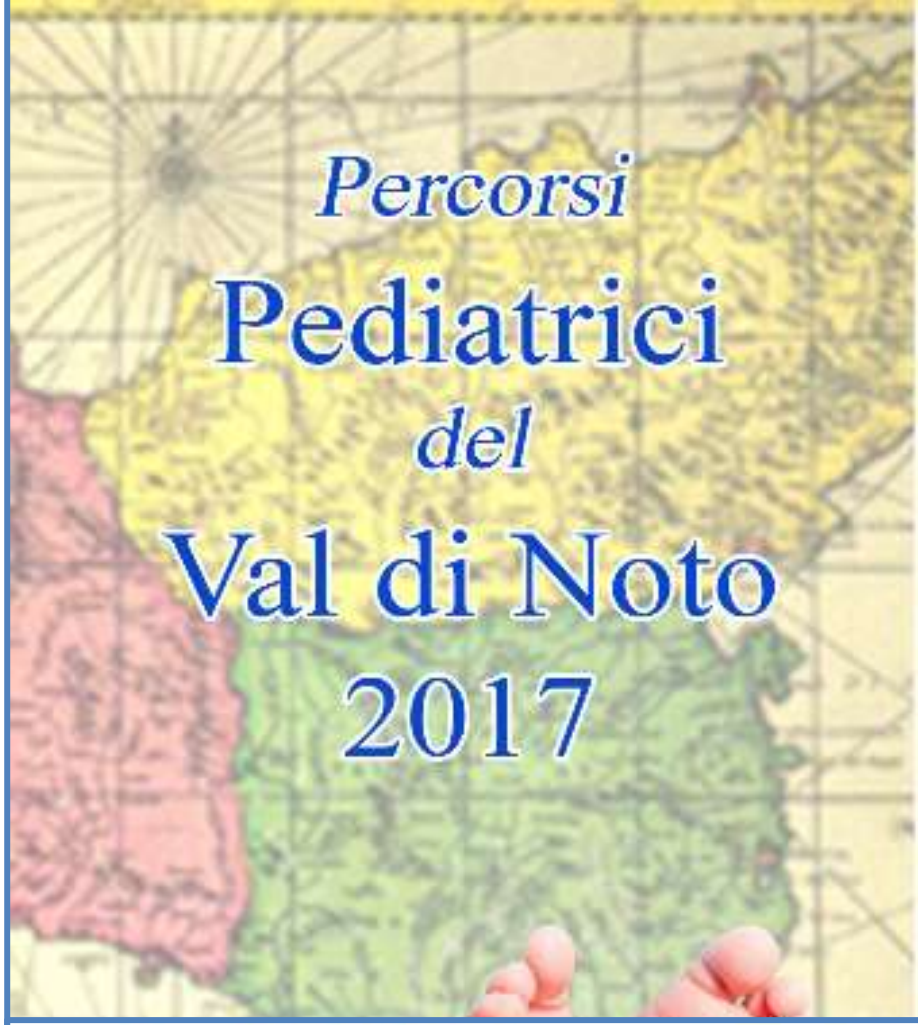
Università degli studi di Messina
AOU Policlinico Universitario G. Martino
Scuola di Specializzazione in Genetica Medica
U.O. C. di Genetica ed Immunologia Pediatrica
Centro di Riferimento Regionale per la Prevenzione, Diagnosi e Cura delle Malattie Genetiche
Direttore Prof. Carmelo Salpietro

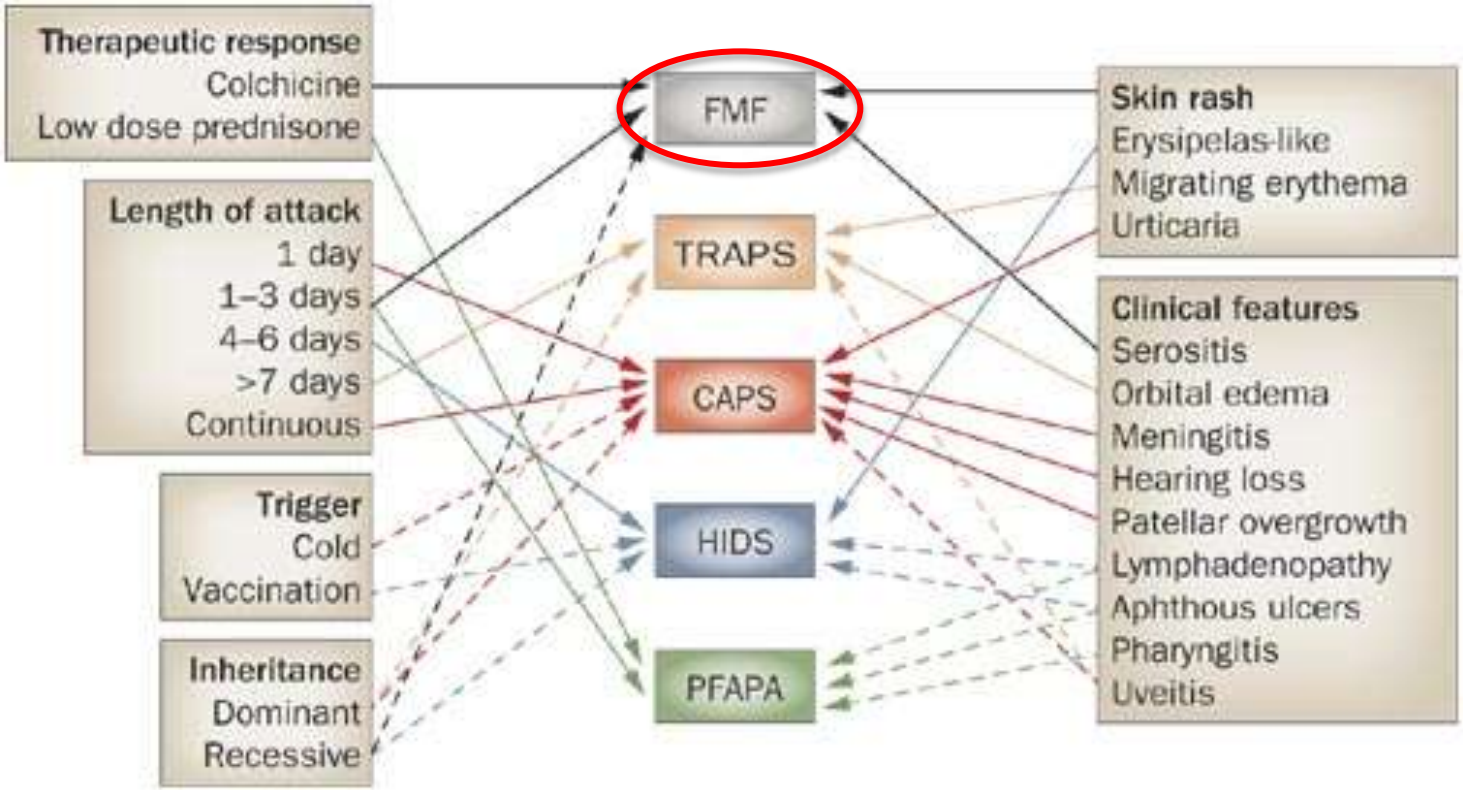
Febbre Mediterranea Familiare



10.02.2017

Sara Manti

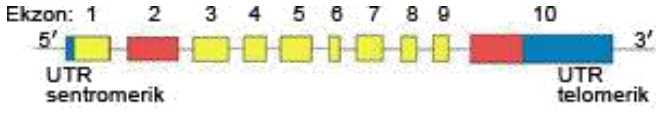
DIAGNOSTIC FEATURES AND DIFFERENTIAL DIAGNOSIS OF RECURRENT FEBRILE SYNDROMES



Hoffman HM and Simon A (2009) Recurrent febrile syndromes—what a rheumatologist needs to know

nature REVIEWS RHEUMATOLOGY

Febbre Mediterranea Familiare (FMF)

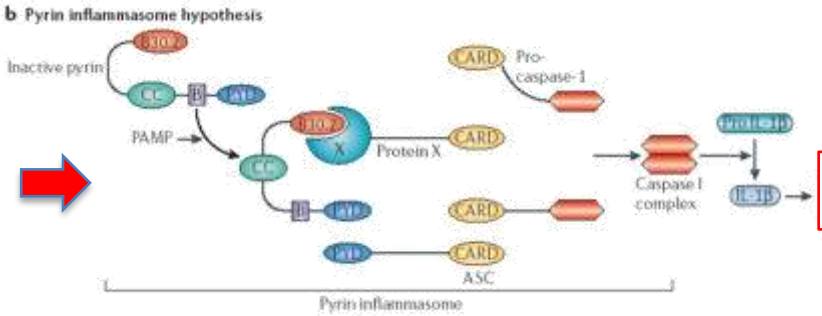


R42W	T267I	P369S	F479L	I591T	R761H	S675N
	E230K	R408Q			V726A	R653H
	E148Q				V704I	G678E
	E148V				M694V	E656A
	L110P				M694del	A744S
					I692del	M694I
					T681I	
					M680I (G/C)	
					M680I (G/A)	
					M680L	
					K695R	

AR

MEFV
pirina "Marenostrina"

(>100 mutazioni)



Fever
Inflammation

CARATTERISTICHE CLINICHE

25-60% <10aa

64-95% <20aa

Durata 1-3giorni

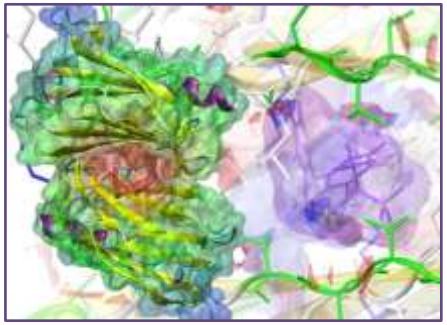
Dolori addominali 95%

Dolore toracico 33-53%

Oligoartrite e/o monoartrite asimmetrica

Eritema erisipela-like delle estremità degli arti inferiori

Mialgie, splenomegalia, cefalea (15%)



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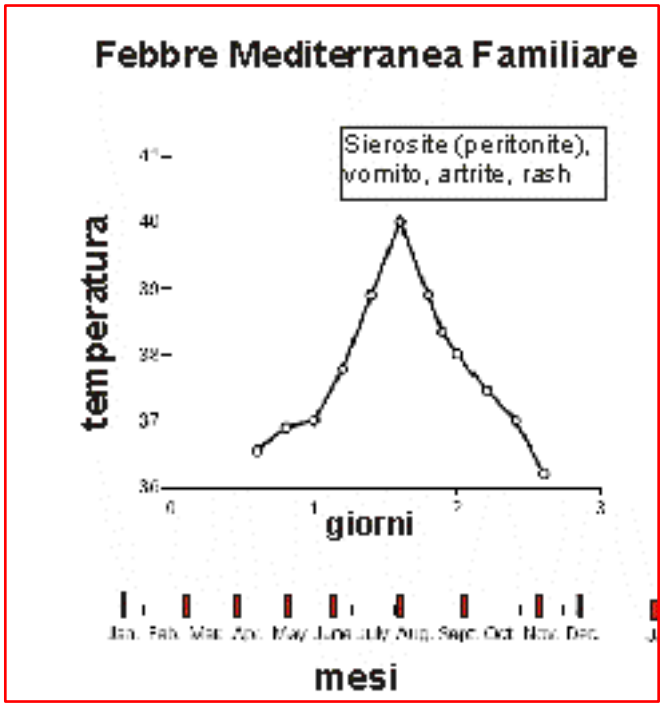
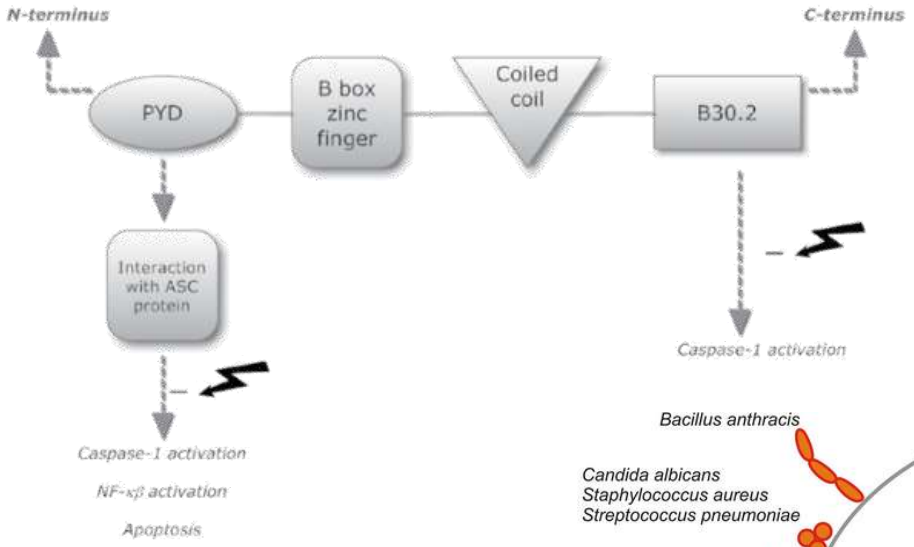
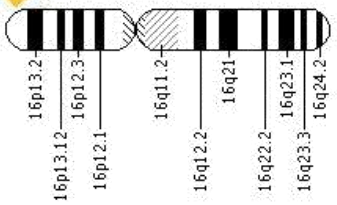
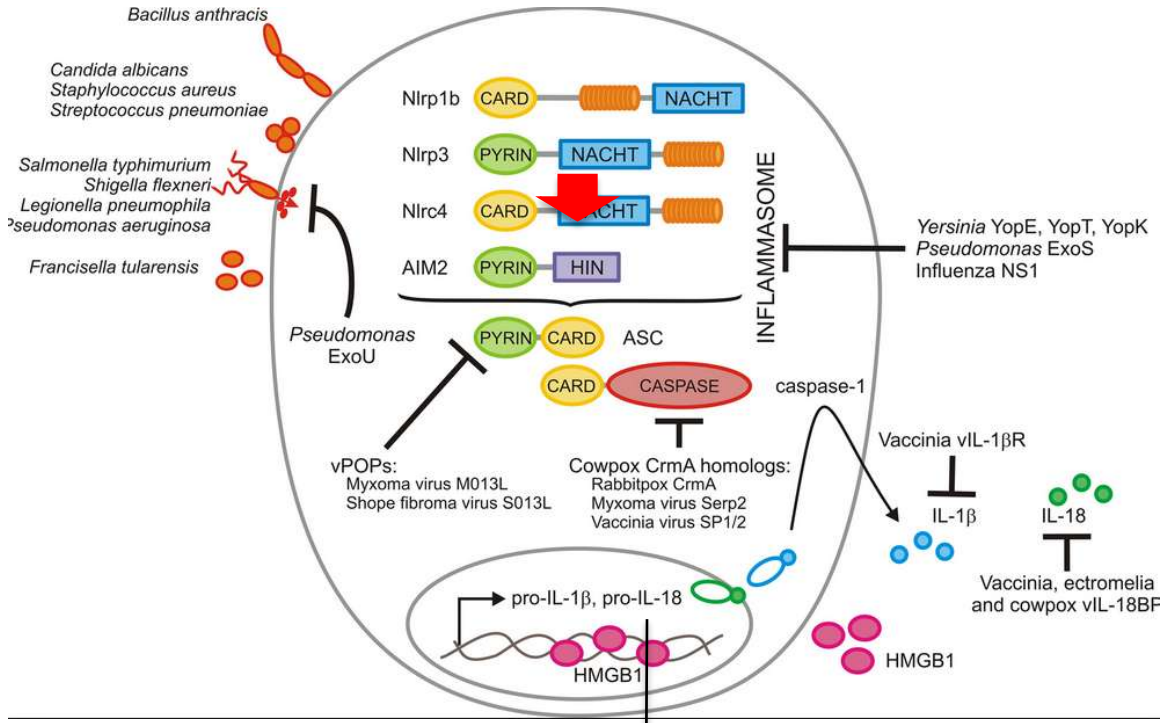
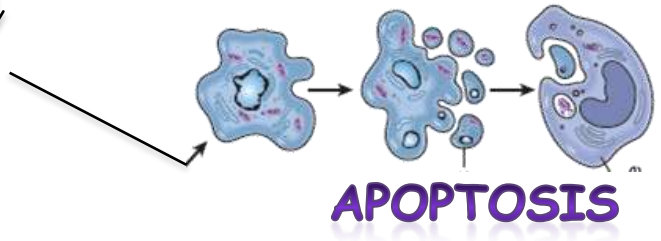


Inflammasome Activators: genes and immunological protagonists









Eu J Immunl

FAMILIAL MEDITERRANEAN FEVER IN THE WORLD

- Circle size is proportional to the size of the FMF community in that country.
- Arrows show the possible ways of spreading the disease.
- Red arrows show the migration of the MEFV mutations in the ancient world
- The yellow arrow corresponds to the Silk Road
- Black arrows denote the migration of the disease in the new world

- Turkey: 1:150-1:10,000.
- Armenia: 1:500
- Sephardic Jews: 1:250-1:1000
- Ashkenazi Jews: 1:73,000
- Arabs: ?
- Brazil: 102 cases
- Middle East and Eastern Europe: 2:1,000,000
- Japan: 170 cases

FMF in Italy: geographical distribution

	Country of origin	Pt (n)	Pt (%)
ITALY	North Italy	8	2.6
	Centre	73	23.5
	South Italy	**164**	**52.7**
	Indef	*24*	*7.7*
	Total	**269**	**86.5**
OTHER COUNTRIES	Armeny	3	0.9
	Israel	10	3.2
	Libya	9	3.0
	Malta	1	0.3
	Morocco	3	0.9
	Syria	3	0.9
	Tunisia	5	1.7
	Others	8	2.6
	Total	**42**	**13.5**
	Total	**311**	**100,0**

Arthritis & Rheumatism (Arthritis Care & Research) Vol. 61, No. 10, October 15, 2009

Clinical and Experimental Rheumatology 2001; 19 (Suppl. 24): S1-S5.

Enigmas in familial Mediterranean fever (FMF)

E. Ben-Chetrit
M. Levy

DEFINIZIONE DI MALATTIA

1. Familial Mediterranean fever (FMF): definition and diagnostic criteria

Familial Mediterranean fever (FMF, OMIM ID: 249100) is an autosomal recessive disease characterized by recurring self-limited short episodes of fever and serositis resulting in pain in the abdomen, chest, joints and muscles; it is the most common of the periodic hereditary fevers.

OMIM Online Mendelian Inheritance in Man — Johns Hopkins University

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance (in progress)
16p13.3	Familial Mediterranean fever, AD	134610	AD
	Familial Mediterranean fever, AR	249100	AR

The presence of two mutations leading to a homozygous state is found in 60% of subjects, and in 10% a mutation was not identified3 (B). However, 30% of patients with a typical clinical presentation of FMF show only a single mutation.

Changing Concepts in Familial Mediterranean Fever: Is It Possible to Have an Autosomal-Recessive Disease With Only One Mutation?

ARTHRITIS & RHEUMATISM, Vol. 60, No. 6, June 2009, pp 1575–1577

A HETEROZYGOTE IS EXPECTED TO BE A CARRIER AND LACK THE CLINICAL PHENOTYPE

- TO HAVE HIGHER LEVELS OF ACUTE-PHASE REACTANTS
- A TENDENCY TO DEVELOP EXCESSIVE FEBRILE EPISODES
- MORE RHEUMATIC DISEASES THAN THE HEALTHY POPULATION

Enhanced innate immune response in the presence of even 1 MEFV mutation

The presence of less common mutations that are missed by routine techniques

Another approach to the investigation of a possible mutation on the second allele is to perform haplotype analysis

unidentified mutation

Digenic inheritance refers to the interaction of 2 genes resulting in the expression of a phenotype

FMF patients with only 1 MEFV mutation may produce a disease phenotype if there is a mutation in a gene for other autoinflammatory diseases or a gene that acts in concert

Other autoinflammatory diseases have to be carefully excluded in these patients (HIDS),(TRAPS), (CAPS)

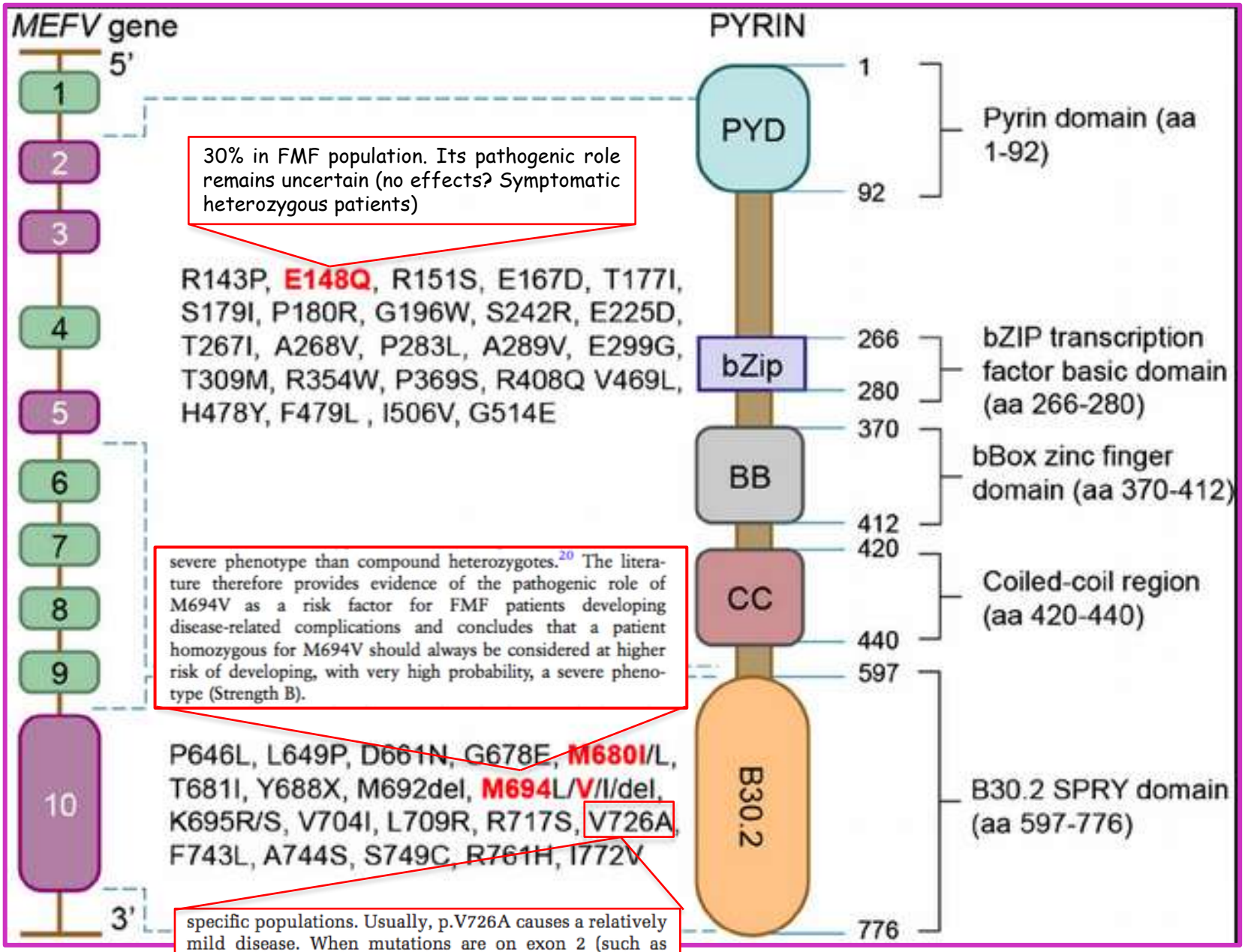
Epigenetics
changes in gene expression that are stable between cell divisions, but do not involve changes in the underlying DNA sequence.
These mechanisms may silence the normal, functional allele

OUR EXPERIENCE

Mutations	Genotypes	Patients N	Patients %
Heterozygous	Met694Val/wt Glu148Gln/wt Met680Ile/wt Ala744Ser/wt Pro369Ser/wt Met694Ile/wt	32	84.21
Compound Heterozygous	Met694Val/Met680Ile Glu148Gln/ Met680Ile	3	7.89
Homozygous	Met680Ile/Met680Ile Arg761His/Arg761His	3	7.89

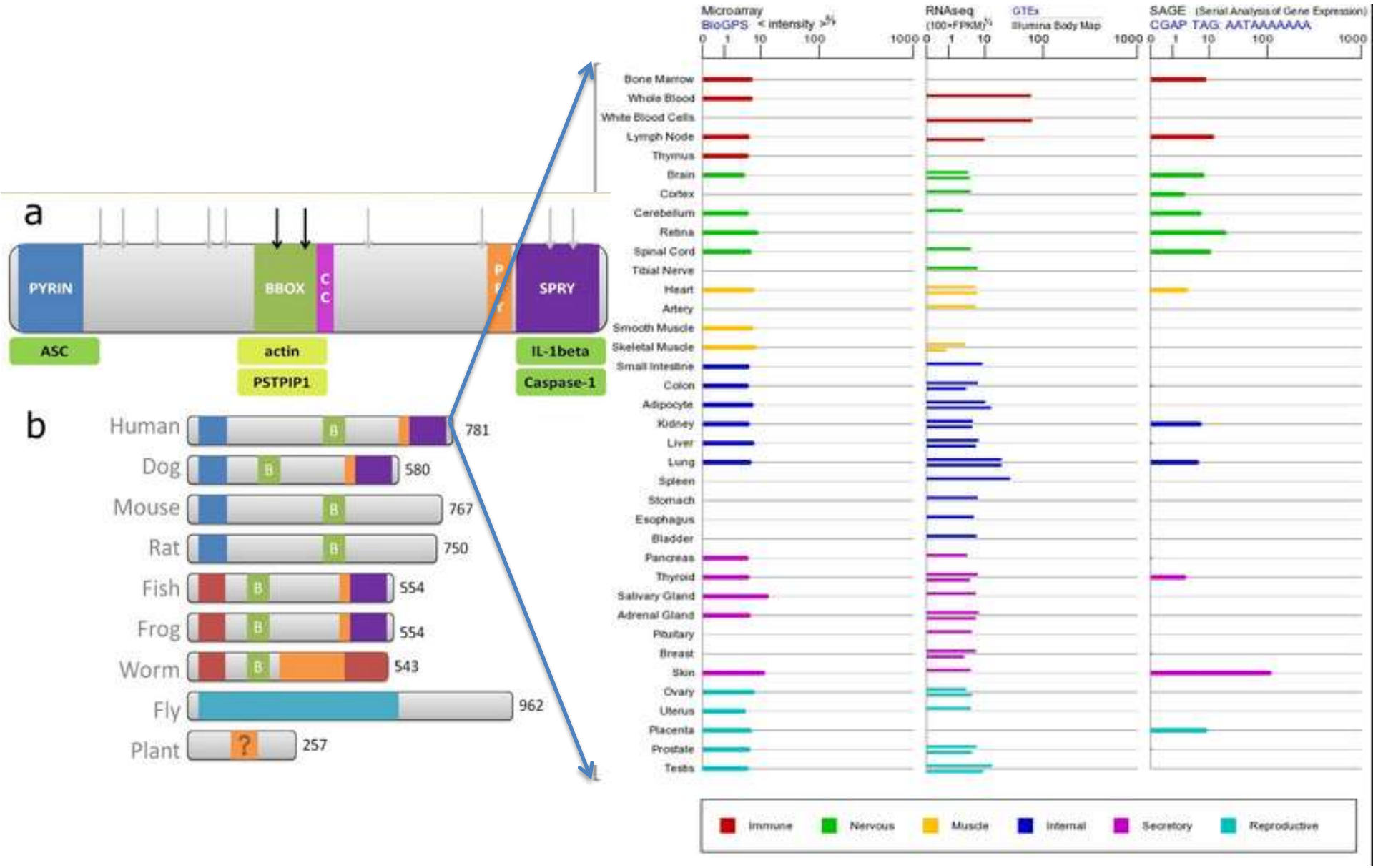
Genotypes	%
p.Met694Val/wt	26.3
p.Glu148Gln/wt	18.4
p.Met680Ile/wt	15.8
p.Val726Ala/wt	10.5
p.Met680Ile/Met680Ile	5.3
p.Met694Val/Met680Ile	5.3
p.Ala744Ser/wt	5.3
p.Glu148Gln/ Met680Ile	3.3
p.Pro369Ser/wt	3.3
p.Met694Ile/wt	3.3
p.Arg761His/wt	3.3
p.Arg761His/Arg761His	3.3

Familial Mediterranean fever: An updated review

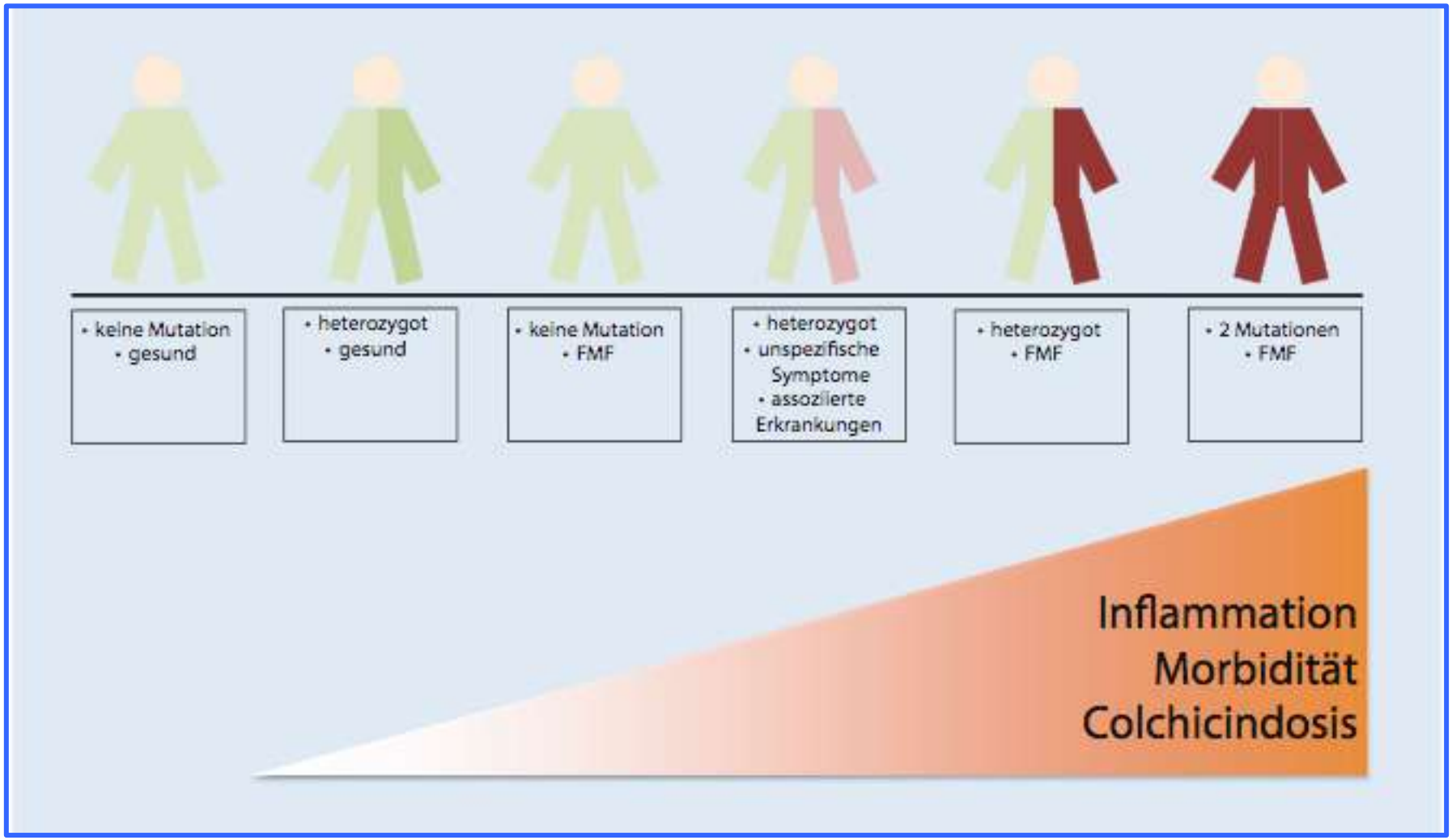


Eur J Rheum 2014; 1: 21-33

MEFV Gene

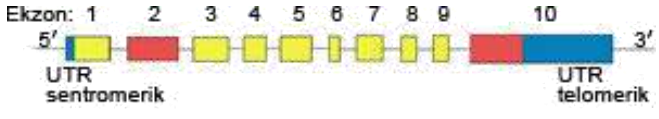

a
PYRIN
BBOX
C C
SPRY
ASC
actin
PSTPIP1
IL-1beta
Caspase-1
b
Human
Dog
Mouse
Rat
Fish
Frog
Worm
Fly
Plant
781
580
767
750
554
554
543
962
257
Microarray
BioGPS
RNAseq
GTEx
Illumina Body Map
SAGE
(Serial Analysis of Gene Expression)
CGAP TAG: AATAAAAAAA
Bone Marrow
Whole Blood
White Blood Cells
Lymph Node
Thymus
Brain
Cortex
Cerebellum
Retina
Spinal Cord
Tibial Nerve
Heart
Artery
Smooth Muscle
Skeletal Muscle
Small Intestine
Colon
Adipocyte
Kidney
Liver
Lung
Spleen
Stomach
Esophagus
Bladder
Pancreas
Thyroid
Salivary Gland
Adrenal Gland
Pituitary
Breast
Skin
Ovary
Uterus
Placenta
Prostate
Testis
Immune
Nervous
Muscle
Internal
Secretory
Reproductive

ROLE OF GENETICS IN FAMILIAL MEDITERRANEAN FEVER



Z Rheumatol. 2017 Feb 2

Febbre Mediterranea Familiare (FMF)



R42W T267I P369S F479L I591T R761H S675N
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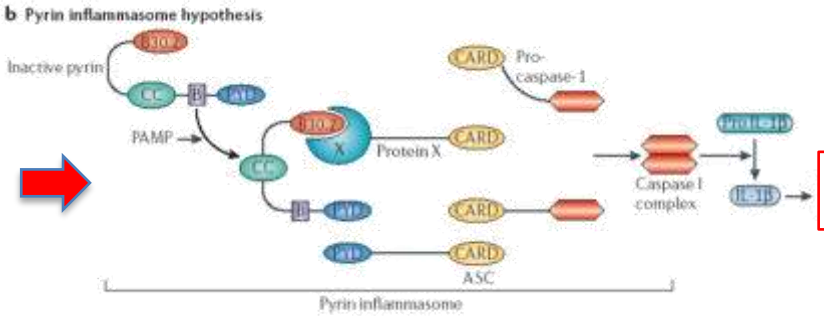

Fever
Inflammation

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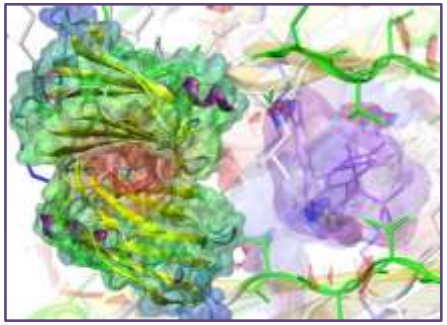

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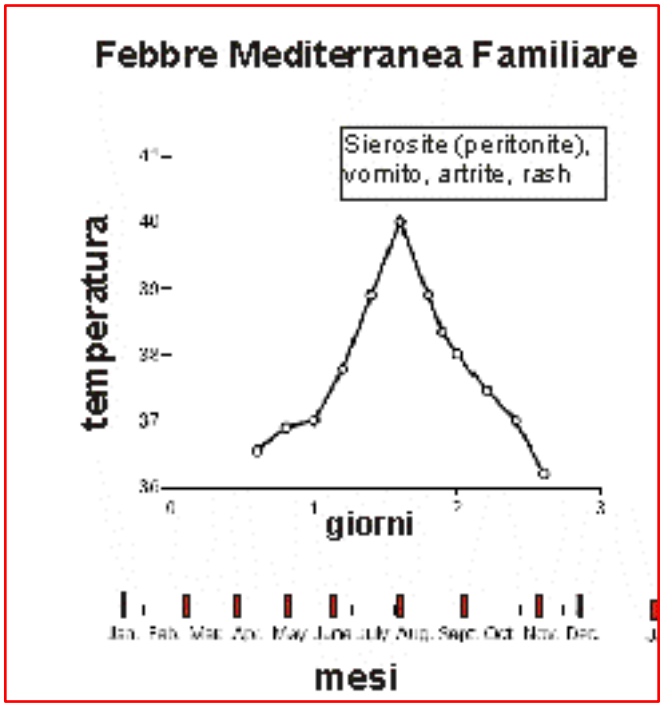
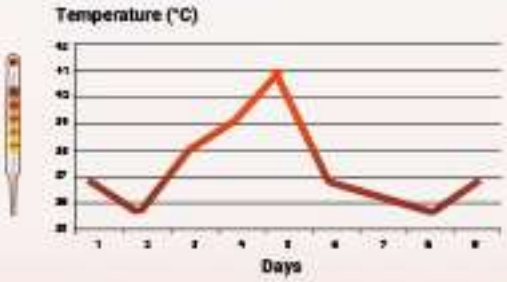


Febbre Mediterranea Familiare (FMF): Phenotypes

PHENOTYPE 1: TYPICAL CLINICAL MANIFESTATIONS

Systemic

Fever: with a typical flare, temperatures above 38°C for 12 to 72 hours



Rash: painful, sharply demarcated, severe skin redness in up to 40% of patients – often in the area of the feet or lower legs

- Secondary amyloidosis is a high-risk issue in 50% of patients
- Some patients have vasculitis-type symptoms
- Some patients have enlarged lymph nodes

Chest cavity

Pain due to an inflammation of the heart sac and/or pleura

Abdominal cavity

Pain due to an inflammation of the lining of the abdomen
Enlarged spleen

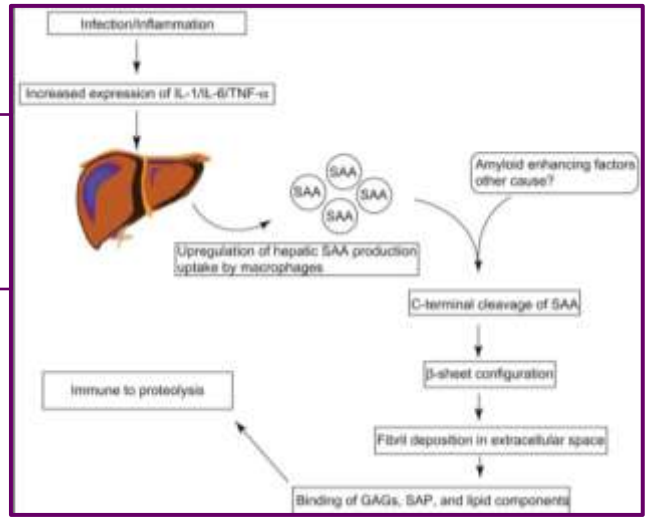
Joints

Inflammation of a joint (monoarthritis), e.g. knee, ankle, wrist

Febbre Mediterranea Familiare (FMF): Fenotipi

PHENOTYPE 2

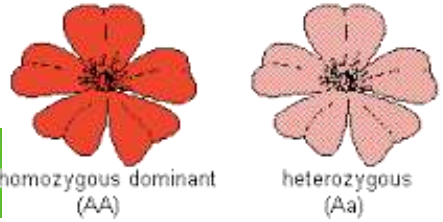
7% to 25%
Usually, the phenotype II is detected in patients receiving a diagnosis of **renal AA amyloidosis** who have relatives with clinically apparent FMF.



PHENOTYPE 3

It is defined as the presence of two MEFV mutations (homozygote or compound heterozygote state) without clinical manifestations of FMF nor of reactive amyloidosis.

asymptomatic



THE 'FMF-LIKE' DISEASE: A NEW PHENOTYPE?

5.7%
heterozygous mutation carriers
episodic arthritis without fever
afebrile abdominal attacks
febrile abdominal attacks in childhood which spontaneously remitted in adult age.

Familial Mediterranean Fever in the World

Arthritis & Rheumatism (Arthritis Care & Research) Vol. 61, No. 10, October 15, 2009

Table 3. Main familial Mediterranean fever manifestations in various countries and populations

	Armenia	Turkey	Israel	Arabs	Italy	Crete	Japan
No. of patients	335	2,838	576	175	71	71	80
Fever, %	94	92	100	100	92	80	98
Peritonitis, %	91	93	96	93	91	76	55
Pleuritis, %	84	31	43	32	52	21	61
Arthritis, %	39	47	70	33	63	38	27
Skin rash, %	15	21	40	3	22	11	10
References	33,52,53	5	54,55	56	14	12	57

OUR EXPERIENCE

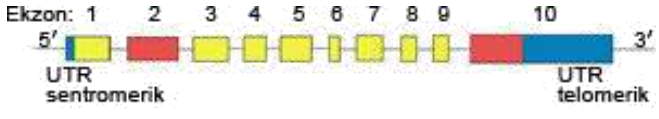
Clinical findings	%
Fever	100
Abdominal Pain	18.4
Joint Pain	5.3
Erysipelas-like erythema	5.3
Leoucocytosis	3.3
Thoracic pain	0

Table 2. The international severity scoring system for familial Mediterranean fever (ISSF)

	Criteria	Points
1	Chronic sequela (including amyloidosis, growth retardation, anemia and splenomegaly)	1
2	Organ dysfunction (nephrotic range proteinuria, FMF related)	1
3	Organ failure (heart, renal and so on, FMF related)	1
4a[a]	Frequency of attacks (average number of attacks between 1 and 2 per month)	1
4b[a]	Frequency of attacks (average number of attacks >2 per month)	2
5	Increased acute-phase reactants (any of C-reactive protein, serum amyloid A, erythrocyte sedimentation rate and fibrinogen) during the attack-free period, ≥2 weeks after the last attack (at least two times 1 month apart)	1
6	Involvement of more than two sites during an individual acute attack (pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia and so on)	1
7	More than two different types of attack during the course of the disease (isolated fever, pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia and so on)	1
8	Duration of attacks (more than 72 h in at least three attacks in 1 year)	1
9	Exertional leg pain (pain following prolonged standings and/or exercising, excluding other causes)	1
	Total score	10

Severe disease ≥6, intermediate disease 3–5 and mild disease ≤2.
[a]Criterion 4a/4b can give 0 or 1 or 2 points altogether according to the definition. ELE, erysipelas-like erythema; FMF, familial Mediterranean fever.
Taken from Demirkaya *et al.* [34▪]

Febbre Mediterranea Familiare (FMF)



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					I692del	M694I
					T681I	
					M680I (G/C)	
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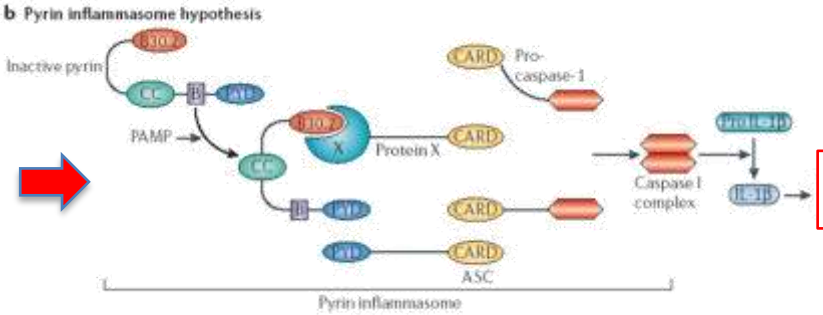

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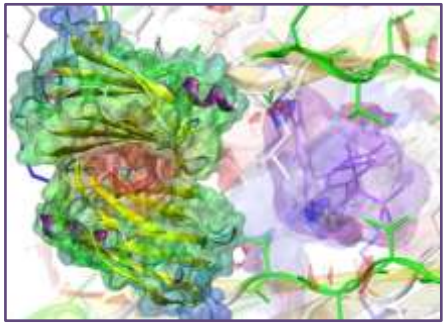

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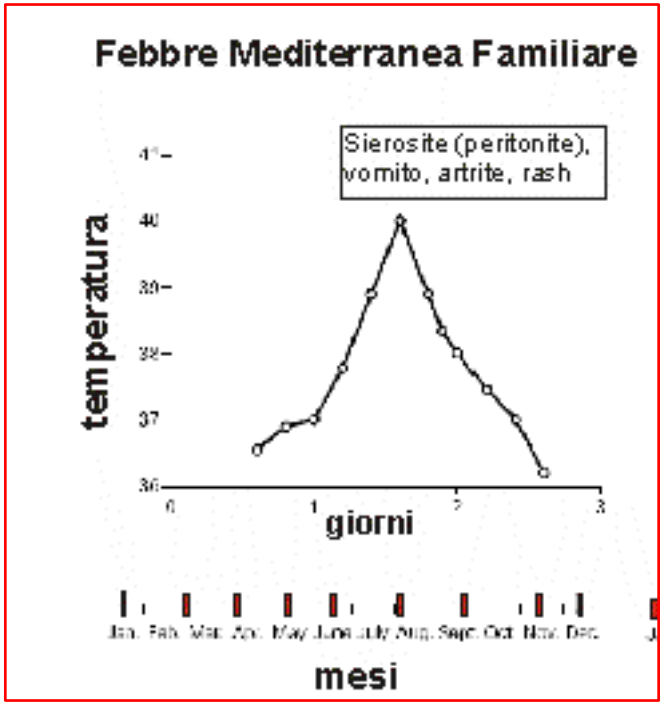
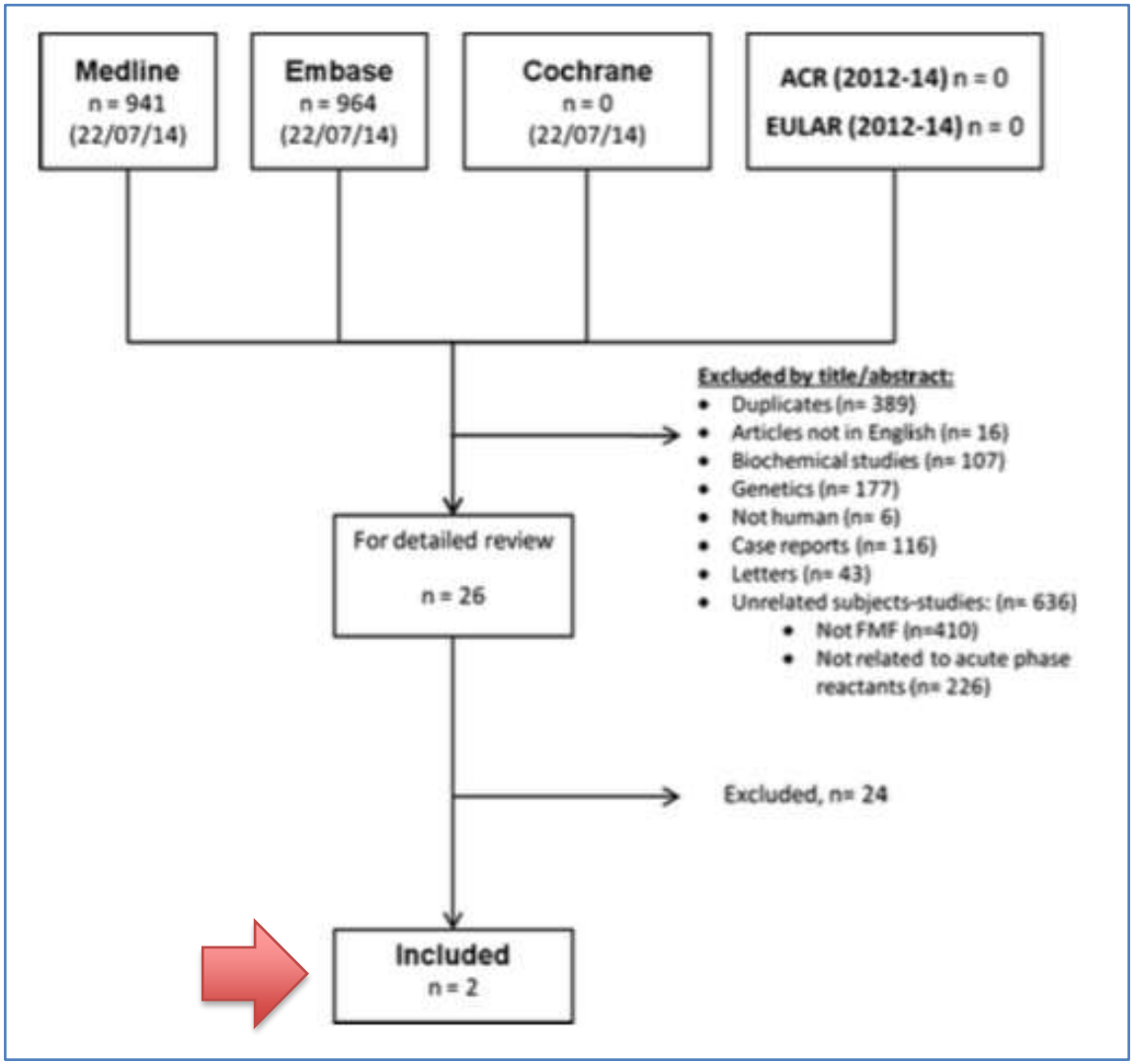


What is the best acute phase reactant for familial Mediterranean fever follow-up and its role in the prediction of complications? A systematic review



Rheumatol Int. 18 September 2015

What is the best acute phase reactant for familial Mediterranean fever follow-up and its role in the prediction of complications? A systematic review

Table 1 Evidence table of studies included in the review

Study	Duzova [14]	Yalcinkaya [16]
Country/setting	Turkey	
Study design	Longitudinal observational retrospective study	
Follow-up	Unclear	
N	183 plus 10 healthy controls	36 (15 with amyloidosis)
Selection criteria	FMF patients according to previously described criteria, during attack-free period (None within the last 14 days)	FMF patients during and in between acute attacks
Tests studied	SAA*	SAA† CRP† ESR†
Blinding	NO	YES
Gold standard/outcome	Amyloidosis (no definition provided)	Amyloidosis (histologically confirmed)
Measure of performance	Comparison of mean values. No performance measures.	

They found that homozygous and compound heterozygous patients had higher SAA levels than the heterozygous patients [129 (8–1500) vs. 29 mg/l (6–216), respectively, ($P < 0.005$)]. SAA was shown to be the best marker of subclinical inflammation in FMF. Although in Duzova's study, SAA was shown to be the best marker of subclinical in ammation in FMF patients when compared to the other APRs such as CRP, erythrocyte sedimentation rate (ESR), fibrinogen and ferritin, APRs with the design and duration of the study failed to provide any prediction for the association with secondary amyloidosis.

Patients with amyloidosis had elevated levels of the three APRs but were not statistically different than those without amyloidosis. Of note, the largest SAA levels were not pre- sent in patients with demonstrated amyloidosis

Rheumatol Int. 18 September 2015

What is the best acute phase reactant for familial Mediterranean fever follow-up and its role in the prediction of complications? A systematic review

Annals of the Rheumatic Diseases
The Eular Journal

2002;61:79–81

Table 2 Levels of acute phase response during the attack and attack-free periods in patients with FMF in comparison with those in the control groups (mean (SD))

APR and urine analysis	FMF, during attack (n=49)	FMF, attack-free (n=49)	Positive controls (n=39)	Healthy controls (n=19)
ESR (>20 mm/1st h)	52 (27)[c] (43/49)+ (88)++	20 (12) (22/42) (52)	75 (32)[c] (39/39) (100)	5 (0. 03) (0/19)
CRP (>6 mg/l)	139 (110)[c] (49/49) (100)	22.1 (38) (15/44) (34)	118 (100) (36/39) (92)	5 (0.3) (1/19) (5)
Fibrinogen (>4 g/l)	4.13 (1.11)[c] (15/24) (63)	2.82 (0.83) (1/24) (4)	3.72 (1.37) (8/26) (31)	2.50 (0.79) (0/10)
Haptoglobin (>2.70 g/l)	2.67 (0.81)[c] (10/24) (42)	1.74 (0.85) (3/24) (13)	2.92 (1.01) (17/26) (65)	1.43 (0.68) (0/10)
WBC (>10×10⁹/l)	10.6 (3.9)[c] (12/24) (50)	7.5 (2.3) (3/24) (13)	10.3 (5.4) (12/26) (46)	7.3 (1.3) (0/10)
Platelets (>400×10⁹/l)	255.8 (62.1) (0/45)	246.5 (64.9) (0/42)	395.7 (163.2)[c] (17/39) (44)	248.0 (59.1) (0/19)
Ferritin (ng/ml)¶	127 (113)[c] (1/25) (4)	72 (52) (0/25)	1159 (1775)[c] (8/13) (62)	80 (59) (0/9)
FVIIIRAg (>200%)	147 (130)[a] (3/17) (18)	61 (43) (0/17)	197 (212) (7/21) (33)	78 (43) (0/7)
Protein electrophoresis*				
α_1 Globulin (g/l)	1.8 (0.7)[f]	1.3 (0.6)	1.7 (0.7) (1/26) (4)	1.3 (0.4)
α_2 Globulin (g/l)	9.6 (2)[b] (4/24) (17)	7.4 (1) (0/24)	8.1 (2.1)[f] (2/26) (8)	6 (0.9)
β Globulin (g/l)	3.7 (3) (3/24) (13)	8.6 (1) (1/24) (4)	8.1 (2.5) (2/26) (8)	8.3 (1.3)
γ Globulin (g/l)	12.1 (3) (2/24) (8)	12.2 (3) (2/24) (8)	14.1 (6.2) (6/26) (23)	9.8 (2.5)
Albumin (<35 g/l)	45 (6) (1/23) (4)	46 (6) (2/22) (9)	34 (9)[b] (10/26) (38)	52 (4) (0/10)
Proteinuria ⩾ trace	10/24 (42)	1/24 (4)	9/26 (35)	1/10 (10)
Haematuria ⩾5RBC	3/24 (13)	0/24	5/26 (19)	0/10

BIOCHEMIA MEDICA
http://www.biochemia-medica.com/

2012 Feb; 22(1): 109–113

	FMF group (N = 35)	Control group (N = 25)	P
IL–1 β (pg/mL)	3.35 (2.15–10.76)	2.80 (2.12–5.44)	**0.018**
CRP (mg/L)	4.4 (3.2–10.1)	4.6 (3.4–7.5)	0.816
ESR (mm/h)	15 (7–35)	11 (5–20)	0.181
Fibrinogen (g/L)	3.17 (2.58–4.23)	3.46 (2.57–4.29)	0.686

Laboratory tests are not specific, with high serum levels of inflammatory proteins in the acute phase of this disease, but often, high levels are found even between attacks. SAA levels may be particularly useful in monitoring the effectiveness of treatment.

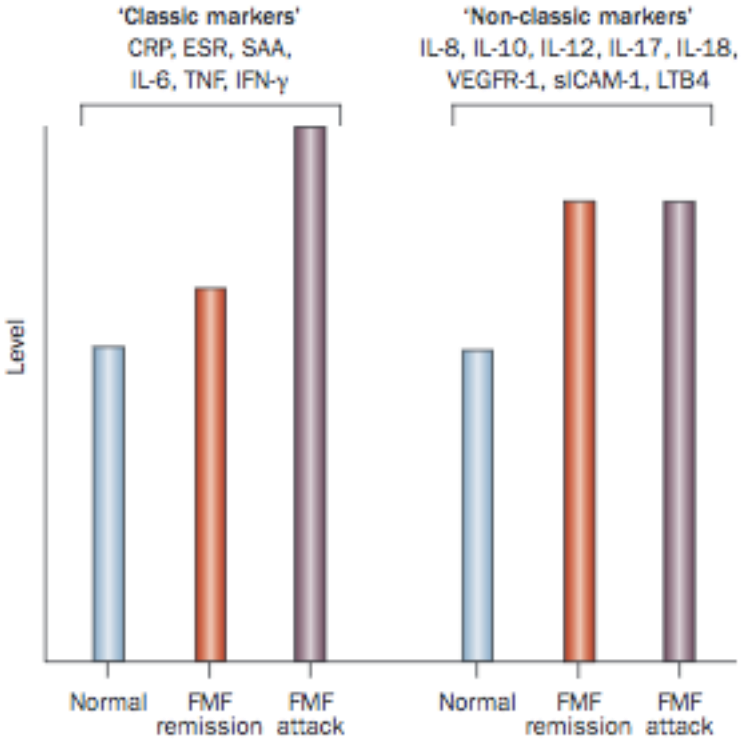
Rheumatol Int. 18 September 2015

Chronic inflammation in FMF: markers, risk factors, outcomes and therapy

Table 1 | Cytokines involved in chronic inflammation in FMF

Cytokine	Function	Study
Proinflammatory		
IL-6	Promotes release of acute-phase proteins	Gang *et al.* (1999),[28] Kiraz *et al.* (1998),[29] Notarnicola *et al.* (2002),[30] Manukyan *et al.* (2010),[35] Akcan *et al.* (2003)[36]
IL-8	Chemoattractant of neutrophils	Kiraz *et al.* (1998),[29] Notarnicola *et al.* (2002)[30]
IL-12	Activates NK cells, enhances phagocytic activity	Erken *et al.* (2006),[34] Simsek *et al.* (2007)[33]
IL-17	Enhances proliferation and chemotaxis of neutrophils	Haznedaroglu *et al.* (2005)[32]
IL-18	Induces IFN-γ, enhances T_H1 immune response	Haznedaroglu *et al.* (2005)[32], Simsek *et al.* (2007)[33]
TNF	Involved in initiation and perpetuation of inflammation	Kiraz *et al.* (1998),[29] Notarnicola *et al.* (2002)[30]
IFN-γ*	Activates NK cells, dendritic cells and neutrophils; essential for T_H1 cell responses	Koklu *et al.* (2005),[40] Centola *et al.* (2000)[45]
MIF	Upregulates macrophage function	Rigante *et al.* (2007)[43]
sICAM-1	Mediates leukocyte migration	Direskeneli *et al.* (1999)[43]
LTB4	Chemoattractant of neutrophils	Bentancur *et al.* (2004)[44]
IL-1β	Involved in initiation and perpetuation of inflammation	Gang *et al.* (1999),[28] Rozenbaum *et al.* (1992)[39]
Anti-inflammatory		
IL-10	Anti-inflammatory Inhibits TNF, IL-1, IL-6	Erken *et al.* (2006),[34] Bagci *et al.* (2004)[31]
VEGFR-1	Nonspecific marker of endothelial cell injury and inflammation	Basar *et al.* (2007)[41]

*Induces expression of the *MEFV* gene in leukocytes.[45] Abbreviations: FMF, familial Mediterranean fever; IFN, interferon; inhibiting factor; NK, natural killer; PBMCs, peripheral blood mononuclear cells; sICAM, soluble intracellular adhesion m endothelial growth factor receptor.



Nature reviews/ Rheumatology. 2011

SETS OF CLINICAL CRITERIA FOR FAMILIAL MEDITERRANEAN FEVER: TEL HASHOMER CRITERIA, LIVNEH CRITERIA, AND TURKISH PEDIATRIC CRITERIA

TEL HASHOMER CRITERIA
Major criteria
1. Recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis
2. Amyloidosis of the AA type without predisposing disease
3. Favorable response to continuous colchicine treatment.
Minor criteria
1. Recurrentfebrile episodes
2. Erysipelas-like erythema
3. FMF in a first-degree relative
Definite diagnosis: 2 major or 1 major and 2 minor criteria
Probable diagnosis: 1 major and 1 minor criteria

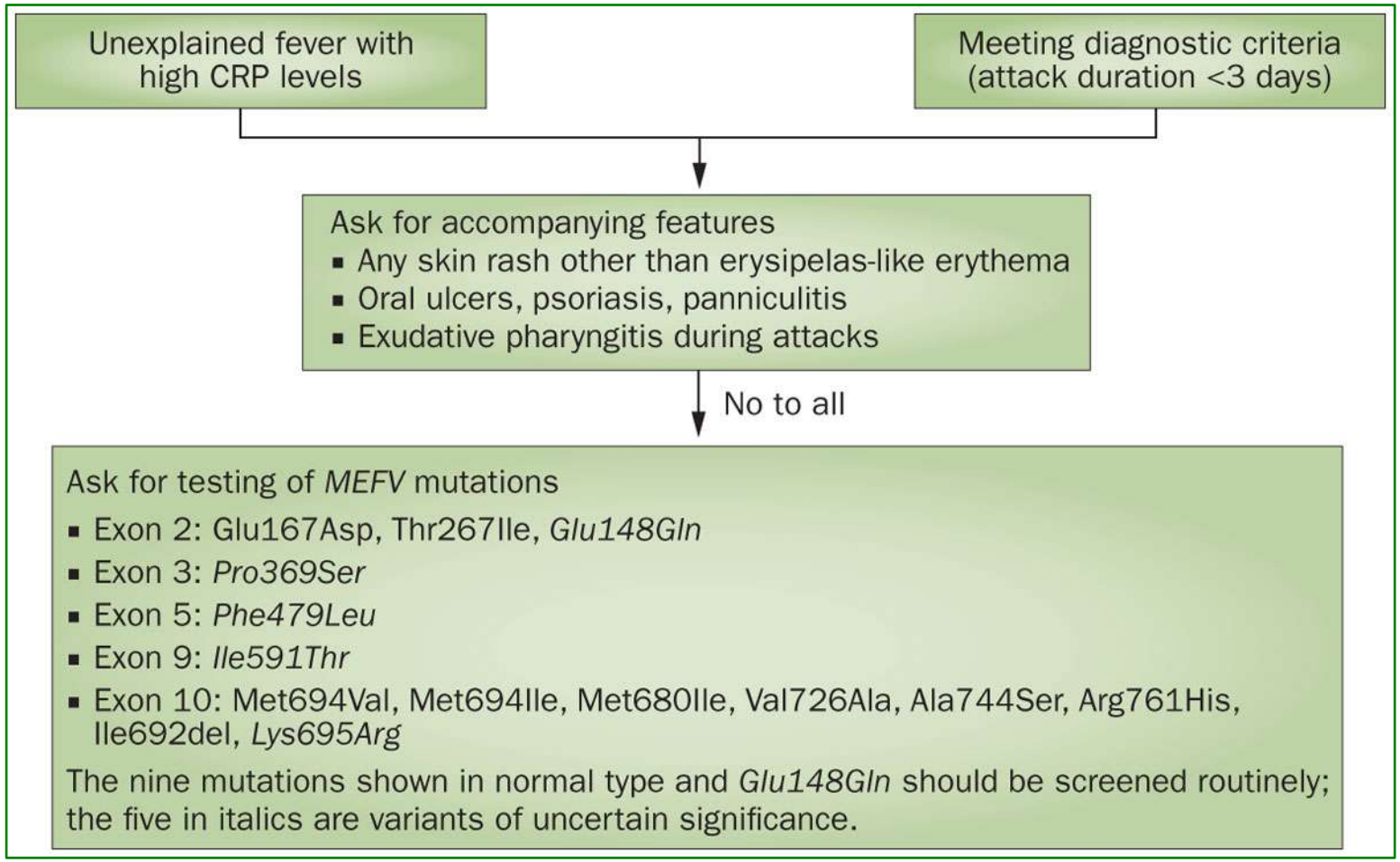
LIVNEH CRITERIA (simplifiedversion)
Major criteria
Typical attacks of:
1. Peritonitis (generalized)
2. Pleuritis or pericarditis (unilateral chest pain)
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
Incomplete abdominal attacks
Minor criteria
1-2 Incomplete attacks involving 1 or more of the following sites:
1. Chest
2. Joint
3. Exertional leg pain
4. Favorable response to colchicine
Diagnosis: 1 major criterion or 2 minor criteria
Typical attacks: recurrent (=3 of the same type), febrile (rectal temperature of 38°C or higher) and short (lasting between 12 hours and 3 days)
Incomplete attacks: painful and recurrent attacks that differ from typical attacks in one or two features, as follows: 1) the temperature is normal or lower than 38°C; 2) the attacks are longer or shorter than specified (but not shorter than 6 hours or longer than a week); 3) no signs of peritonitis are recorded during the abdominal attacks; 4) the abdominal attacks are localized; 5) the arthritis is in joints other than those specified

TURKISH PEDIATRIC CRITERIA	
Criteria	**Description**
Fever	Axillary temperature of > 38°C, 6-72 hours of duration, ≥ 3 attacks
Abdominalpain	6-72 hours of duration, ≥ 3 attacks
Chestpain	6-72 hours of duration, ≥ 3 attacks
Arthritis	6-72 hours of duration, ≥ 3 attacks, oligoarthritis
Family history of FMF	
The presence of at least two out of five criteria: sensitivity (86.5%) and specificity (93.6%) for the diagnosis of FMF	

Giancane G, et al. Ann Rheum Dis 2015;74:635–641

nature REVIEWS RHEUMATOLOGY

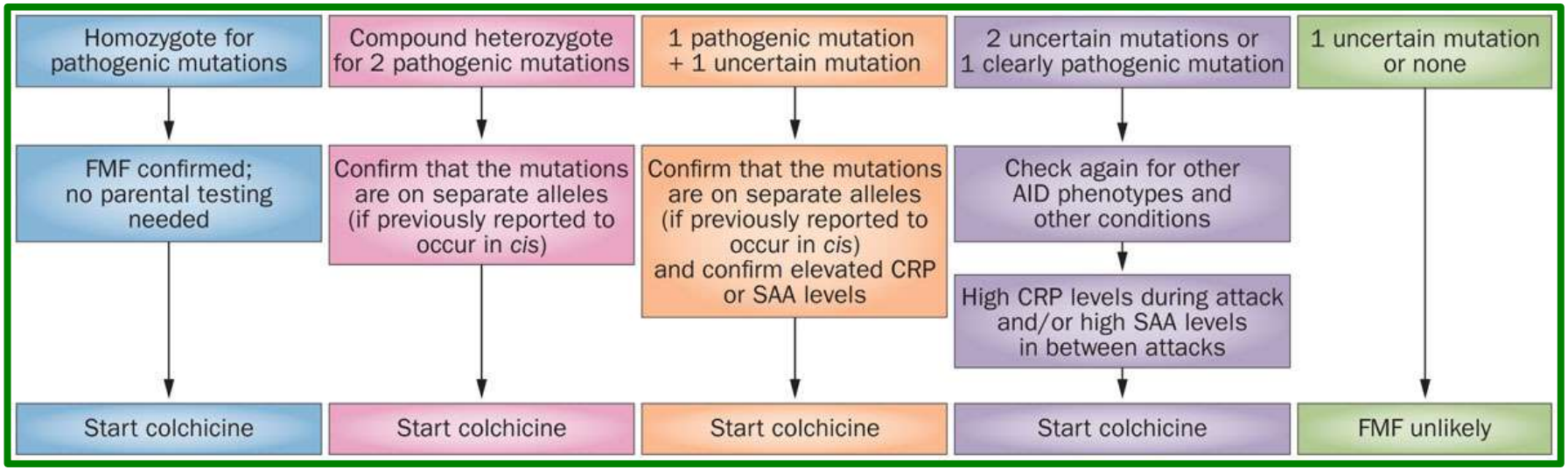
A FLOWCHART TO GUIDE REQUESTS FOR *MEFV* MUTATION ANALYSIS



Ozen, S. & Bilginer, Y. (2013) A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin

nature REVIEWS RHEUMATOLOGY

ALGORITHM TO GUIDE DIAGNOSIS AND TREATMENT DECISIONS AFTER *MEFV* GENOTYPE ANALYSIS



A genetic diagnosis of FMF in the absence of clinical manifestations or subclinical inflammation is not necessarily an indication to start treatment, BUT such patients must remain under surveillance since they may develop clinically significant disease in future, even without symptoms. In countries where secondary amyloidosis is frequent, the physician may consider treatment, especially if there are similar cases in the family.

Ozen, S. & Bilginer, Y. (2013) A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin

EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF FAMILIAL MEDITERRANEAN FEVER

Table 1 EULAR recommendations for the management of FMF with the level of agreement, of evidence and grade of recommendation (GR)

Recommendation	A	LoE	GR
01. Ideally, FMF should be diagnosed and initially treated by a physician with experience in FMF	7.6	5	D
02. The ultimate goal of treatment in FMF is to reach complete control of unprovoked attacks and minimising subclinical inflammation in between attacks	9.3	4	C
03. Treatment with colchicine should start as soon as a clinical diagnosis is made	8.9	1b	A
04. Dosing can be in single or divided doses, depending on tolerance and compliance	9.4	5	D
05. The persistence of attacks or of subclinical inflammation represents an indication to increase the colchicine dose	9.7	3	C
06. Compliant patients not responding to the maximum tolerated dose of colchicine can be considered non-respondent or resistant; alternative biological treatments are indicated in these patients	9.8	2b	B
07. FMF treatment needs to be intensified in AA amyloidosis using the maximal tolerated dose of colchicine and supplemented with biologics as required	9.5	2b	C
08. Periods of physical or emotional stress can trigger FMF attacks, and it may be appropriate to increase the dose of colchicine temporarily	7.6	5	D
09. Response, toxicity and compliance should be monitored every 6 months	8.6	5	D
10. Liver enzymes should be monitored regularly in patients with FMF treated with colchicine; if liver enzymes are elevated greater than twofold the upper limit of normal, colchicine should be reduced and the cause further investigated	8.4	5	D
11. In patients with decreased renal function, the risk of toxicity is very high, and therefore signs of colchicine toxicity, as well as CPK, should be carefully monitored and colchicine dose reduced accordingly	9.3	4	C
12. Colchicine toxicity is a serious complication and should be adequately suspected and prevented	9.4	4	C
13. When suspecting an attack, always consider other possible causes. During the attacks, continue the usual dose of colchicine and use NSAID	9.5	2b	C
14. Colchicine should not be discontinued during conception, pregnancy or lactation; current evidence does not justify amniocentesis	9.3	3	C
15. In general, men do not need to stop colchicine prior to conception; in the rare case of azoospermia or oligospermia proven to be related to colchicine, temporary dose reduction or discontinuation may be needed	8.2	3	C
16. Chronic arthritis in a patient with FMF might need additional medications, such as DMARDs, intra-articular steroid injections or biologics	9.5	2b	C
17. In protracted febrile myalgia, glucocorticoids lead to the resolution of symptoms; NSAID and IL-1-blockade might also be a treatment option; NSAIDs are suggested for the treatment of exertional leg pain	9.3	2b	C
18. If a patient is stable with no attacks for more than 5 years and no elevated APR, dose reduction could be considered after expert consultation and with continued monitoring	8.0	5	D

A, agreement (/10); APR, acute phase reactants; CPK, creatinine phosphokinase; DMARDs, disease modifying antirheumatic drugs; EULAR, European League Against Rheumatism; FMF, familial Mediterranean fever; IL-1, interleukin 1; LoE, level of evidence; NSAID, non steroidal anti inflammatory drugs.

Ozen S, et al. Ann Rheum Dis 2016;0:1-8

EULAR recommendations for the management of familial Mediterranean fever

January 2016

TREATMENT WITH COLCHICINE SHOULD BE STARTED AS SOON AS A CLINICAL DIAGNOSIS IS MADE

- Colchicine is very efficacious in preventing FMF attacks and associated amyloidosis.
- A starting dose of ≤0.5 mg/day for children <5 years of age,
  0.5–1.0 mg/day for children 5–10 years of age
  1.0–1.5 mg/in children >10years of age and in adults is recommended

M694V GENOTYPE AMONG SYMPTOMATIC PATIENTS

PRE-EXISTING COMPLICATIONS

GREATER DISEASE ACTIVITY

DOSING CAN BE IN SINGLE OR DIVIDED DOSES, DEPENDING ON TOLERANCE AND COMPLIANCE

Colchicine has an excellent long-term safety profile, but is commonly associated with GASTROINTESTINAL side effects.

LACTOSE INTOLERANCE AND DIARRHOEA

ANTIDIARRHOEAL AND SPASMOLYTIC AGENTS

DOSE REDUCTION

SPLIT DOSES

TEMPORARY REDUCTION OF DAIRY PRODUCTS

THE PERSISTENCE OF ATTACKS OR SUBCLINICAL INFLAMMATION REPRESENTS AN INDICATION TO INCREASE COLCHICINE DOSE

If inflammation persists despite adherence to the treatment colchicine dose may be increased

MONITORING CRP, SAA PROTEIN OR BOTH AT LEAST EVERY 3 MONTHS

DOSE MAY BE INCREASED BY 0.5 MG/DAY

UP TO A DAILY DOSE OF 2 MG IN CHILDREN AND 3 MG IN ADULTS

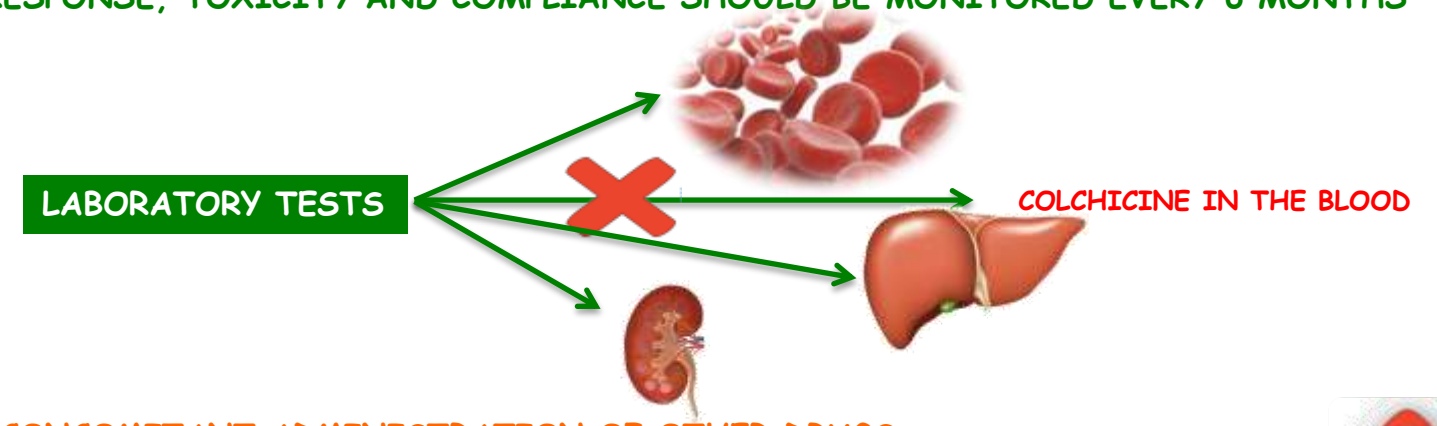
EULAR recommendations for the management of familial Mediterranean fever

January 2016

PERIODS OF PHYSICAL OR EMOTIONAL STRESS CAN TRIGGER FMF ATTACKS

- Some authors recommend increasing the dose of colchicine to pre-empt trigger events

RESPONSE, TOXICITY AND COMPLIANCE SHOULD BE MONITORED EVERY 6 MONTHS



CONCOMITANT ADMINISTRATION OF OTHER DRUGS

MACROLIDES, KETOCONAZOLE, RITONAVIR, VERAPAMIL, CICLOSPORIN, STATINS

200-300%

COLCHICINE BLOOD LEVELS

DURING THE ATTACKS, CONTINUE THE USUAL DOSE OF COLCHICINE AND USE NSAIDS

NAPROXEN, DICLOFENAC, INDOMETHACIN, ETC.
GLUCOCORTICOIDS may decrease the duration of attacks, but may also increase their frequency.
IL-1 BLOCKERS during attacks

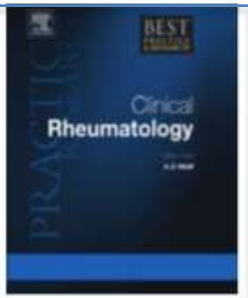
COLCHICINE SHOULD NOT BE DISCONTINUED DURING CONCEPTION, PREGNANCY OR LACTATION

TO REDUCE COLCHICINE DOSE

Among such patients, particularly those who have been stable (5y) with no attacks for several years and have not had elevated apr. Dose decrement must be performed gradually by no more than 0.5 mg on each occasion. The suggested interval for colchicine dose reduction is 6 months.

Approach to the patients with inadequate response to colchicine in familial Mediterranean fever

Best Practice & Research Clinical Rheumatology xxx (2016) 1e8



Approximately 5–10% of FMF patients do not respond to colchicine treatment and another 5% are intolerant to colchicine because of side effects [5]. The mechanism of colchicine resistance is not clear; one study showed that colchicine-resistant patients had inadequate colchicine concentration in their mononuclear cells, probably resulting from a genetic defect unrelated to the underlying FMF [6]. Clinically, colchicine unresponsiveness is defined as the occurrence of at least one attack per month despite daily treatment with 2 mg of colchicine or more [7,8]. Some of the patients who do not respond to standard colchicine treatment may respond to higher doses of daily colchicine or to the addition of a weekly intravenous infusion of colchicine [9]. Nevertheless, a substantial number

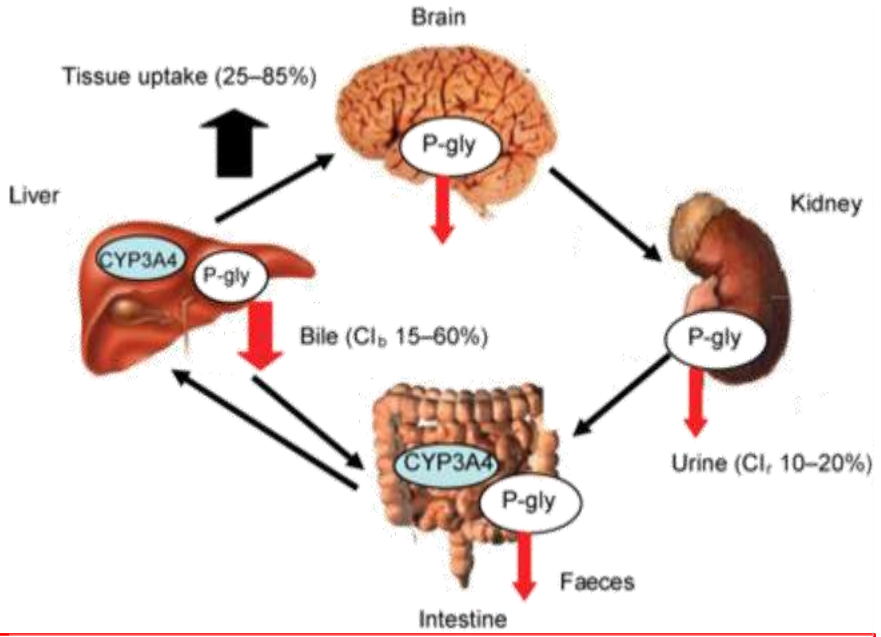


Table 1

Recommendations for approaching to a familial Mediterranean fever (FMF) patient with an inadequate response to colchicine.

1. First, confirm the diagnosis of FMF and rule out other hereditary and acquired autoinflammatory disorders or phenotypes
2. Assure that the patient is on an effective colchicine dose and fully compliant for at least 3–6 months
3. Observe and document the recurrence of typical attacks and inflammatory findings in between attacks while the patient is using stable doses of colchicine regularly
4. Add an IL-1 blocking agent on top of colchicine and follow the inflammatory findings and recurrence of attacks; consider uptitrating or downtitrating the dosage according to clinical findings and acute-phase response

Approach to the patients with inadequate response to colchicine in familial Mediterranean fever

Best Practice & Research Clinical Rheumatology xxx (2016) 1e8

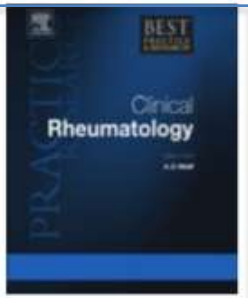


Table 2
Factors affecting the response to colchicine in familial Mediterranean fever [10].

A. Factors associated with higher inflammatory activity or severe disease course in FMF
- a. Homozygosity for p.Met694Val variant in exon 10 of the MEFV gene
- b. Other genetic factors aggregating within families and increasing the inflammatory burden
- c. Environmental factors
- d. Accompanying inflammatory conditions (e.g., spondyloarthritis and systemic vasculitis)

B. Factors associated with colchicine bioavailability
- a. Compliance
- b. Absorption, metabolism, and intracellular concentration
  - i. Genetic polymorphisms affecting the transport and metabolism of colchicine
- c. Drug interactions
  - i. Drugs interacting with CYP3A4 and ABCB1 proteins
- d. Intolerance
  - i. Individual factors affecting the gastrointestinal tolerance to colchicine treatment

EVALUATION OF RESPONSE TO TREATMENT

EXTENDED REPORT

FMF50: a score for assessing outcome in familial Mediterranean fever

Ozen and colleagues

At the final consensus conference the requirements for assessing the outcome of the disease were defined as:

- ❑ Compliance should be ascertained.
- ❑ Efficacy of the treatment should be assessed after 3–6 months of treatment.
- ❑ The dose of colchicine should be 2 mg/day for adults and it should be the appropriate maximum dose for the age and weight of a child

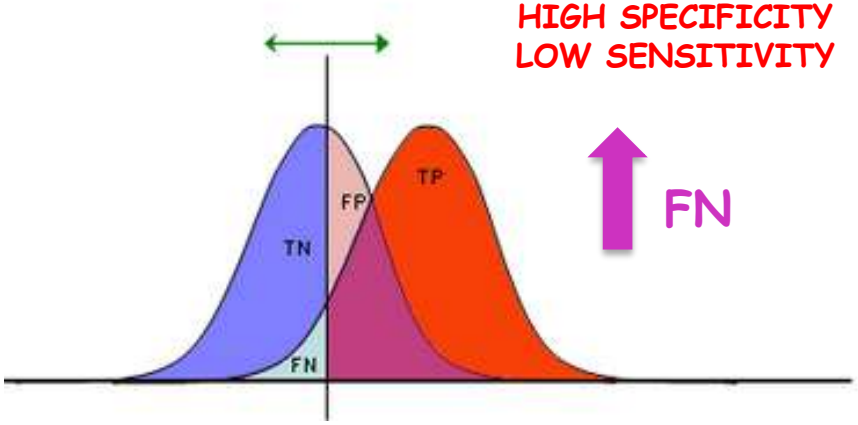
Box 1 Final domains in the core set for the evaluation of response to treatment in familial Mediterranean fever (FMF): an FMF50 response is required which shows at least 50% improvement in at least five of these parameters with no worsening in one

Outcome measures to define the response to treatment in FMF

1. Percentage change in the frequency of attacks with the treatment
2. Percentage change in the duration of attacks with the treatment
3. Patients/parents' global assessment of disease severity (10 cm VAS)
4. Physicians' global assessment of disease severity (10 cm VAS)
5. Percentage change in arthritis attacks with the treatment
6. Percentage change in CRP, ESR or SAA level with the treatment (at least 2 weeks after the last attack)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; SAA, serum amyloid A; VAS, visual analogue scale.

HIGH SPECIFICITY
LOW SENSITIVITY



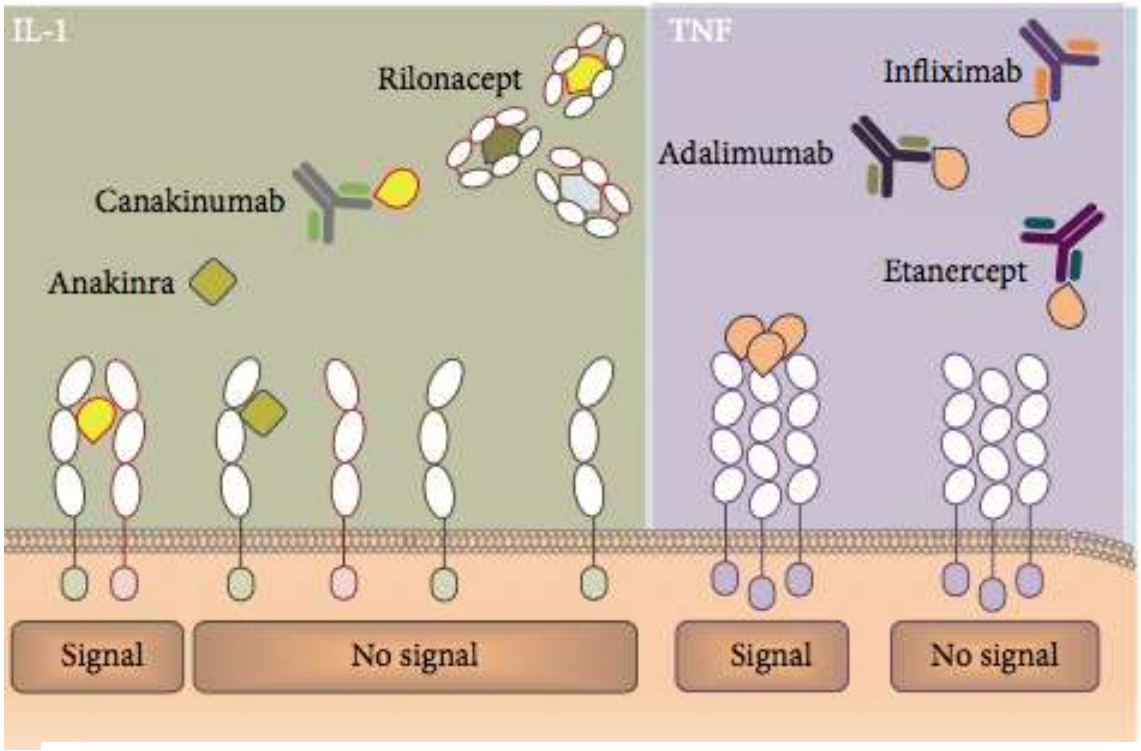
The Familial Mediterranean Fever (FMF) 50 Score: Does it Work in a Controlled Clinical Trial? Re-Analysis of the Trial of Rilonacept for Patients with Colchicine-Resistant or Intolerant FMF

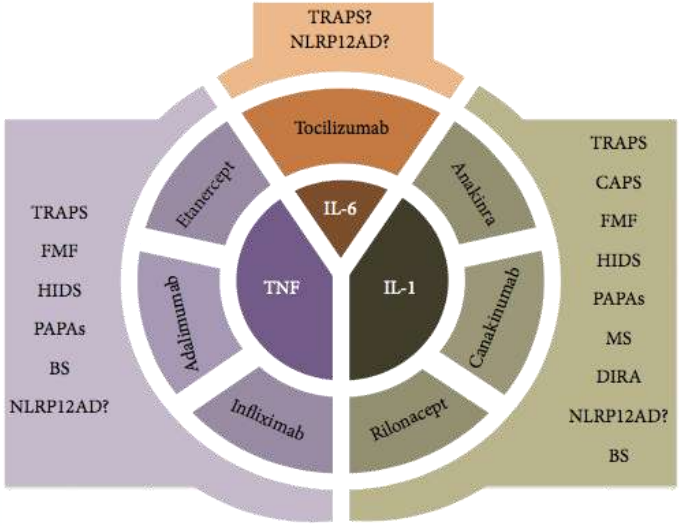
IMAJ • VOL 17 • March 2015

REPORTED THAT FMF50 WAS NOT SUCCESSFUL IN DIFFERENTIATING RESPONDERS FROM NON RESPONDERS

BIOLOGICAL TREATMENTS: NEW WEAPONS IN THE MANAGEMENT OF MONOGENIC AUTOINFLAMMATORY DISORDERS

Mediators of Inflammation Volume 2013, Article ID 939847, 16 pages





= gp130

= IL-6R

= IL-6

= sIL-6R

= IL-1RI

= IL-1β

= IL-1RAcP

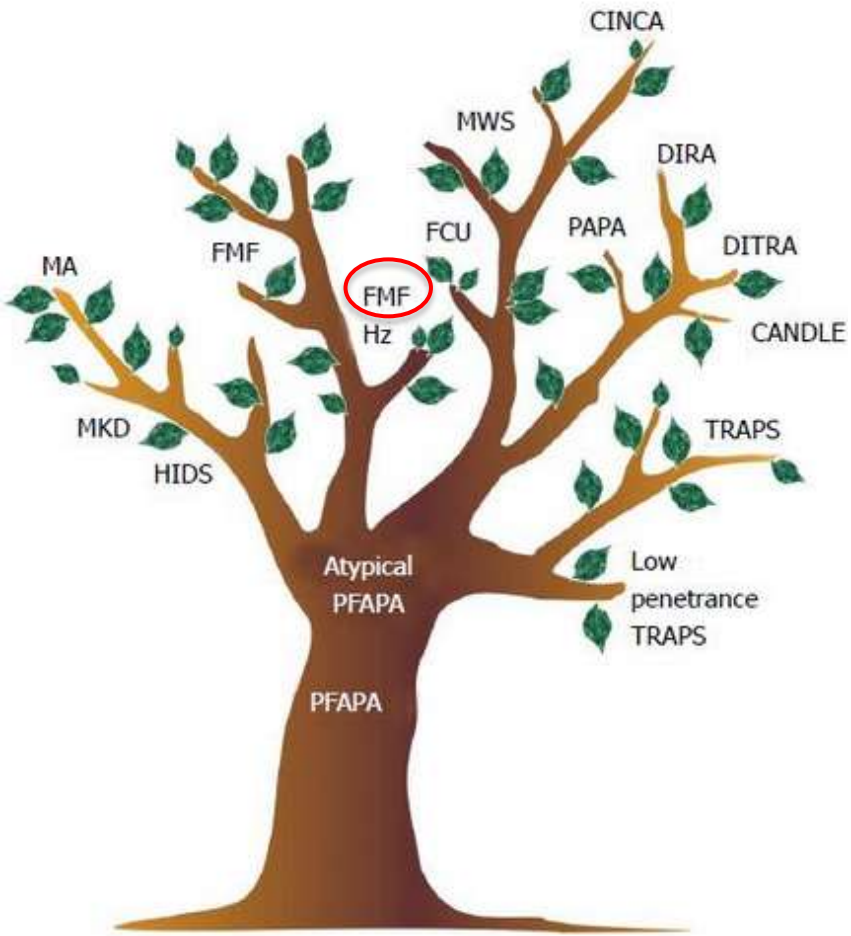
= IL-1α

= IL-1RA

= TNF-α

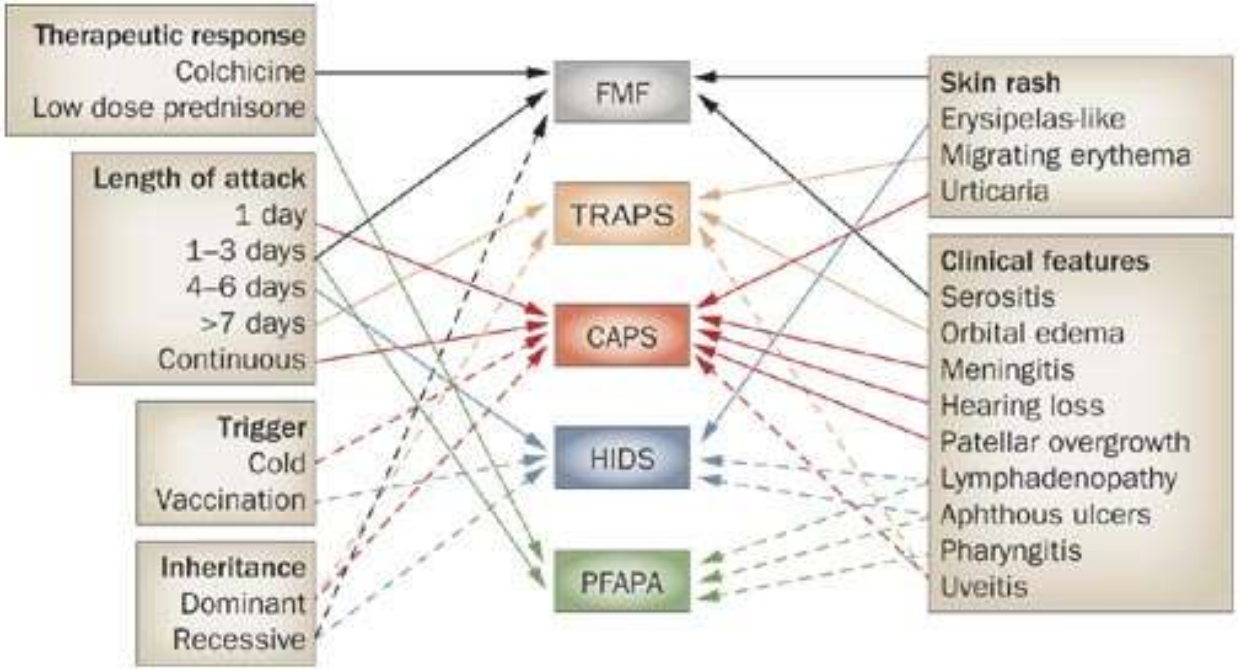
= TNFR

TAKE HOME MESSAGES



- ❑ DIAGNOSI CLINICA
- ❑ DIAGNOSI GENETICA DI SUPPORTO
- ❑ ESAMI DI LABORATORIO ??
- ❑ DIAGNOSI TEMPESTIVA
- ❑ PREVENIRE COMPLICANZE
- ❑ COLCHICINA
- ❑ STRETTO MONITORAGGIO
- ❑ STUDI FUTURI

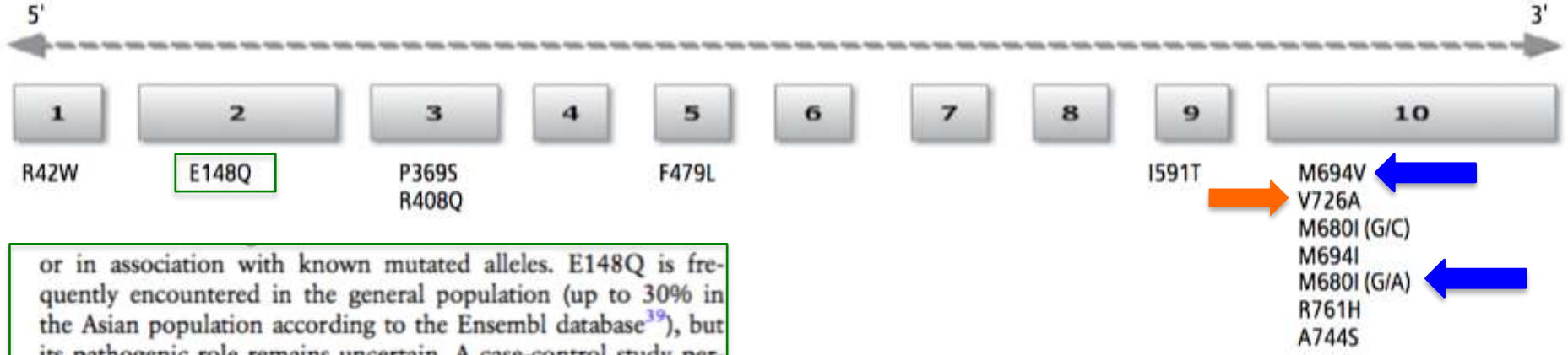
Diagnostic features and differential diagnosis of recurrent febrile syndromes



Hoffman HM and Simon A (2009) Recurrent febrile syndromes—what a rheumatologist needs to know

nature REVIEWS RHEUMATOLOGY

Familial Mediterranean fever: An updated review



or in association with known mutated alleles. E148Q is frequently encountered in the general population (up to 30% in the Asian population according to the Ensembl database[39]), but its pathogenic role remains uncertain. A case-control study per-

causing mutation or a sequence variant with no functional effect. The authors found a similar E148Q mutation frequency

healthy population, the pathogenic role of E148Q remains debateable as demonstrated by the association with other rheumatic diseases[17] or by its role in symptomatic heterozygous patients when the second allele was not known.[15] In conclusion,

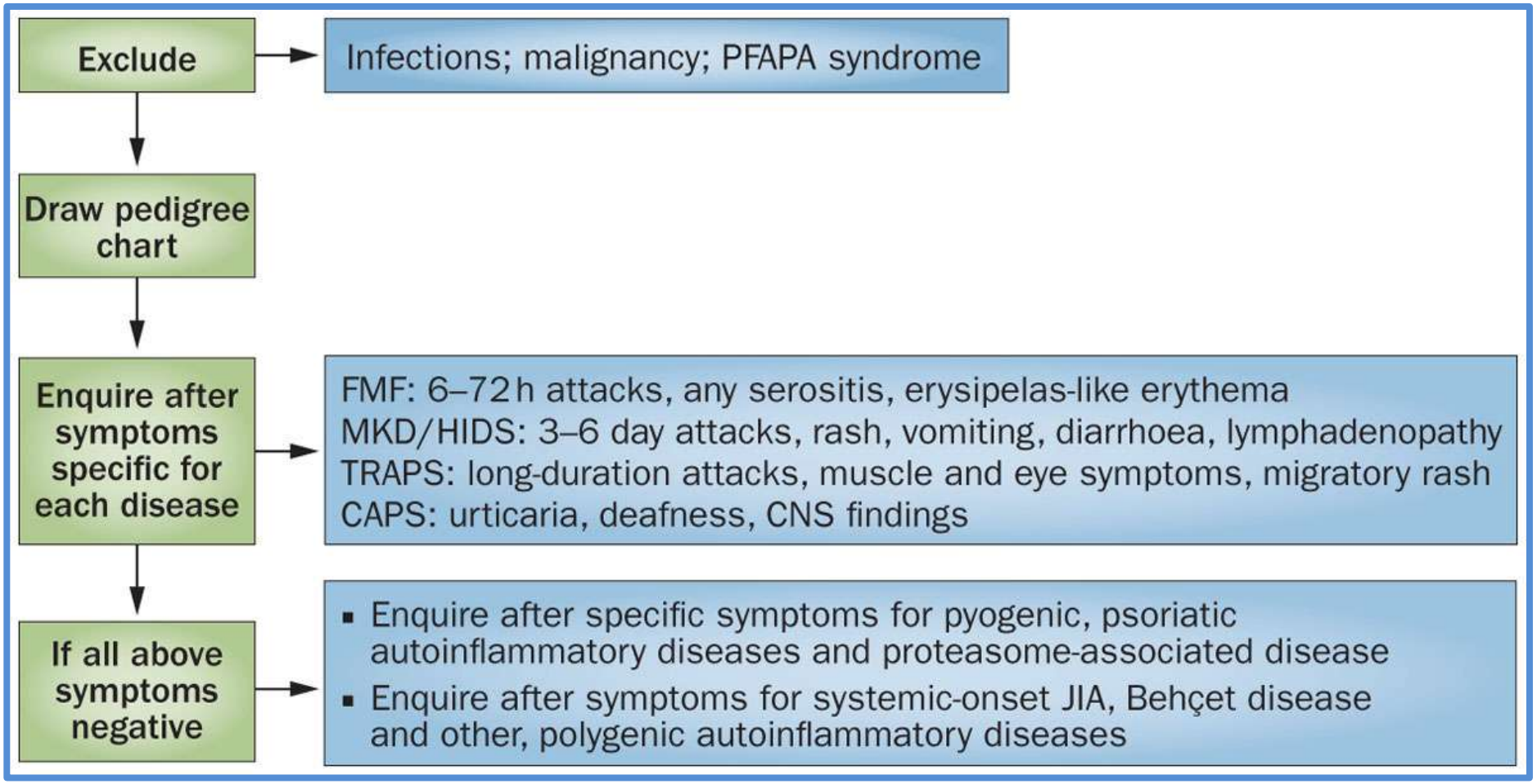
severe phenotype than compound heterozygotes.[20] The literature therefore provides evidence of the pathogenic role of M694V as a risk factor for FMF patients developing disease-related complications and concludes that a patient homozygous for M694V should always be considered at higher risk of developing, with very high probability, a severe phenotype (Strength B).

specific populations. Usually, p.V726A causes a relatively mild disease. When mutations are on exon 2 (such as

Eur J Rheum 2014; 1: 21-33

nature REVIEWS RHEUMATOLOGY

DIFFERENTIAL DIAGNOSIS IN A CHILD REFERRED WITH FEVER



Ozen, S. & Bilginer, Y. (2013) A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin

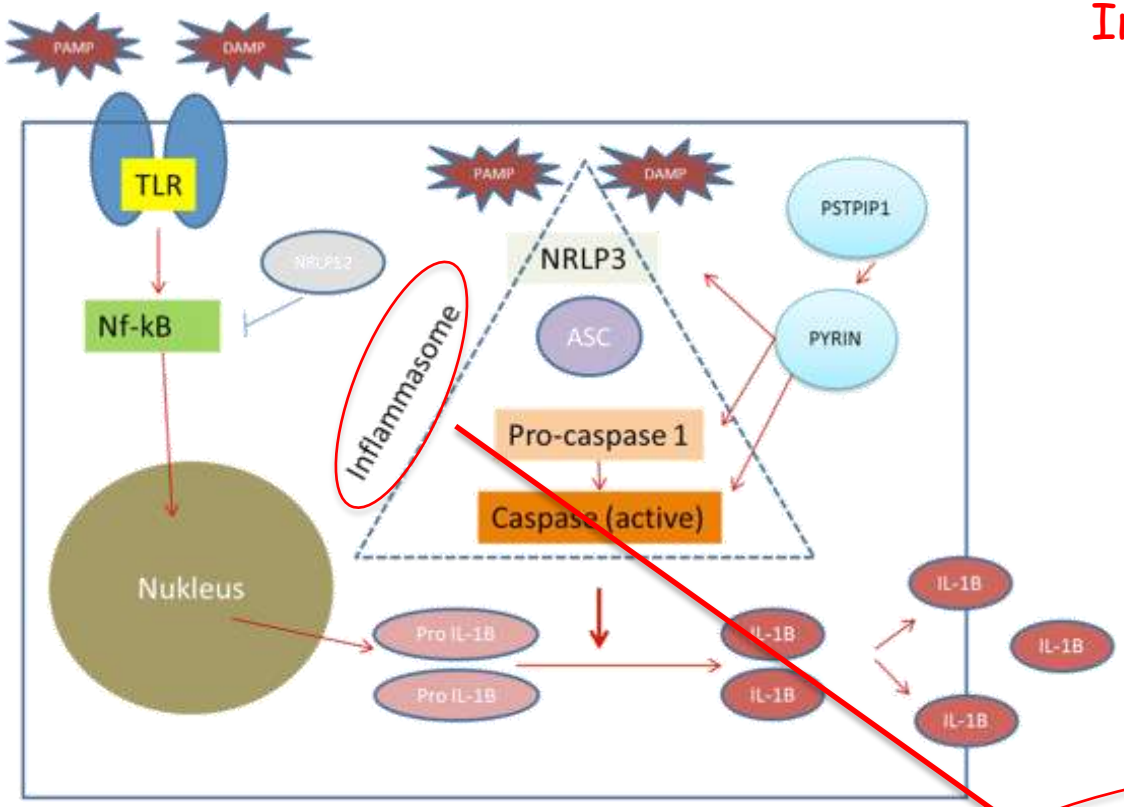
Gene-Phenotype Relationships

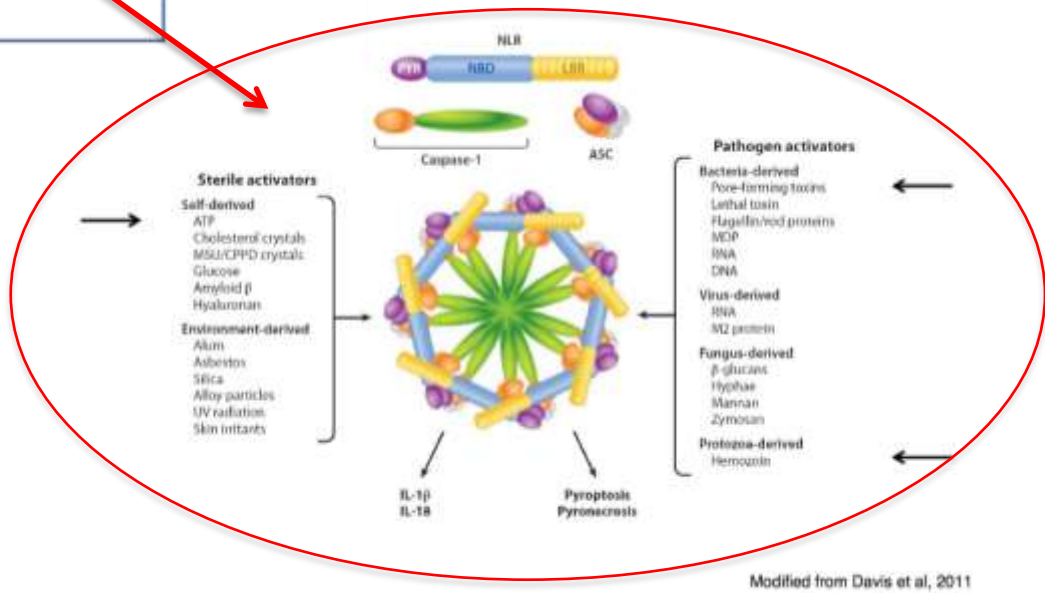
Location	Phenotype	Phenotype MIM number	Inheritance (in progress)
16p13.3	Familial Mediterranean fever, AD	134610	AD
	Familial Mediterranean fever, AR	249100	AR

Table I. Enigmas in FMF.

Autosomal dominant transmission
Non-familial cases
Phenotype II FMF
Genotype - Phenotype in-correlation
Defective gene in neutrophils and polyserositis
None - response to colchicine

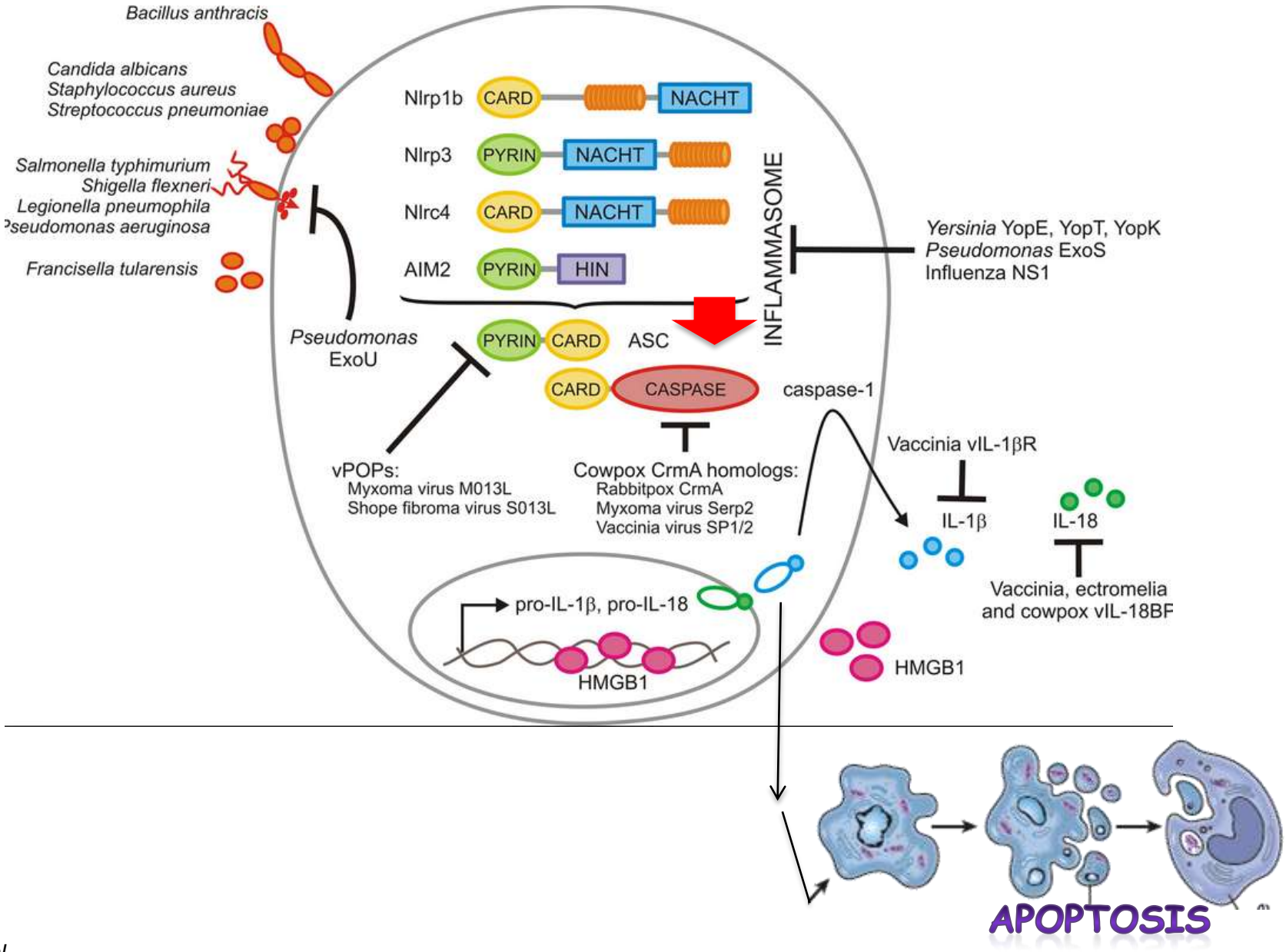
Inflammasome Activators





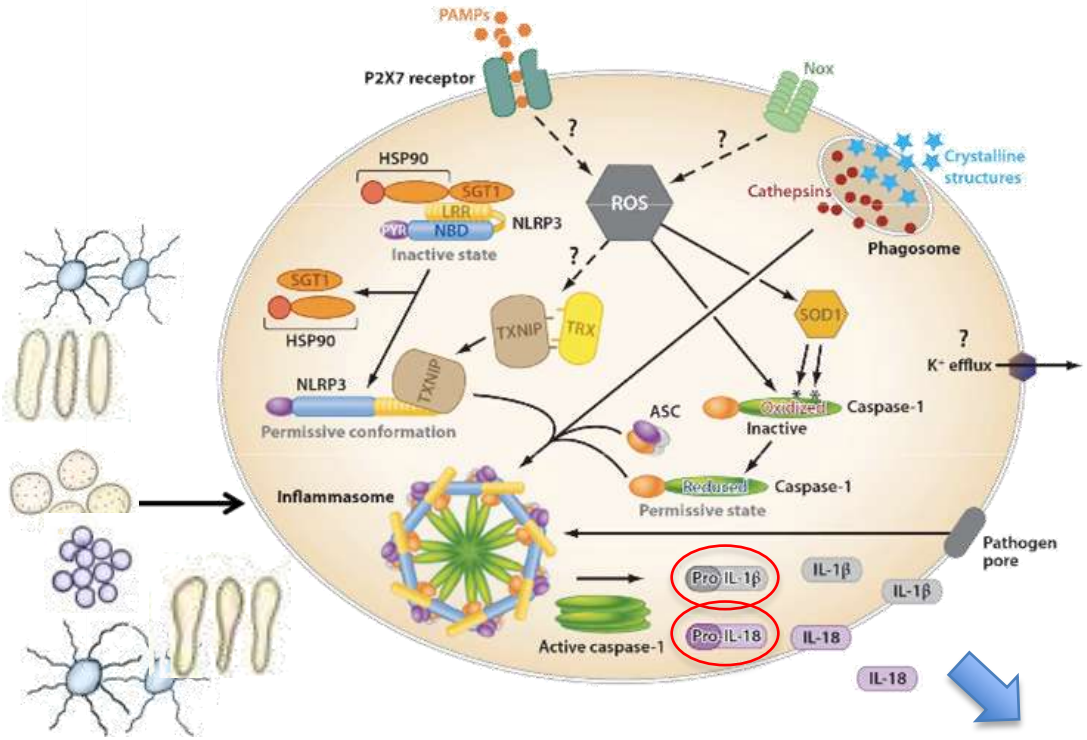
Modified from Davis et al, 2011

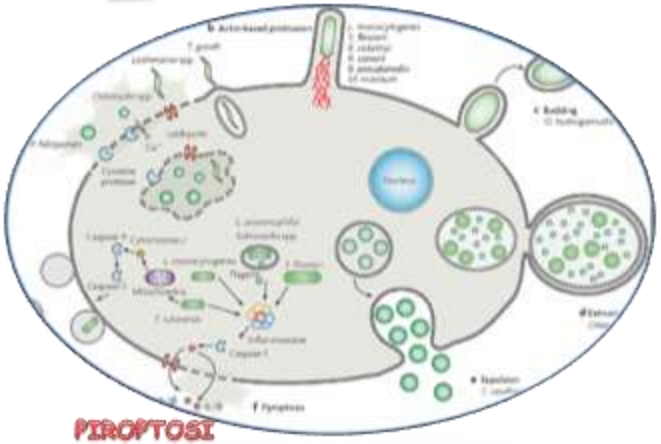
Inflammasome Activators: genes and immunological protagonists



Eu J Immunl

Inflammasome Activators: genes and immunological protagonists





PIROPTOSI
programmed cell death associated with antimicrobial responses during inflammation

Davis et al 2011

SDR AUTOINFIAMMATORIE SISTEMICHE (KASTNER et al)

Sindromi	OMIM	Ereditarietà	Geni o fattori di rischio
Febbri periodiche familiari			
Febbre mediterranea familiare (FMF)	249100	Autosomica recessiva	MEFV
Sindrome periodica associata al recettore per il TNFα (TRAPS)	142680	Autosomica dominante	TNFRSF1A
Sindrome da iper-IgD (HIDS)	260920	Autosomica recessiva	MVK
Sindrome autoinfiammatoria da freddo (FCAS)	120100	Autosomica dominante	CIAS1/NALP3/PYPAF1
Sindrome di Muckle-Wells (MWS)	191900	Autosomica dominante	CIAS1/NALP3/PYPAF1
Sindrome infiammatoria multisistemica ad esordio infantile (NOMID)/sindrome cronica infantile neurologica-cutanea-articolare (CINCA)	607105	Sporadica, autosomica dominante	CIAS1/NALP3/PYPAF1
Sindromi febbrili idiopatiche			
Sindrome periodica febbrile con stomatite aftosa, faringite ed adenopatie cervicali (PFAPA)	-	Solitamente non familiare	-
Artrite giovanile idiopatica ad esordio sistemico	604302	Complessa	IL-6
Malattia di Still dell'adulto	-	Solitamente non familiare	-

SDR AUTOINFIAMMATORIE SISTEMICHE (KASTNER et al)

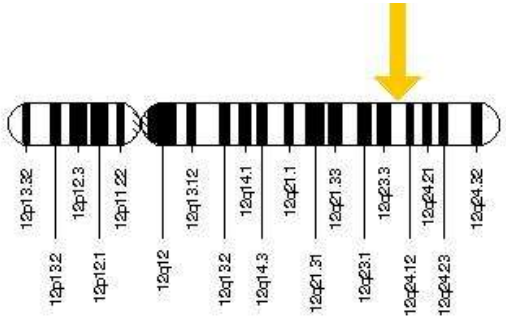
Malattie granulomatose			
Malattie di Crohn	266600	Complessa	NOD2/CARD15, ABCB1 (Ala893), MEFV (?)
Sinovite granulomatosa cronica con uveite e neuropatia cranica (sindrome di Blau)	186580	Autosomica dominante	NOD2/CARD15
Sarcoidosi ad esordio giovanile	609464	Sporadica, autosomica dominante	NOD2/CARD15
Malattie piogeniche			
Sindrome artrite sterile piogenica, pioderma gangrenoso, acne (PAPA)	604416	Autosomica dominante	PSTPIP1
Osteomielite cronica multifocale ricorrente (CRMO)	259680	Sporadica, autosomica recessiva	LPIN2, quando associato con una anemia diseritropoietica congenita (sindrome di Majeed)
Sindrome sinovite, acne, pustolosi, iperostosi ed osteite (SAPHO)	-	Solitamente non familiare	-
Disordini emofagocitici			
Linfoistiocitosi emofagocitica primaria	603553 607624	Autosomica recessiva	PRF1, RAB27A
Sindrome d'attivazione macrofagica (MAS)	-	Solitamente non familiare	-
Disordini del complemento			
Angioedema ereditario	106100	Autosomica dominante	C1NH
Vasculiti			
Malattia di Behçet	109650	Complessa	HLAB51

CARATTERISTICHE CLINICHE DELLE FEBBRI PERIODICHE EREDITARIE

	FMF	HIDS	MWS	FCAS	NOMID/ CINCA	TRAPS	Sindrome di Blau	PAPA
Numero OMIM	249100	260920	191900	120100	607115	142680	186580	604416
Ereditarietà	autosomica recessiva	autosomica recessiva	autosomica dominante	autosomica dominante	autosomica dominante/ *de novo*	autosomica dominante	autosomica dominante	autosomica dominante
Gene	MEFV	MVK	CIAS1	CIAS1	CIAS1	TNFRSF1A	CARD15/ NOD2	CD2BP1/ PSTPIP1
Cromosoma	16p13	12q24	1q44	1q44	1q44	12p13	16q12	15q24
Proteina interessata	pirina (marenostrina)	mevalonato kinasi	criopirina	criopirina	criopirina	recettore del TNF di tipo I (p55)	CARD15	CD2BP1/ PSTPIP1
Manifestazioni cutanee	eritema erisipeloide	rash eritemato-maculo-papuloso	rash simil-orticarioide	rash simil-orticarioide indotto dal freddo	rash simil-orticarioide	rash migrante su aree di mialgia	rash eritemato-papulare granulomatoso	pioderma gangrenoso; acne
Manifestazioni oculari	non comuni	non comuni	congiuntiviti	congiuntiviti	papilledema con possibile cecità; uveiti	congiuntiviti e/o edema periorbitale molto comuni	uveiti; iridocicliti	non segnalate
Manifestazioni muscolo-scheletriche	monoartrite	artralgie; occasionalmente oligoartrite; raramente mialgie	dolori trafittivi muscolari; artralgie comuni; artriti possibili	artralgie comuni; occasionalmente modeste mialgie	ossificazione precoce peri-epifisaria	mialgie severe molto comuni; occasionalmente monoartrite	artrite granulomatosa non caseosa	artrite sterile piogenica
Manifestazioni addominali	peritonite sterile –85%	dolore severo comune	possibili	nessuna	epato-splenomegalia	dolore severo molto comune	nessuna	nessuna
Caratteristiche distintive	eritema erisipeloide	linfoadenopatie; elevate IgD sieriche; elevati valori di mevalonato urinario durante gli attacchi	progressiva sordità neurosensoriale	rash simil-orticarioide indotto dal freddo	meningite asettica cronica; sordità neurosensoriale; artropatia	carattere migratorio delle mialgie e del rash; edema periorbitale	carattere granulomatoso delle lesioni	flogosi ricorrenti e distruttive di articolazioni, cute e muscoli

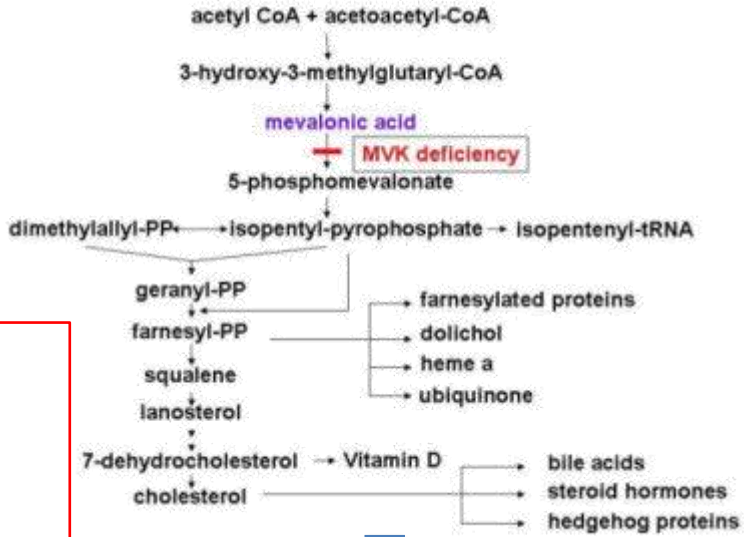
OMIM

Sdr Iper-IgD o Deficit Mevalonato Kinasi



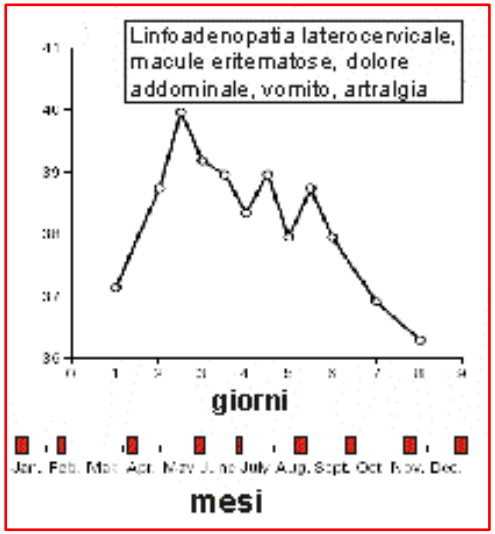
V310M e A334T: severe
V377I: mild

ritardo mentale severo
atassia,
ritardo di crescita
miopatia
cataratta
dolore addominale
Alterazioni rash eritemato maculare
aftosi del cavo orale
Oligo-monoartrite simmetrica



Mevalonato
IL-1
Ck pro-infiammatorie

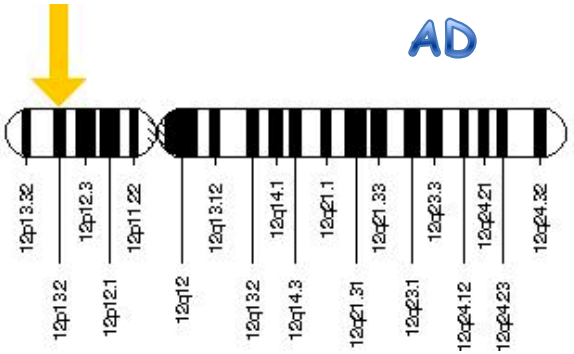
#B#Aspetti	Febbre mediterranea familiare	Sindrome da Iper-IgD	S. periodica associata al recettore del TNF
Origine	Ebrea, Turca	Olandese, Francese	Scozzese, Irlandese
Trasmissione familiare	Orizzontale*	Orizzontale*	Verticale*
Età all'inizio in anni	< 20 anni	< 1 anno	< 20 anni
Durata tipica dell'attacco in giorni	< 2	4-6	> 14
Sintomi, oltre la febbre	Sierosità, interessamento dello scroto, eritema	Linfoadenopatia cervicale	Congiuntivite, mialgia , localizzata
Reperti di laboratorio	Bassi livelli di inibitore del C5 nei liquidi delle sierose	IgD seiriche elevate (>100 UI/mL)	Bassi livelli sierici del recettore del TNF tipo 1 (< 1 ng/mL)
Gene	*MEFV*	Gene della mevalonato chinasi	Gene del recettore del TNF tipo 1
Proteina	Pirina	Mevalonato chinasi	Recettore del TNF tipo 1
Terapia	Colchicina	Cure non disponibili	Corticosteroidi, etanercept



TERAPIA: anti-IL1 ??

TRAPS (TNFR-Associated Periodic Syndrome)

AD



CARATTERISTICHE CLINICHE

3-20 aa

Durata 1-3 settimane

Dolori addominali, alterazioni alvo (diarrea o stipsi)

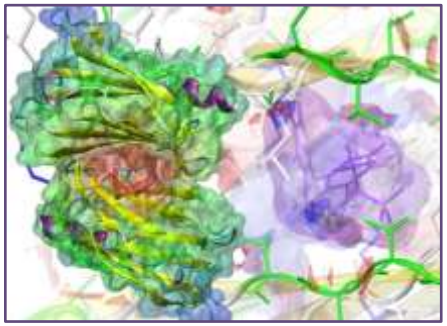
Dolore toracico

Artralgie delle piccole articolazioni

Rash maculare al tronco ed alle estremità

Mialgie, artromialgie, congiuntivite, edema periorbitario

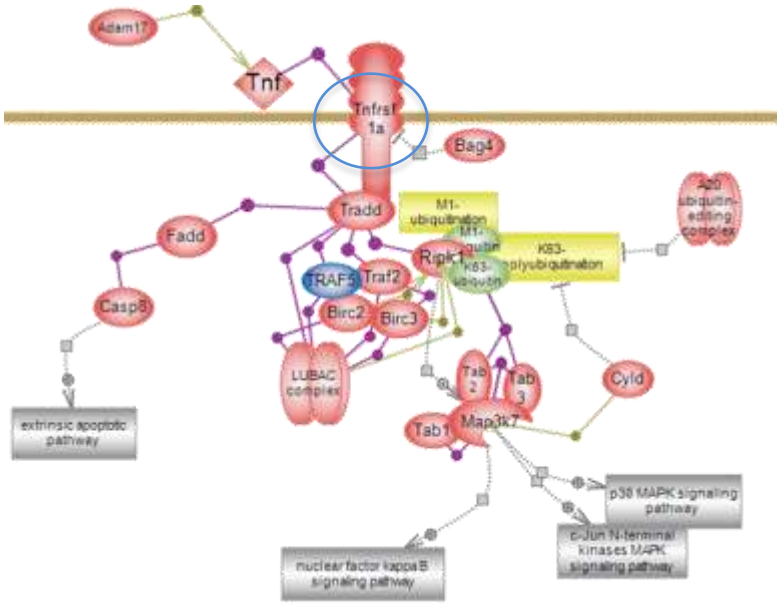
Spiccata Neutrofilia
Aumento della SAA
Anemia ipocromica



AMILOIDE

15-20%

TNFRSF1A



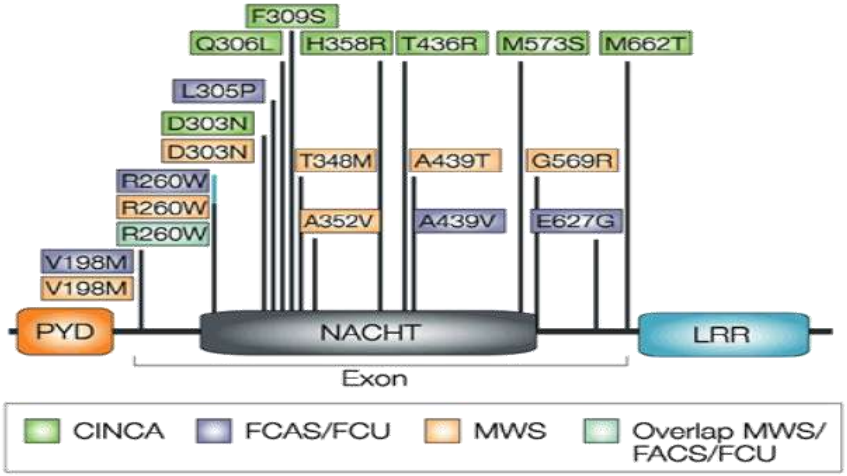
Prolungamento della risposta infiammatoria

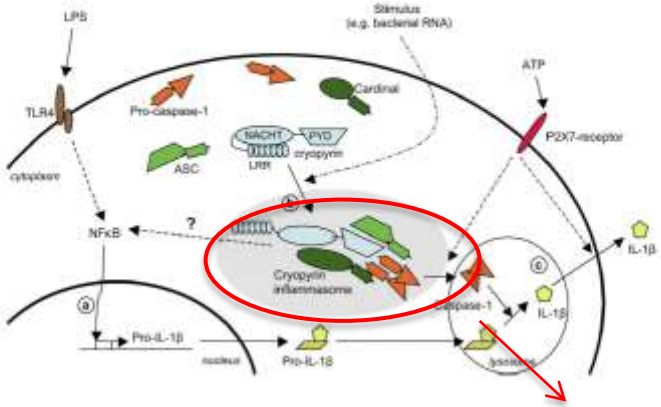
TERAPIA

Corticosteroidi
anti-TNF: *Etanercept* (Enbrel) artrite
anti-IL-1: *Anakinra* (Kineret), *Canakinumab* (Ilaris)

AD NLPR3 o CIAS-1 O CRIOPIRINA

CRIOPIRINOPATIE





IL-1

Chronic Inflammatory Neurological Cutaneous Articular

Esordio nei primi giorni di vita
(2/3 dei casi alla nascita,
1/3entro i 6 mesi)
Parto pretermine
Febbre intermittente
Sintomi infiammatori a carico di:
- ❑ SNC (meningite asettica)
- ❑ Organi di senso
  (cecità, sordità percettiva)
- ❑ Apparato osteoarticolare
  bozze frontali prominenti,
  ipoplasia mandibolare
  naso a sella
  macrocranio
  Dolore e tumefazione articolare
  (1 aa)
  Bassa statura

Familial Cold Autoinflammatory Syndrome (Fcas)

Esordio nei primi **mesi** di vita
Durata < 24h
Indotta da freddo
Parto pretermine
Febbre
Rash orticarioide non pruriginoso
Artromialgie
Congiuntivite
Assenti complicanze a lungo termine

Diagnosi Differenziale

Episodi orticarioidi scatenati dal freddo
- Manifestazioni cutanee localizzate nelle parti esposte al freddo
- Non associata a febbre né a rialzo indici flogosi
- Test al cubetto di ghiaccio positivo (negativo nella FCAS)

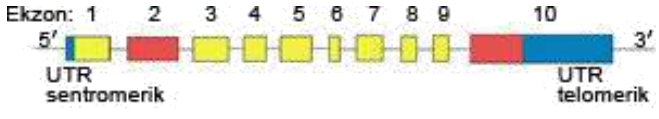
Muckle-Wells Syndrome (Mws)

Esordio nei primi **mesi** di vita
Indotta da freddo, stanchezza, stress
Febbre
Rash cutaneo
Artromialgie/artrite
Congiuntivite
Complicanze a lungo termine
Sordità neurosensoriale
Amiloidosi renale

TERAPIA

Evitare Freddo
CS
Anakinra
Canakinumab

Febbre Mediterranea Familiare (FMF)

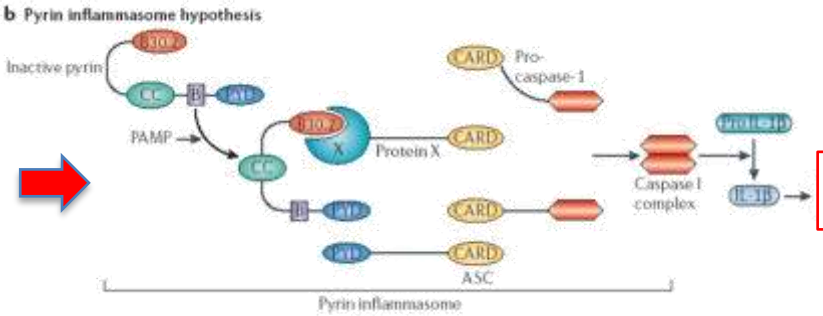


R42W	T267I	P369S	F479L	I591T	R761H	S675N
	E230K	R408Q			V726A	R653H
	E148Q				V704I	G678E
	E148V				M694V	E656A
	L110P				M694del	A744S
					I692del	M694I
					T681I	
					M680I (G/C)	
					M680I (G/A)	
					M680L	
					K695R	

AR

MEFV
pirina "Marenostrina"

(>100 mutazioni)



Fever
Inflammation

CARATTERISTICHE CLINICHE

25-60% <10aa

64-95% <20aa

Durata 1-3giorni

Dolori addominali 95%

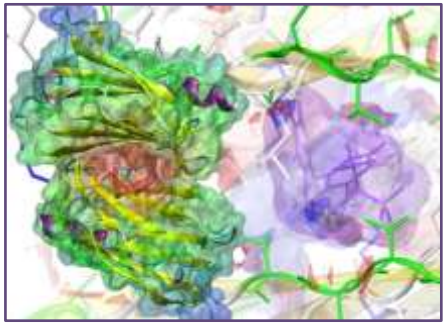
Dolore toracico 33-53%

Oligoartrite e/o monoartrite asimmetrica

Eritema erisipela-like delle estremità degli arti inferiori

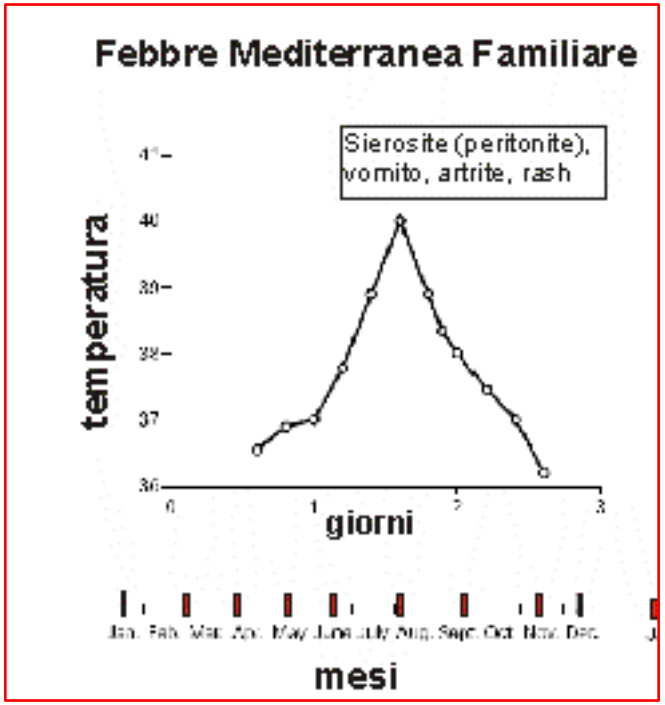
Mialgie, splenomegalia, cefalea (15%)

Spiccata Neutrofilia
Aumento della VES

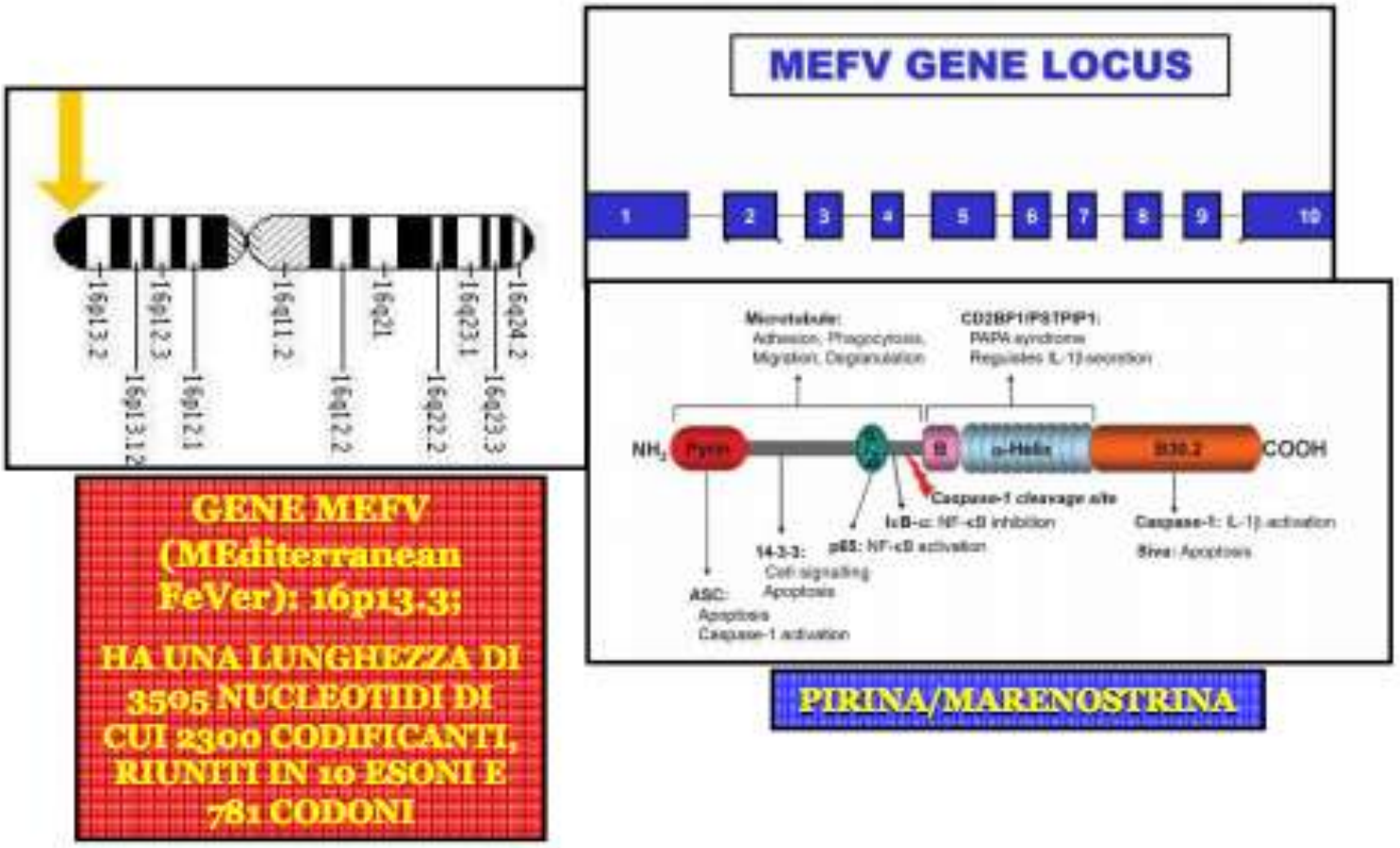


AMILOIDE

Proteinuria
IRC
<1% all'esordio FMF



FEBBRE MEDITERRANEA FAMILIARE: PECULIARITA' GENETICHE

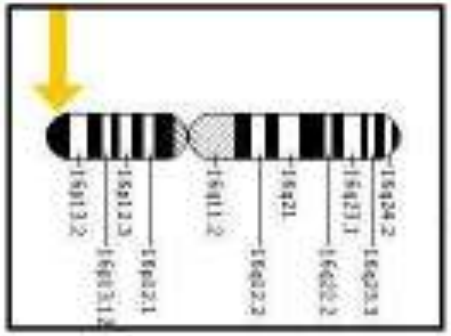


GENE MEFV (MEditerranean FeVer): 16p13.3;

HA UNA LUNGHEZZA DI 3505 NUCLEOTIDI DI CUI 2300 CODIFICANTI, RIUNITI IN 10 ESONI E 781 CODONI

Levon Yepiskoposyan et al. Population genetics of familial Mediterranean fever: a review. European Journal of Human Genetics (2007)

FEBBRE MEDITERRANEA FAMILIARE: PECULIARITA' GENETICHE



OLTRE 40 MUTAZIONI NOTE:

LE PIÙ FREQUENTI A CARICO DEGLI ESONI 10, 2, 3 E 5.

MUTAZIONI RARE DESCRITTE NEGLI ESONI 1, 7 E 9

La maggior parte delle mutazioni note sono sostituzioni aminoacidiche, 78 sono mutazioni missenso, una sola mutazione nonsense (Y688X), 2 sono piccole delezioni (I692del, M694del), 17 sono localizzate negli introni, una è una duplicazione e 2 sono inserzioni.

REGISTRO INFEVERS → http://fmf.igh.cnrs.fr/ISSAID/Infevers/

Isabelle Touitou, European Journal of Human Genetics, 2001

FLOW-CHART PER I PAZIENTI CON FEBBRE PERIODICA

a) Escludi le principali cause di febbre periodica in età pediatrica (vedi tabella II)

↓

b) Escludi le malattie associate a NALP { Sensibilità al freddo? / Rash urticarioide? / Sordità neurosensoriale? } → Valuta test genetico per *NALP3* o *NALP12*

↓

c) Paziente con febbre periodica su base infiammatoria

↓

Score Diagnostico (www.printo.it/periodicfever)

Alto rischio (> 15%)

↓

Esegui test genetico:

↓

- Se etnia & criteri FMF positivi e/o febbre ≤ 2 giorni → *MEFV*
- Se febbre >7 giorni → *TNFRSF1A*
- Se febbre dai 3 ai 6 giorni { Vomito e/o splenomegalia + → *MVK* / Vomito e/o splenomegalia - → *MEVF* }

Basso rischio (>15%)

↓

Follow-up (6-12 mesi)

↓

Persistenza (nuovi sintomi?) → *Esegui test genetico*

Risoluzione o miglioramento → Follow-up (6-12 mesi)

Aim

Since spontaneous inflammation is an important contributor to FMF, genetic variants mediating inflammation are of interest. We investigated gene variants in Mediterranean population and their association with susceptibility and severity of FMF.

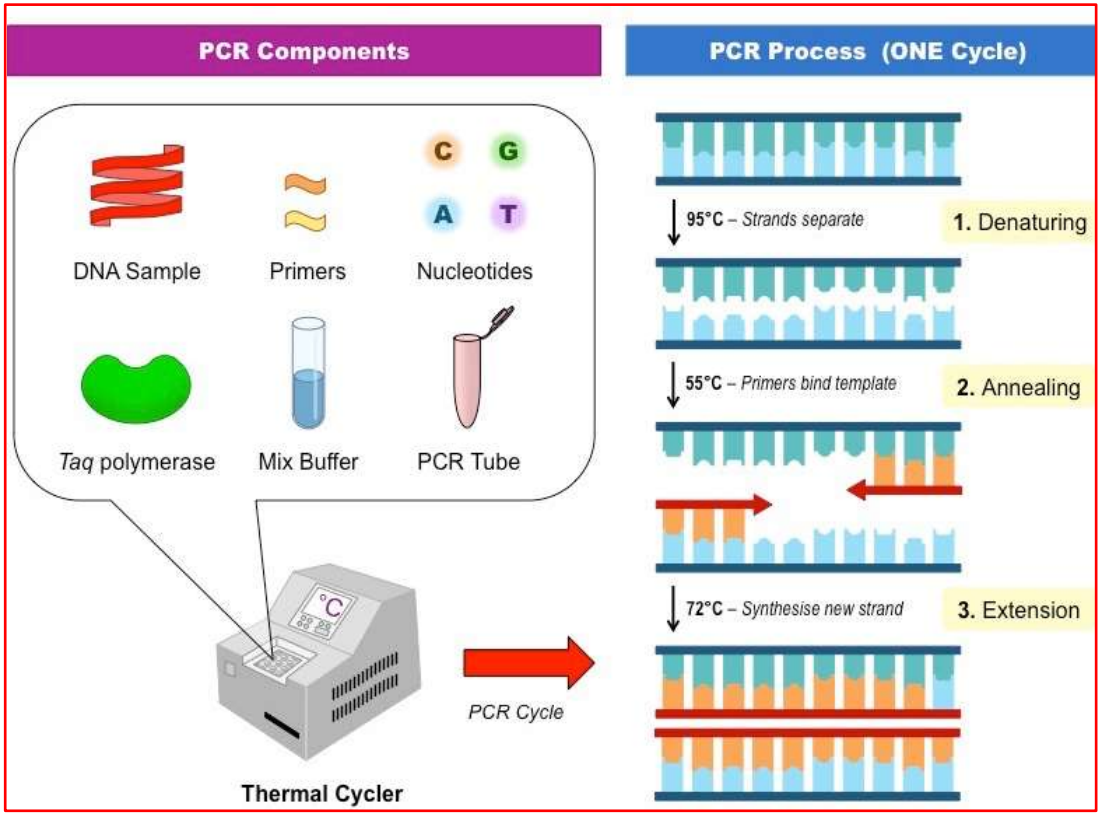
September 2013 and December 2015

Materials & Methods

56 pz. 12 a+/-2.34

M:F 32:24

Patients showing family history of FMF or renal failure or with positive medical history for fever, abdominal pain, arthritis, arthralgia, erysipelas-like erythema, pleurisy, headache, vomiting, diarrhea, constipation, myalgia, fatigue were enrolled in the study.



Results

Mutations	Genotypes	Patients N	Patients %
Heterozygous	Met694Val/wt Glu148Gln/wt Met680Ile/wt Ala744Ser/wt Pro369Ser/wt Met694Ile/wt	32	84.21
Compound Heterozygous	Met694Val/Met680Ile Glu148Gln/ Met680Ile	3	7.89
Homozygous	Met680Ile/Met680Ile Arg761His/Arg761His	3	7.89

Table 1. *Genotype distribution of patients*

Clinical findings	%
Fever	100
Abdominal Pain	18.4
Joint Pain	5.3
Erysipelas-like erythema	5.3
Leoucocytosis	3.3
Thoracic pain	0

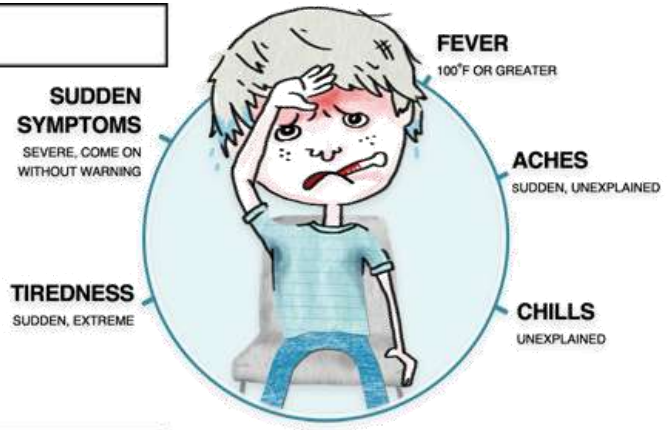


Table 2. *FMF characteristics of all patients*

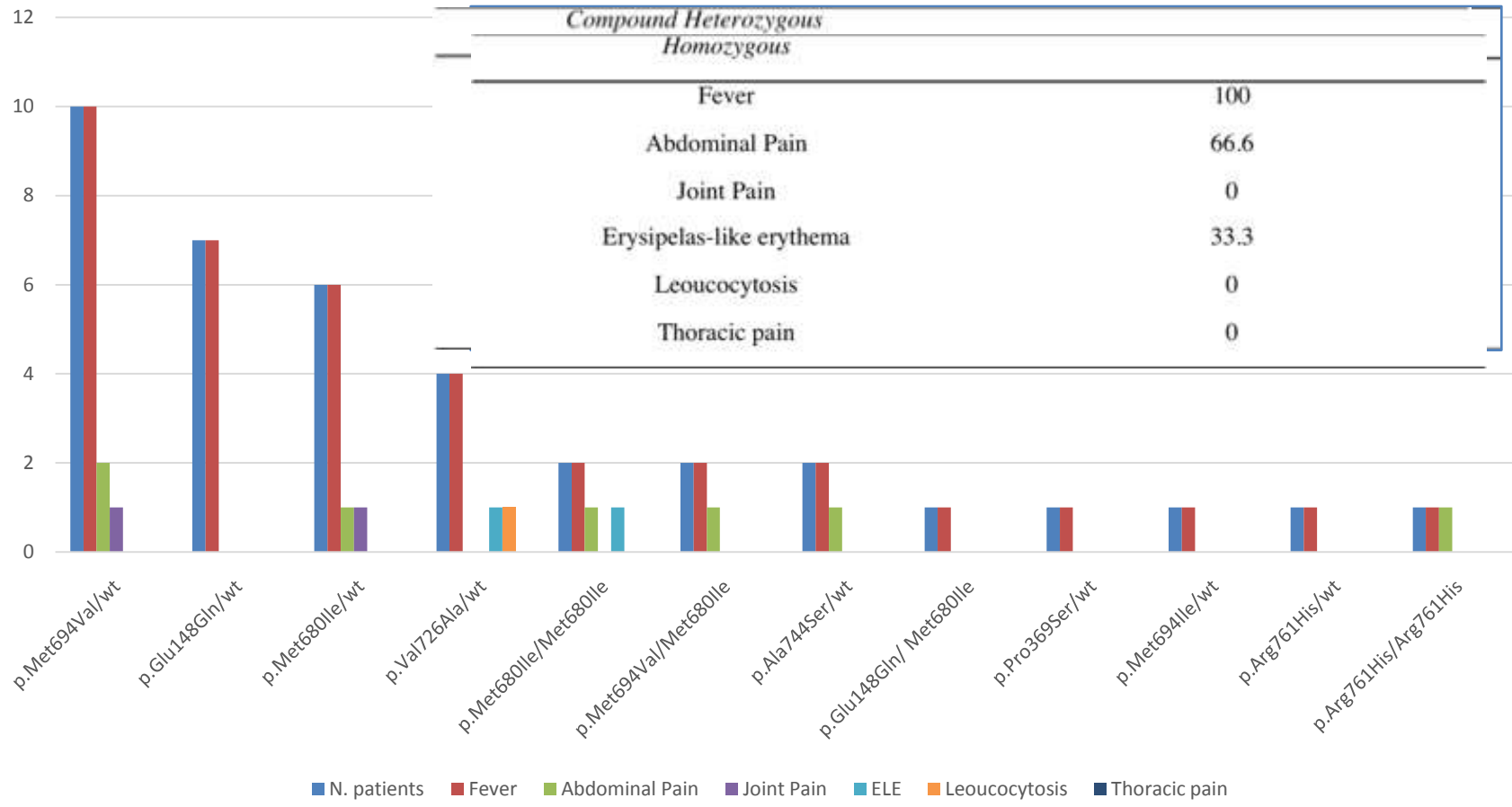
Results

Genotypes	%
p.Met694Val/wt	26.3
p.Glu148Gln/wt	18.4
p.Met680Ile/wt	15.8
p.Val726Ala/wt	10.5
p.Met680Ile/Met680Ile	5.3
p.Met694Val/Met680Ile	5.3
p.Ala744Ser/wt	5.3
p.Glu148Gln/ Met680Ile	3.3
p.Pro369Ser/wt	3.3
p.Met694Ile/wt	3.3
p.Arg761His/wt	3.3
p.Arg761His/Arg761His	3.3

Table 3. *Frequencies of the mutations.*

Results

Genotype–phenotype correlation



Compound Heterozygous Homozygous	
Fever	100
Abdominal Pain	66.6
Joint Pain	0
Erysipelas-like erythema	33.3
Leoucocytosis	0
Thoracic pain	0