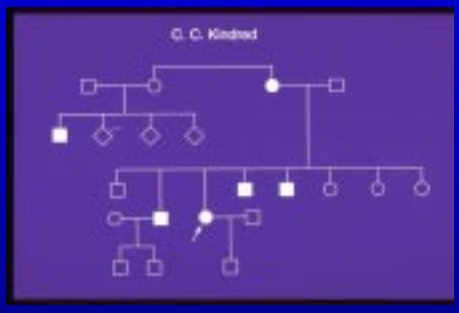




December, 2003: The Hereditary Periodic Fever Genes

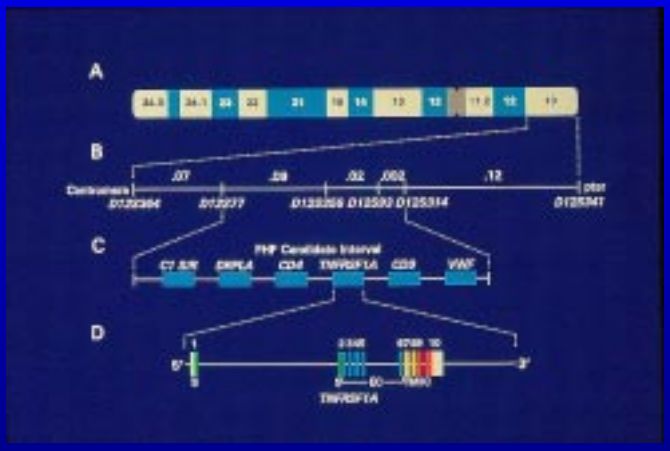
Disease	Gene	Chr	Protein	Known Mutations
FMF	*MEFV*	16 p13.3	pyrin (marenostrin)	41
HIDS	*MVK*	12 q24	mevalonate kinase (MK)	23
TRAPS	*TNFRSF1A*	12 p13	55 kDa TNF receptor	33
MWS/ FCAS/ NOMID	*CIAS1*	1q44	cryopyrin/ PYPAF1/ NALP 3	23

Christina



- 27 y/o Irish woman
- 14 yr hx 3-5 wk febrile episodes
- Periorbital edema, migratory rash, abdominal pain
- Seen 1 wk postpartum
- WBC 29K, ESR 126, CRP 16.3
- Therapeutic response to steroids but not colchicine

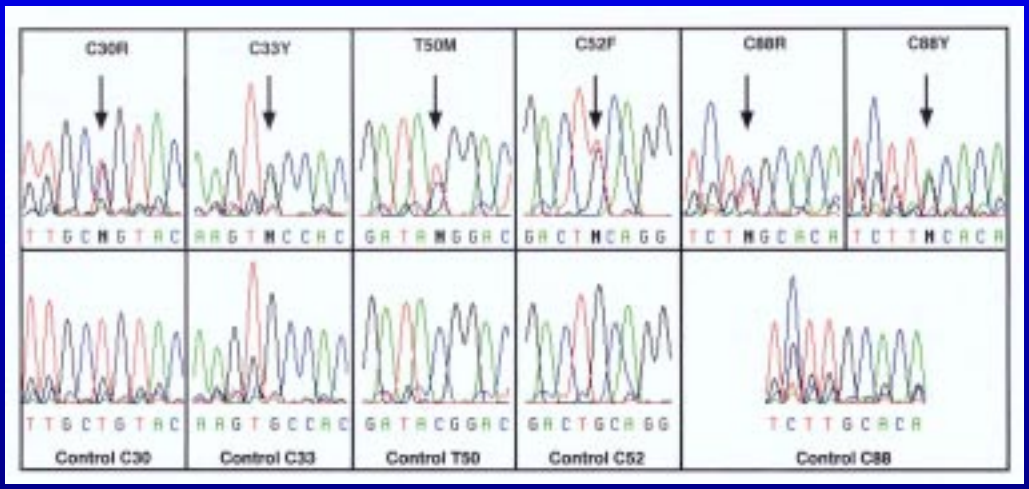
The Gene Causing the Dominant Periodic Fevers is Located on the Short Arm of Chromosome 12



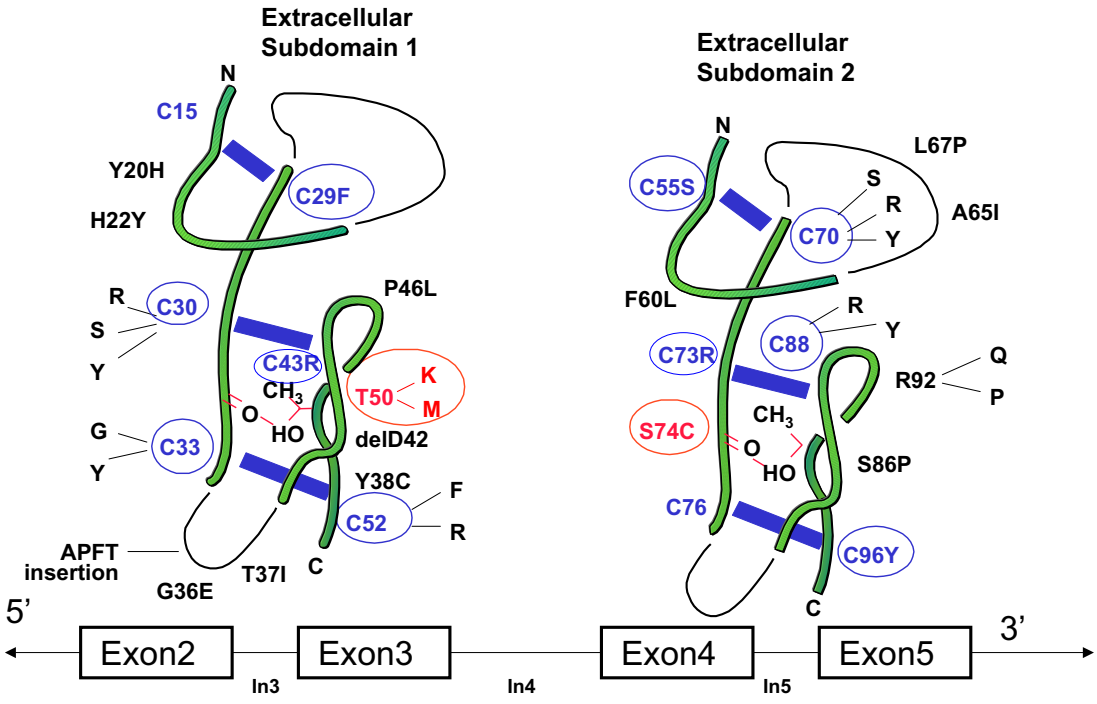
Mike McDermott

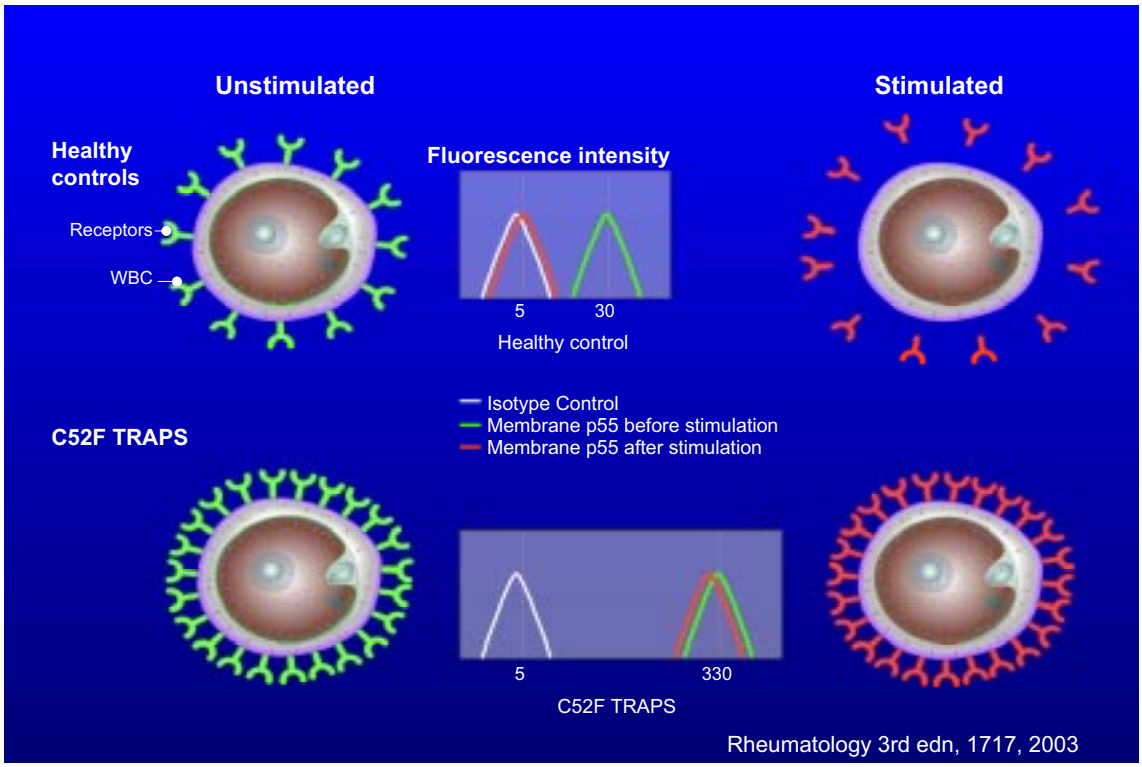
Curr Opin Immunol 12:479, 2000

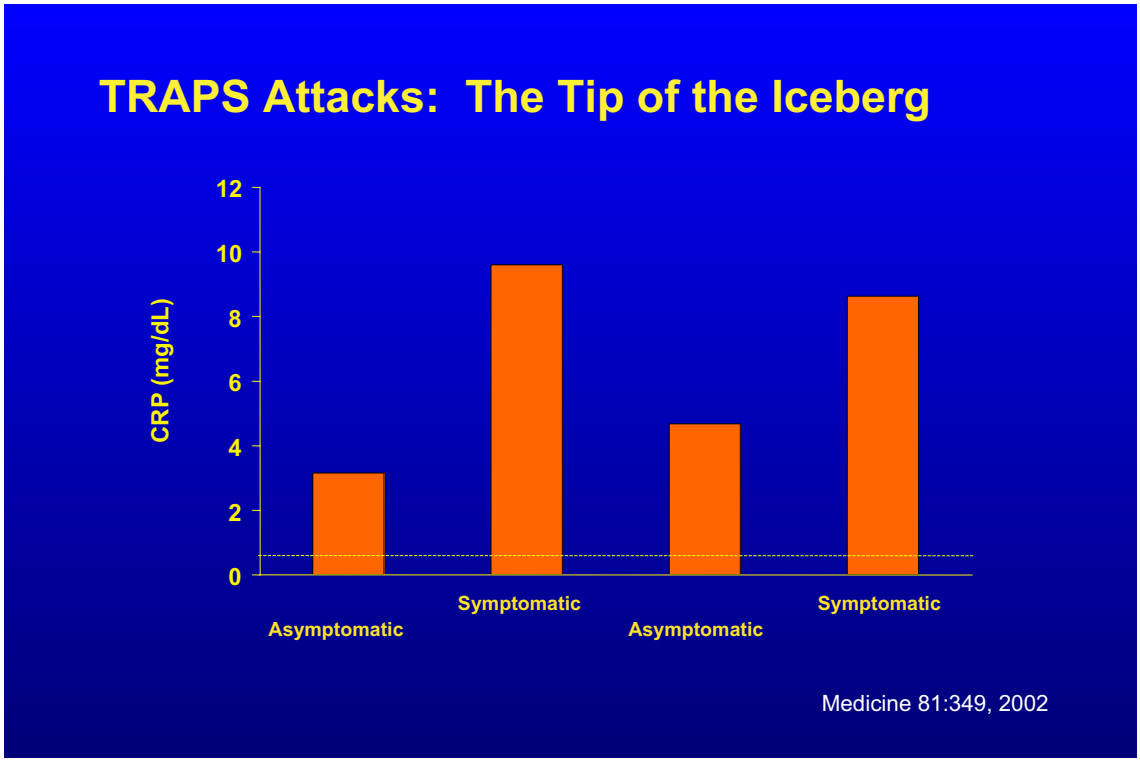
p55 TNF Receptor Mutations in Patients with Dominantly Inherited Periodic Fevers



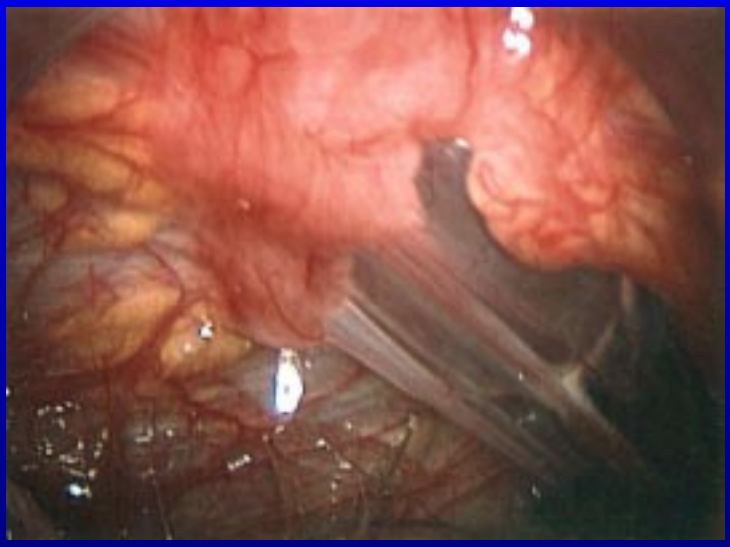
Cell 97:133, 1999



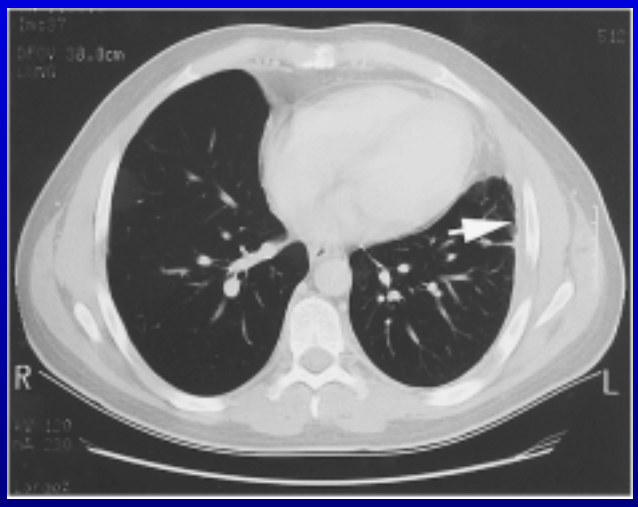

Unstimulated
Stimulated
Healthy controls
Receptors
WBC
Fluorescence intensity
5
30
Healthy control
Isotype Control
Membrane p55 before stimulation
Membrane p55 after stimulation
C52F TRAPS
5
330
C52F TRAPS
Rheumatology 3rd edn, 1717, 2003


TRAPS Attacks: The Tip of the Iceberg
CRP (mg/dL)
12
10
8
6
4
2
0
Asymptomatic
Symptomatic
Asymptomatic
Symptomatic
Medicine 81:349, 2002

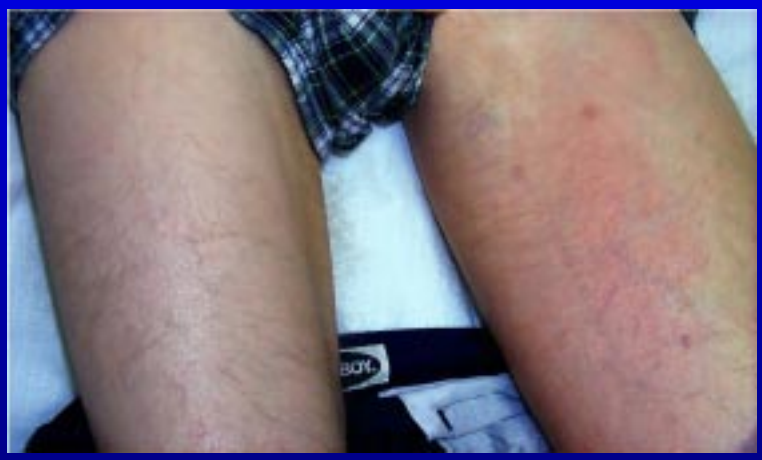
TRAPS: Peritoneal Adhesions



TRAPS: Chronic Pleural Reaction

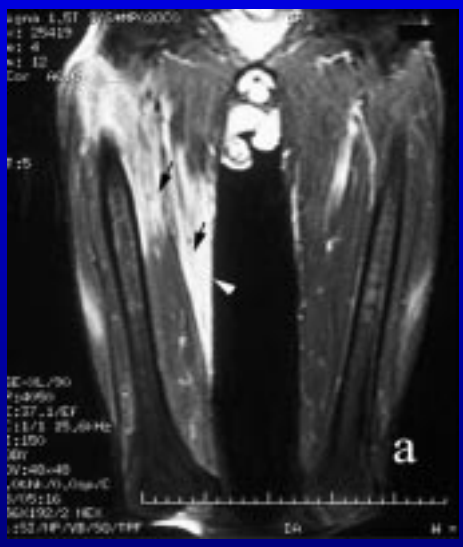


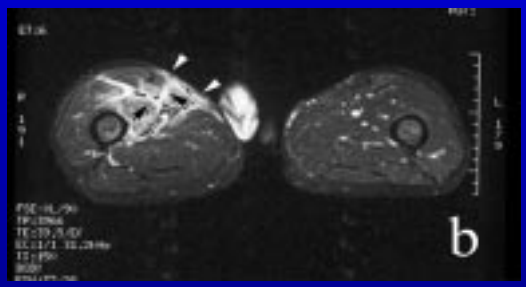
TRAPS: Migratory Rash and Myalgia



Arthritis Rheum 46:2189, 2002

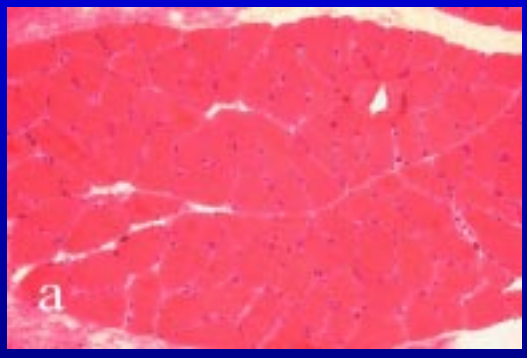
Myalgia in TRAPS

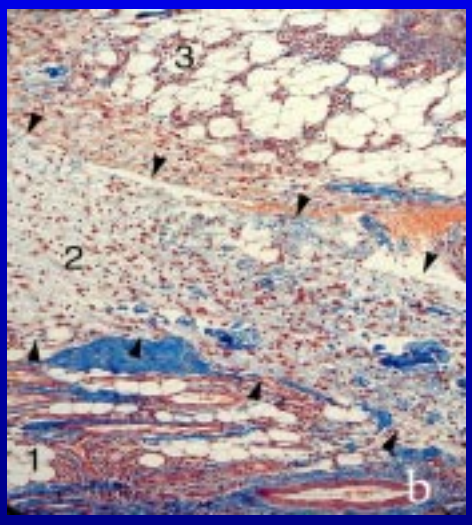




Medicine 81:349, 2002

Monocytic Fasciitis in TRAPS

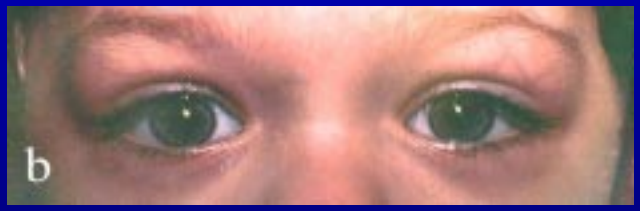




Medicine 81:349, 2002

TRAPS: Ocular Findings

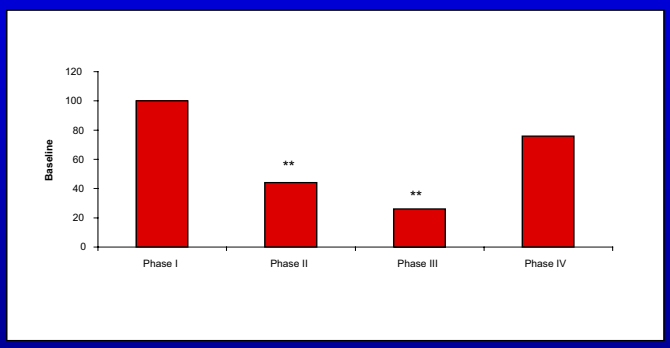
Conjunctivitis



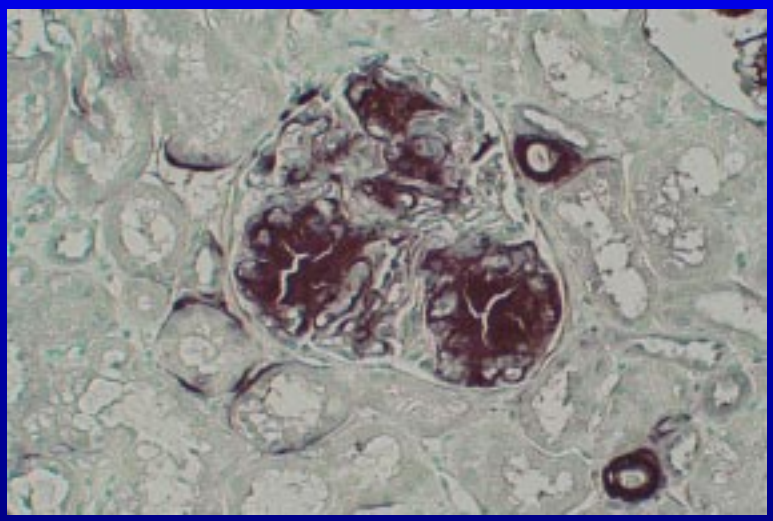
Periorbital edema

Medicine 81:349, 2002

TRAPS-Etanercept Trial



Progression of Amyloidosis on Etanercept Therapy in a Patient with Marked Clinical Improvement without Normalization of SAA Levels

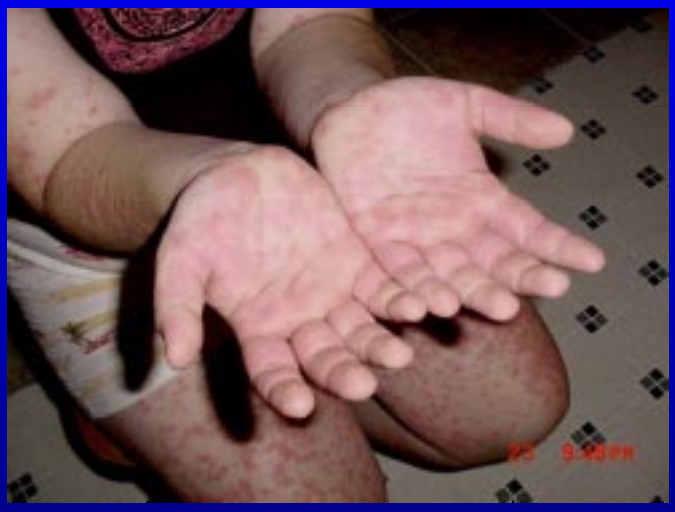


Rheumatology 3rd edn, 1717, 2003

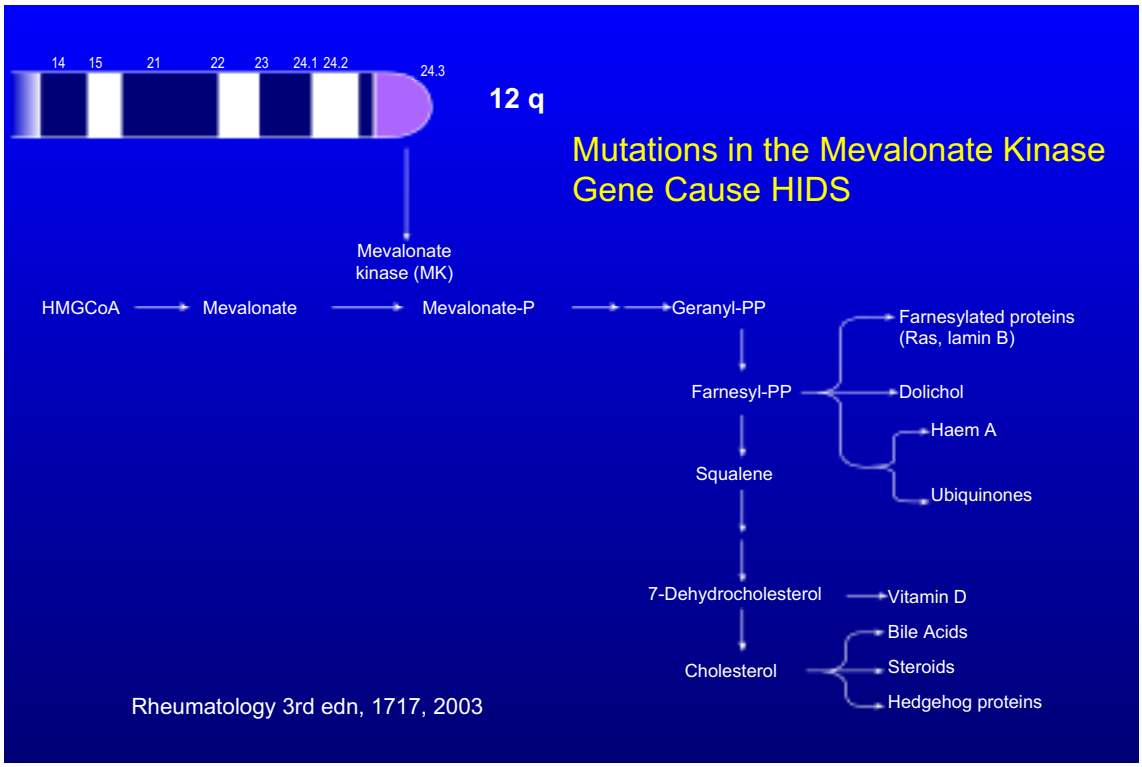
Case 3: Liri

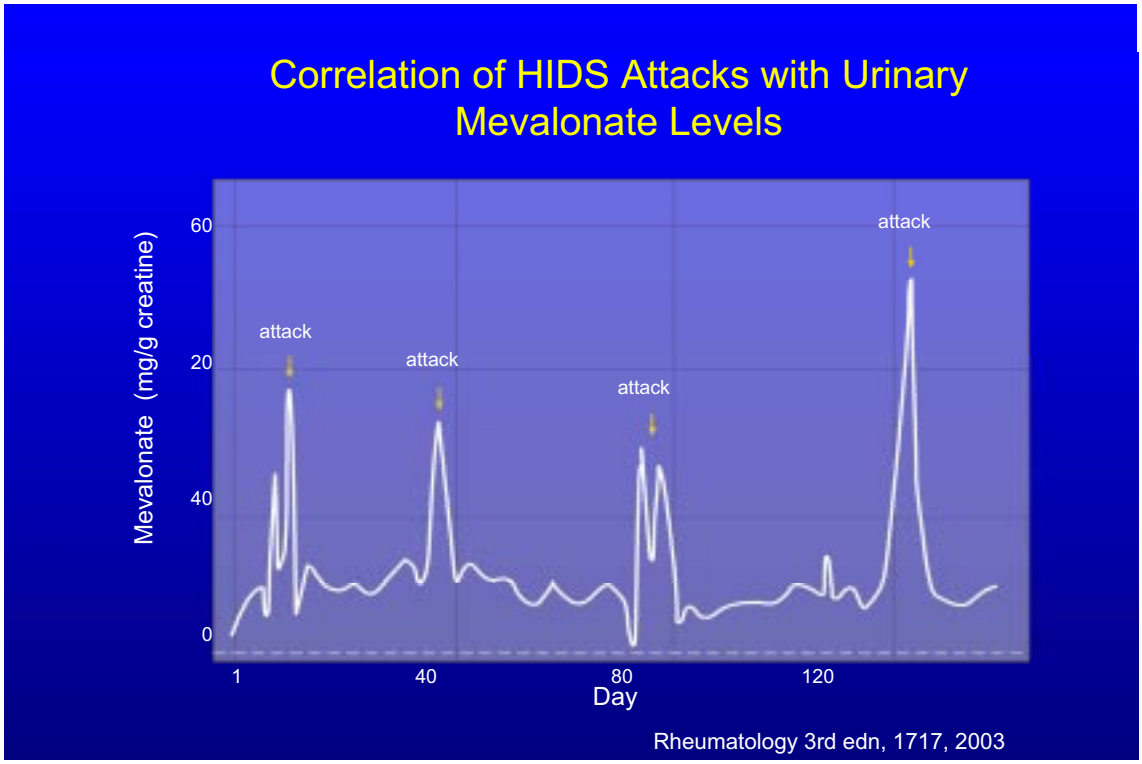
- Irish/Albanian ancestry
- Age 6 wks: 7 day attacks of fever, erythematous maculopapular rash, diarrhea
- Subsequent attacks:
  - Fever
  - Rash
  - Abdominal pain, diarrhea
  - Generalized arthralgia, myalgia
  - Tender, enlarged cervical LN
  - Sometimes oral ulcers
- Last 4 - 10 days, occur q 4 - 6 wks

Liri



Arthritis Rheum 48:2645, 2003


14 15 21 22 23 24.1 24.2 24.3
12 q
Mutations in the Mevalonate Kinase Gene Cause HIDS
Mevalonate kinase (MK)
HMGCoA
Mevalonate
Mevalonate-P
Geranyl-PP
Farnesylated proteins (Ras, lamin B)
Farnesyl-PP
Dolichol
Haem A
Squalene
Ubiquinones
7-Dehydrocholesterol
Vitamin D
Bile Acids
Cholesterol
Steroids
Hedgehog proteins
Rheumatology 3rd edn, 1717, 2003


Correlation of HIDS Attacks with Urinary Mevalonate Levels
Mevalonate (mg/g creatine)
60
20
40
0
attack
attack
attack
attack
1
40
80
120
Day
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Diagnosing HIDS

- "Classic HIDS"---elevated IgD, increased urinary mevalonate, *MVK* mutations
- "Variant HIDS"---increased IgD with normal urinary mevalonate, no *MVK* mutations
- Rarely---increased urinary mevalonate, *MVK* mutations with normal IgD
- If clinical suspicion is high, order serum IgD and either *MVK* genetic testing (V377I) or urinary mevalonate