

Familial Mediterranean Fever

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Familial Mediterranean Fever

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- Summary and Back to the Case.....

Clinical Case

- AA 32 y.o. female, post-doc U of T presents with fever, acute abdo and pleuritic pain
- PMHx:
 - FMF dx 21y.o. – multiple attacks
 - First attack age 5, multiple dx JRA
 - Attacks: fever, chest pain, abdo pain, arthritis knees, occasional rash lasting 3 days
 - Rx: colchicine 0.6 mg BID (1.2mg), developed pancytopenia Oct/01
 - Multiple attacks every 40 days since Jan 2001, 6 requiring hospitalizations

Clinical Case

- PMHx
 - FMF:
 - Hepatosplenomegaly Oct/01
 - Liver biopsy: Dec/01: negative for amyloidosis
 - Remicade Jan/02
 - Hypothyroidism: Grave's disease 1997, rx radioactive iodine
 - Cholecystectomy: ?December 2000
 - Depression: suicidal ideation May 2001
 - ?Asthma

Clinical Case

- Meds

- L-thyroxine
- Serzone
- OCP
- Tylenol #3

- FHx

- Mother, brother, sister: FMF
- Palestinian descent, born and raised in Winnipeg

Clinical Case

- Case

- Developed abdo pain (nausea/vomiting), fever, chest pain
- Arthralgias in knees
- Lab investigations: normal CBC, normal u/a, normal ECG, AXR/CXR normal
- Rx: iv fluids, gravol, PCA
- Full septic w/u normal
- Trigger? Menses

Introduction

- Historical perspective
 - 1945 Dr. Siegal reported 5 cases “recurrent paroxysms of severe abdo pain with fever... all in men and all starting in early life”
 - Early 1960’s Prof Heller autosomal recessive d/o, amyloidosis part of disease, named it familial Mediterranean fever
 - 1972 Goldfinger discovered decrease febrile abdo pain and arthralgia serendipously treated ‘gout’ with colchicine

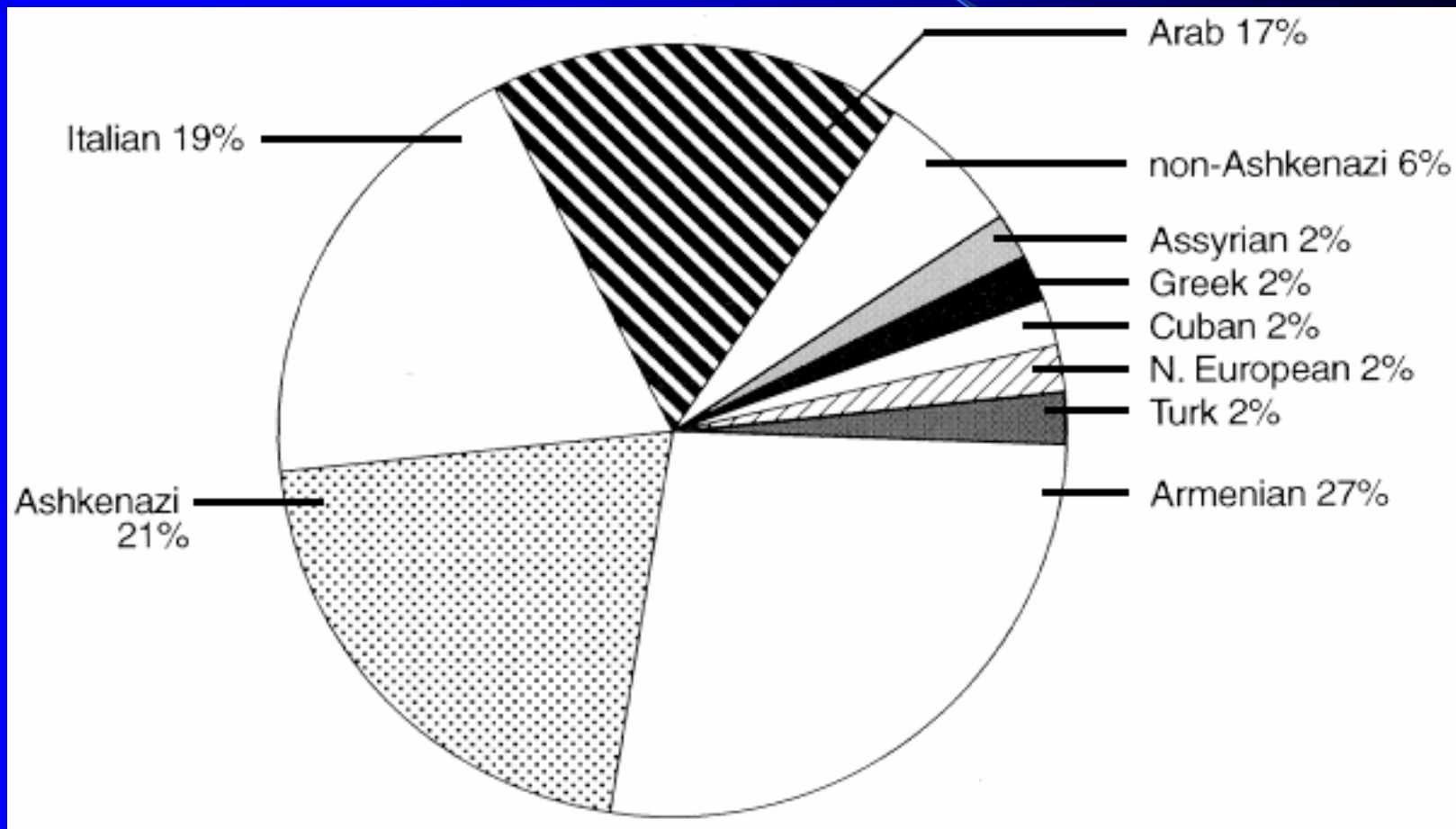
Introduction

- Historical perspectives cont'd
 - 1997 NIH and French consortium identified gene Chromosome 16p, 8 missense mutations:
 - gene: encoded pyrin/marenostrin

Familial Mediterranean Fever

- Recurrent polyserositis, periodic disease
- Recurrent attacks fever and peritonitis, pleuritis, arthritis, or erysipelas-like skin disease
- Male: female – 1.5-2:1
- Carrier frequency – 1:6 African Jews; 1:7 Armenians
- Populations affected: Jews, Armenians, Turks and Arabs
- North American populations:

Familial Mediterranean Fever



Familial Mediterranean Fever

- High gene frequency: genetic drift, founder effect and heterozygote advantage
- >90% Jews: Sephardic and not Ashkenazi
- Israel: 5000 pts; 1:500 prevalence
- 10,000 patients worldwide
- Isolation of gene and genetic mutations: geneology and migration of peoples

Familial Mediterranean Fever

- Hallmark: inflammatory reaction affecting serosal tissues: pleura, peritoneum, synovium
- Chemotactic activity PMNs with massive influx granulocytes (neutrophils)
- Triggers: physical and emotional stress, menstruation, high-fat diet

Clinical Presentation

- Symptoms: first decade of life, only 5% develop disease after age 30
- Typical attack: fever and serositis from 1-4 days
- Frequency of attacks vary weekly to 1:3-4 weeks
- Severity and frequency decreases pt gets older

Clinical Presentation

- Fever

- Occurs every attack; Temp 38-40°C
- Rigors may precede fever
- Duration 12h and 3 days

- Peritonitis

- Abdominal pain 95% patients – ‘acute peritonitis’
- Constipation
- Pain usu precedes fever by few hours, persist 1-2 days after defervescence
- 30-40% will undergo exploratory laparotomy, mimics acute abdomen; appendicitis, cholecystitis, PID

Clinical Presentation

- Pleuritis

- 25-80% patients
- Transient effusion: not common
- Simultaneous occurrence with pericarditis

- Pericarditis

- 0.5% patients
- Few cases constrictive pericarditis

Clinical Presentation

● Arthritis

– Common feature: North African Jews

● Asymmetrical, non-destructive arthritis (75%)

- Short duration, abrupt onset, 1-2 joints large effusions, knees, ankles and wrists

● Chronic, destructive arthritis, including sacroiliitis (2-5%)

- Hips and knees
- Damage result from protracted attack or repeated short attacks
- Sacroiliitis rare (0.4%), HLA-B27 –ve

● Migratory Polyarthritis, resembles acute rheumatic fever

- Same age, misdiagnosis

Clinical Presentation

- Erysipelas-like skin lesions
 - 7-40%
 - Extensor surfaces leg, ankle joint or dorsum, commonly unilateral
 - Spontaneous resolution 2-3 days
- Myalgia
 - Arms and legs +/- arthritis
 - May last more than 3 weeks
- Other organs
 - CNS, meninges: Mollaret's meningitis
 - Splenomegaly (30-50% patients)
 - Acute orchitis with scrotal edema and pain

Clinical Presentation

- Amyloidosis

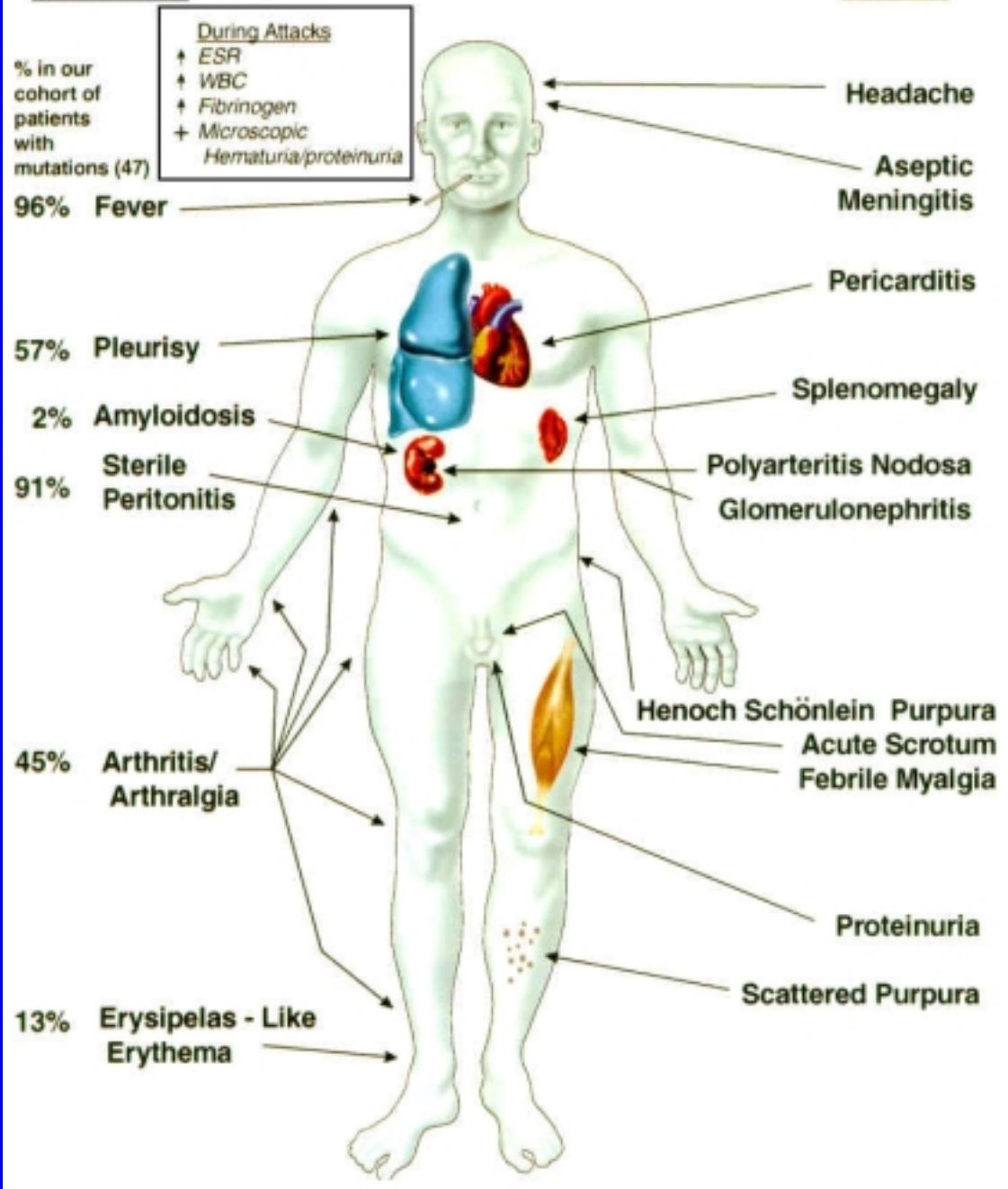
- Significant complications – usu affecting kidneys: ESRD
- May also affect GI, liver, spleen, heart and testes
- AA type – secondary amyloidosis
- “Phenotype II” – amyloidosis without presentation of attacks of serositis
- More frequent among north African Jews and Turks
- When present, develops before age 40

Clinical Presentation

- Laboratory Investigations
 - Elevated ESR
 - Leukocytosis
 - Increase acute phase reactants: CRP, fibrinogen, serum amyloid A
 - Microscopic hematuria/proteinuria

CARDINAL

OTHER



Major Criteria

Typical attacks (≥ 3 of the same type, rectal temp. $\geq 38^\circ\text{C}$, attacks lasting 12 hr to 3 d):

1. Peritonitis
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone

Minor Criteria

1–3. Incomplete attacks (typical attacks with 1 or 2 of the following exceptions: 1) temperature $< 38^\circ\text{C}$, 2) attacks lasting 6–12 hours or 3–7 days, 3) no signs of peritonitis during abdominal attacks, 4) localized abdominal pain, 5) arthritis in joints other than hip, knee, or ankle) involving 1 or more of the following sites:

1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
5. Favorable response to colchicine

Supportive criteria

1. Family history of FMF
2. Appropriate ethnic origin
3. Age < 20 yr at disease onset
- 4–7. Features of attacks
 4. Severe, requiring bed rest
 5. Spontaneous remission
 6. Symptom-free interval
 7. Transient inflammatory response, with 1 or more abnormal test result(s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
8. Episodic proteinuria/hematuria
9. Unproductive laparotomy or removal of white appendix
10. Consanguinity of parents

*An FMF diagnosis requires ≥ 1 major criteria, or ≥ 2 minor criteria, or 1 minor criterion plus ≥ 5 supportive criteria, or 1 minor criterion plus ≥ 4 of the first 5 supportive criteria.

Clinical Presentation

Duration of attacks

> 72 hours:	3 points
24–72 hours:	2 points
≤ 24 hours:	1 point

Frequency of attacks

> 2 per month:	3 points
1–2 per month:	2 points
< 1 per month:	1 point

Response to colchicine

None:	3 points
Partial:	2 points
Complete:	1 point

Mild disease = 3–4 points

Moderate disease = 5–6 points

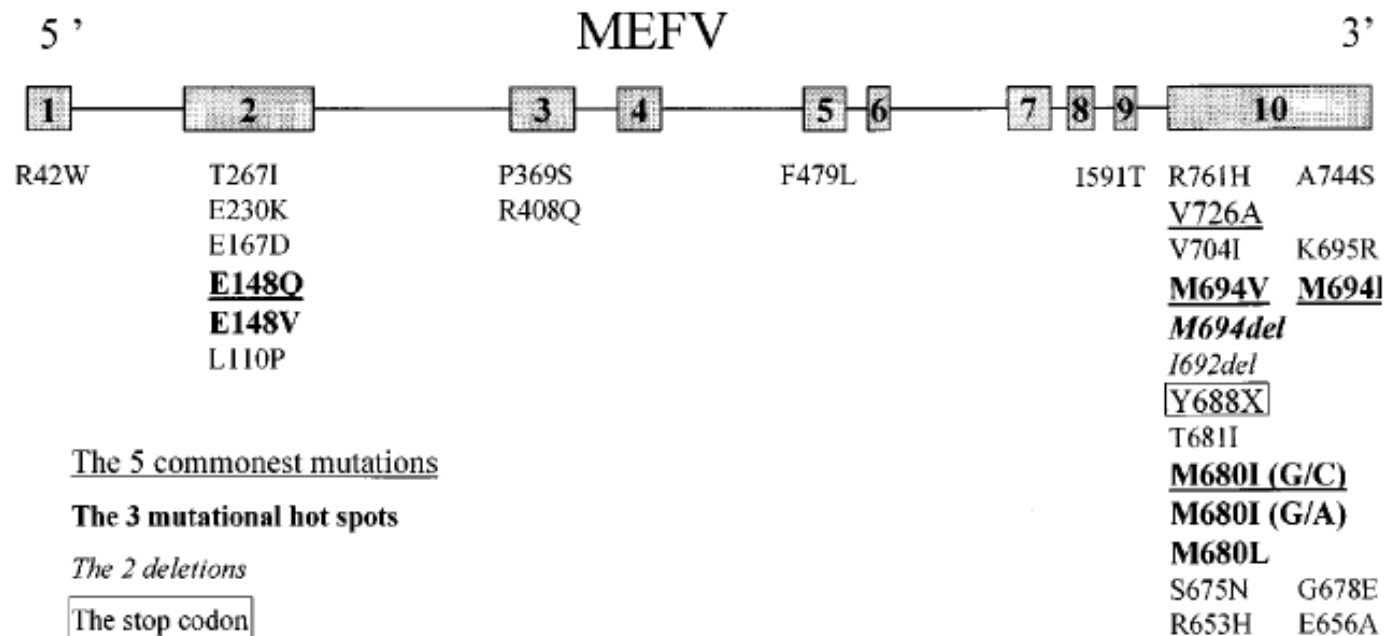
Severe disease = 7–9 points

Genetics

- Positional cloning: *M*editerranean *F*e*V*er gene (MEFV) was identified 16p13.3
- Gene: 10-exon, 3505 nucleotide cDNA encoding a predicted protein 781 aa
- 4 missense mutations identified
 - M694V, V726A, M680I, M694I
- 29 disease-associated mutations have now been identified
- Speculation to genealogy: different ethnic groups share mutations: ?common ancestors

Genetics

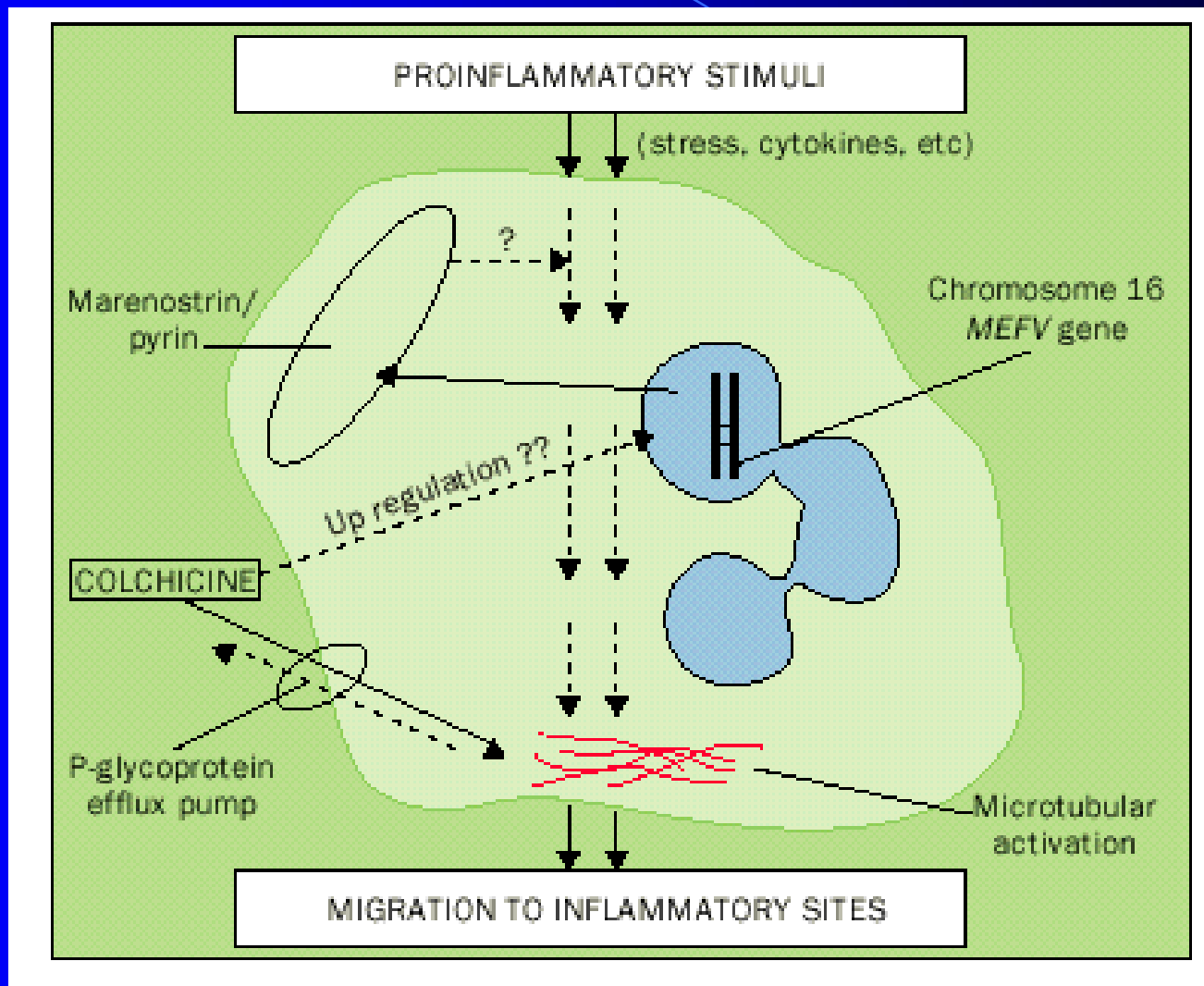
The spectrum of MEFV mutations

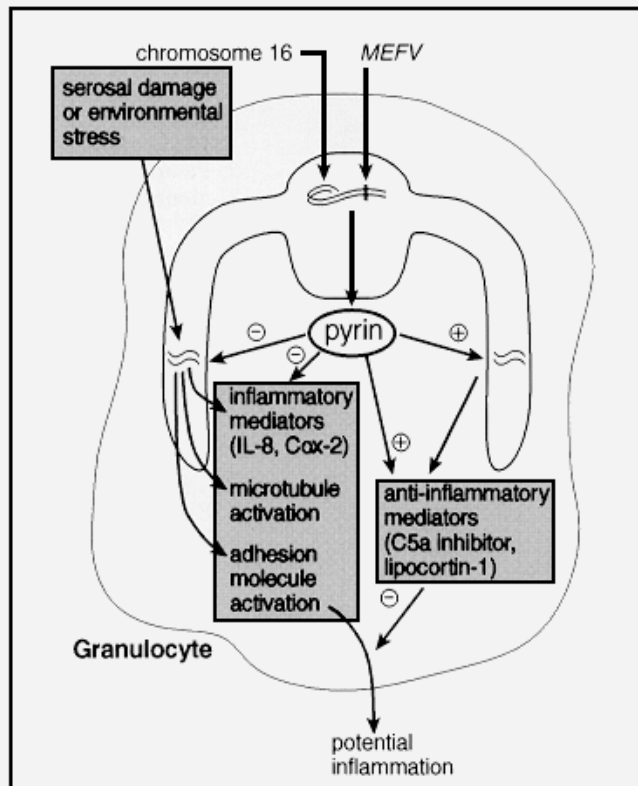


Pyrin

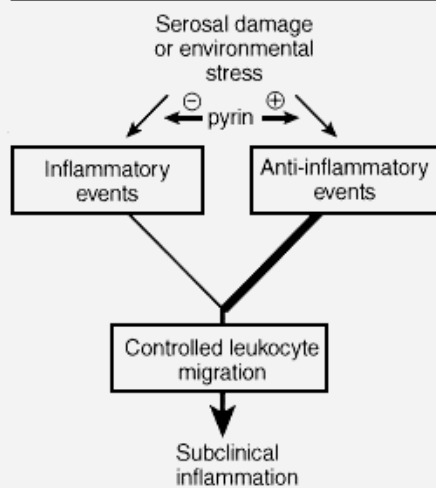
- 781 aa predicts positively charged protein:
 - PYRIN/MARENOSTRIN
 - Expression: almost exclusively present in neutrophils and their precursors
 - Function: direct or indirect downregulator of inflammation, specifically in neutrophils
 - ?Transcription factor
 - -?cytoplasm of mature neutrophils and monocytes - ?regulates neutrophil-mediated inflammation

Pathophysiology

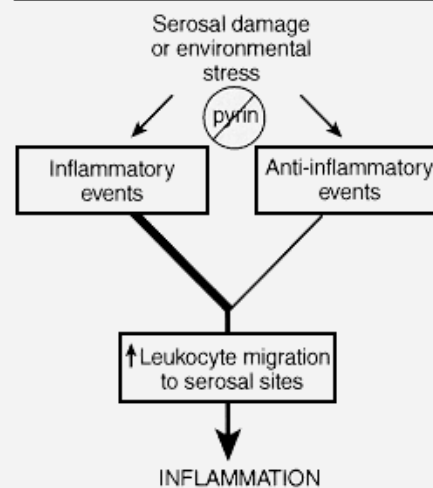




Wild type and Carriers



FMF Patients



Genotype/Phenotype

- High frequency of M694V mutation in North African Jewish population: tend to have more severe disease and higher risk of amyloidosis
- Iraqi Jewish and Arab Druze populations: less severe FMF: V726A mutation
- No significant mutation-specific differences

Treatment

- Colchicine
 - Oral: 1-2 mg/day
 - Prevention of amyloidosis
- IFN-alpha
 - Adjuvant therapy for acute flares and
 - Colchicine-resistant patients
- TNF-alpha blockers
- Supportive therapy: analgesia, hydration

Future Directions

- Identifying new mutations
- Crystal structure of protein
- Understanding function of protein
- Treatment options
 - Autoimmune mechanisms of disease
 - Polyclonal increase in serum immunoglobulins
 - In vitro: induction of IL-1 and TNF-alpha
 - Low level of INHIBITOR for IL-8 and Chemotactic factor C5a

FMF-like Diseases

- **Hibernian fever:** Irish patients, TNF-receptor associated periodic syndrome (TRAPS), conjunctivitis, localized myalgia
- **HyperIgD:** recessive inheritance, week-long fevers, abdo pain, lymphadenopathy, skin eruptions, and/or symmetrical oligoarticular arthritis, high WBC, high IgD levels

Summary

- Recessively inherited disease of episodic fever with combination of severe abdo pain, pleurisy, arthritis, characteristic ankle rash
- Flares last for up to 3 days, followed by asymptomatic periods
- Treatment with colchicine
- Complication: development of amyloidosis
- FMF gene 16p, expression limited to granulocytes

Back to the Case...

- What other treatments?
 - Remicade
 - Etanercept
 - Restart Colchicine?
- Genetic testing at NIH Feb/02