Familial Mediterranean fever

(FMF)

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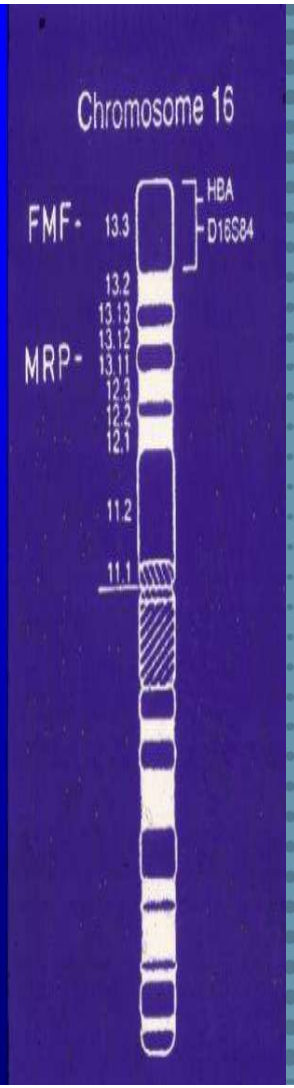
Genetics and Pathogenesis

- Familial Mediterranean fever (FMF) is the most common **monogenic autoinflammatory disease** characterized by recurrent **bouts of fever** and **serosal inflammation**.
- Resulting from mutations in **MEFV**, which encodes the protein **pyrin**. plays an important role in the **innate immune system** ,including
  - granulocytes,
  - cytokine–activated monocytes,
  - dendritic cells,
  - and serosal and synovial fibroblasts which constitutes a primary defense against external pathogens and other noxious agents

In 1992 the FMF gene was located to the short arm of chromosome 16.

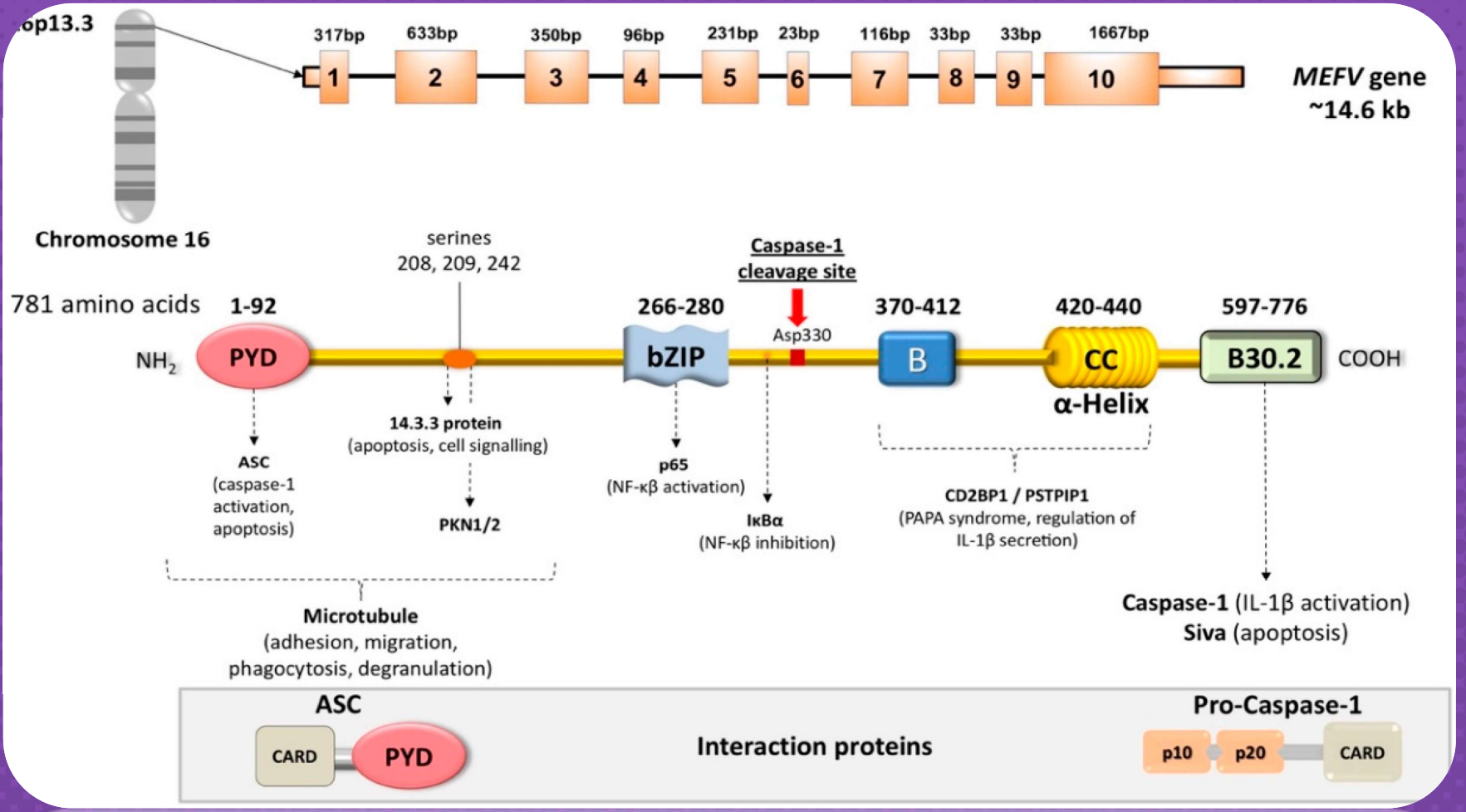
E Pras et al. NEJM

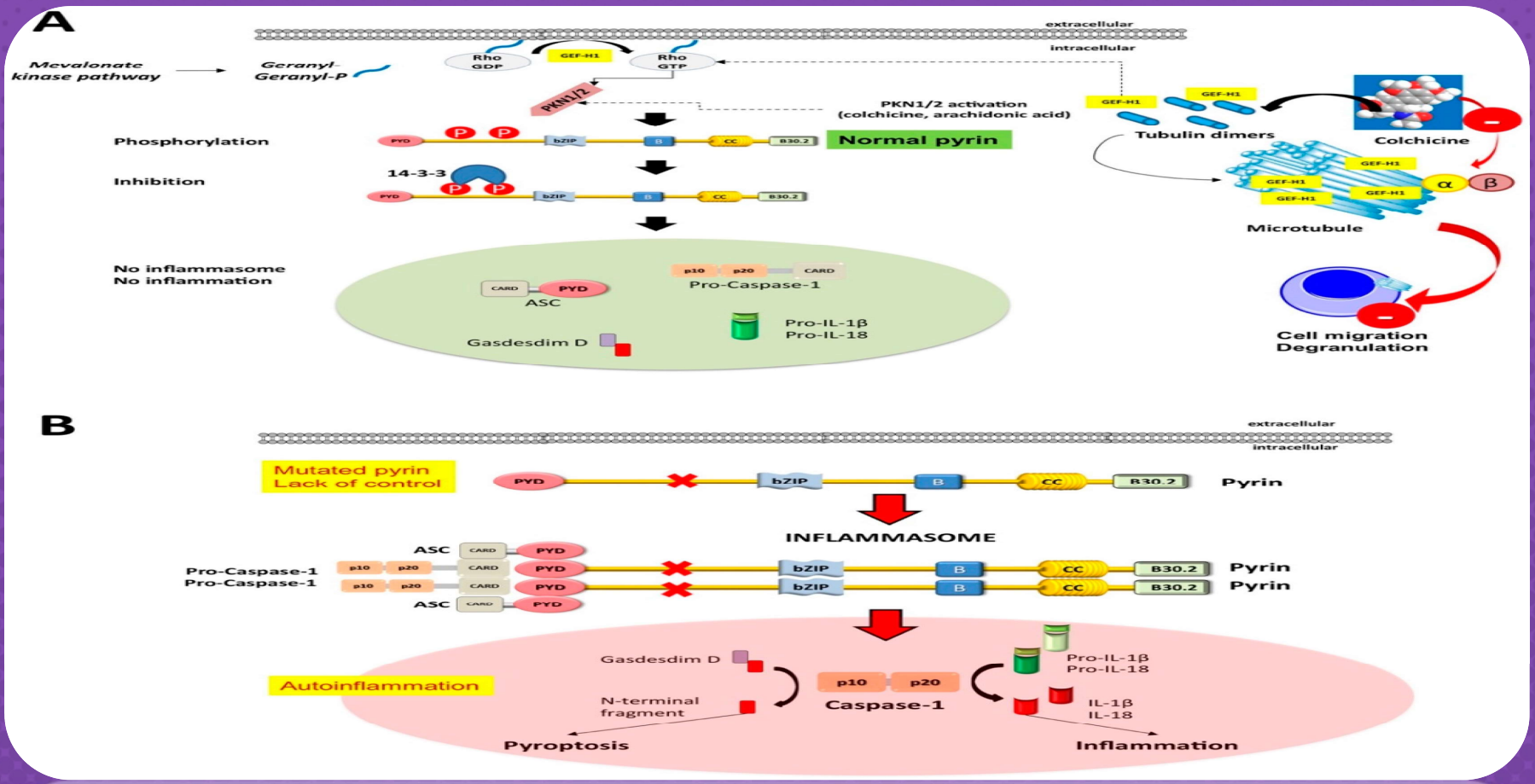


Pathogenic mutations in the MEFV gene cause

Gain of function of

pyrin protein


6p13.3
317bp
633bp
350bp
96bp
231bp
23bp
116bp
33bp
33bp
1667bp
1
2
3
4
5
6
7
8
9
10
MEFV gene
~14.6 kb
Chromosome 16
serines
208, 209, 242
Caspase-1
cleavage site
781 amino acids
1-92
266-280
Asp330
370-412
420-440
597-776
NH2
PYD
bZIP
B
CC
B30.2
COOH
α-Helix
14.3.3 protein
(apoptosis, cell signalling)
ASC
(caspase-1
activation,
apoptosis)
PKN1/2
p65
(NF-κβ activation)
IκBα
(NF-κβ inhibition)
CD2BP1 / PSTPIP1
(PAPA syndrome, regulation of
IL-1β secretion)
Microtubule
(adhesion, migration,
phagocytosis, degranulation)
Caspase-1 (IL-1β activation)
Siva (apoptosis)
ASC
CARD
PYD
Interaction proteins
Pro-Caspase-1
p10
p20
CARD


A
extracellular
intracellular
Mevalonate kinase pathway
Geranyl-Geranyl-P
Rho GDP
GEF-H1
Rho GTP
PKN1/2
PKN1/2 activation (colchicine, arachidonic acid)
Phosphorylation
Normal pyrin
Inhibition
14-3-3
PYD
bZIP
B
CC
B30.2
Tubulin dimers
Colchicine
Microtubule
α
β
No inflammasome
No inflammation
ASC
CARD
Pro-Caspase-1
p10
p20
Pro-IL-1β
Pro-IL-18
Gasdesdim D
Cell migration
Degranulation
B
Mutated pyrin
Lack of control
Pyrin
INFLAMMASOME
Pro-Caspase-1
Autoinflammation
N-terminal fragment
Caspase-1
IL-1β
IL-18
Pyroptosis
Inflammation

Genetics and Pathogenesis

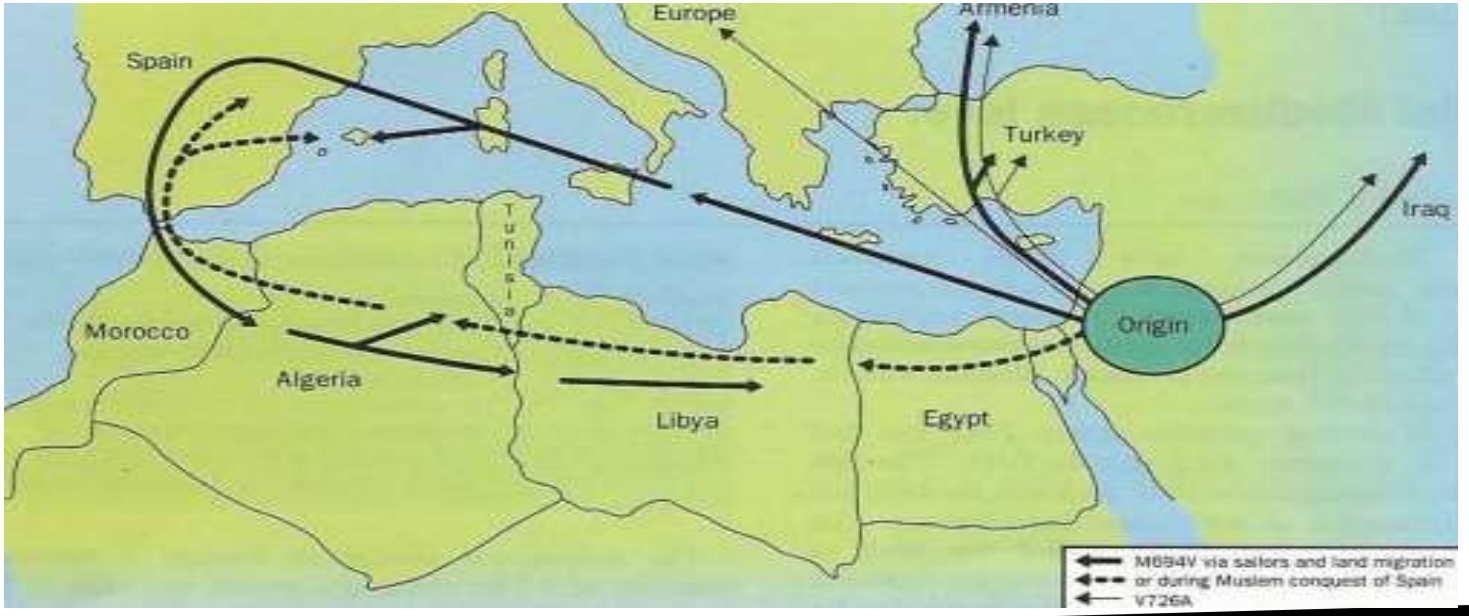
- FMF was initially thought to be an autosomal-recessive disease resulting from loss-of-function mutations in pyrin
- Several clues from human studies and mouse models began to cast doubt on the loss-of function hypothesis.
- Approximately one-third of people with clinical FMF have only one identified mutation in *MEFV,* despite extensive searches for a second mutation
- In addition, some asymptomatic carriers of *MEFV* mutations have evidence of inflammation with elevated acute phase reactants.

Genetics and Pathogenesis

- Furthermore, no null mutations in *MEFV* have been identified in people with FMF.
- Analysis of mous models also supports the concept that FMF-associated mutations are gain-of-function with a gene-dosage effect In humans.
- a singl mutation may result either in subclinical biochemical inflammation or overt FMF.
- whereas the carriage of two mutations is more likely to be clinically significant

Epidemiology

- FMF occurs most frequently among Sephardi and Ashkenazi Jewish, Arab, Armenian, Italian, and Turkish populations, with carrier frequencies as high as 1:3 to 1:5 in population-based surveys

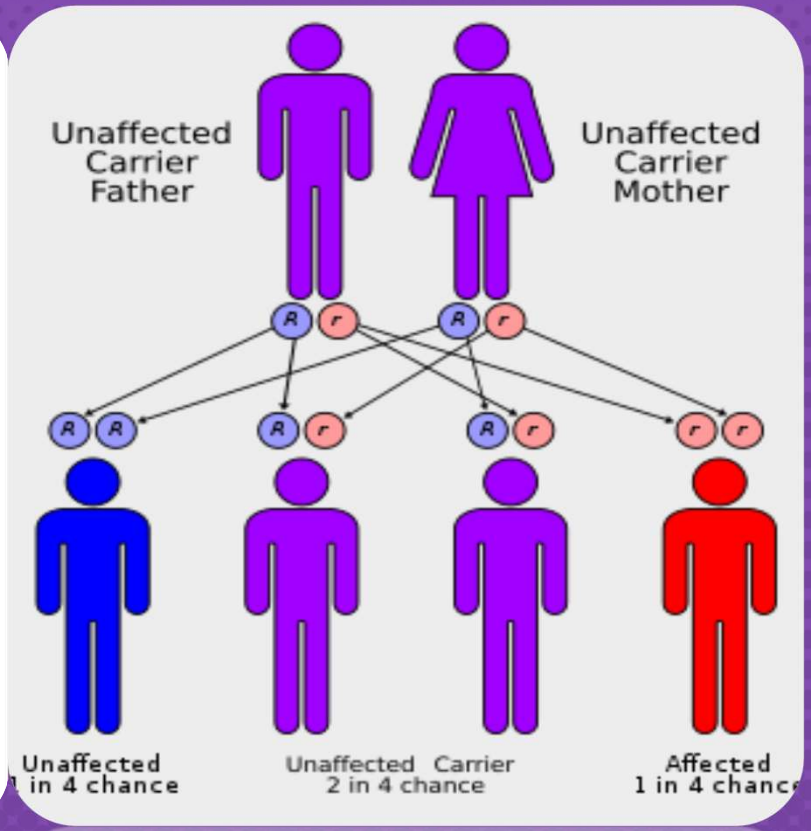


Epidemiology

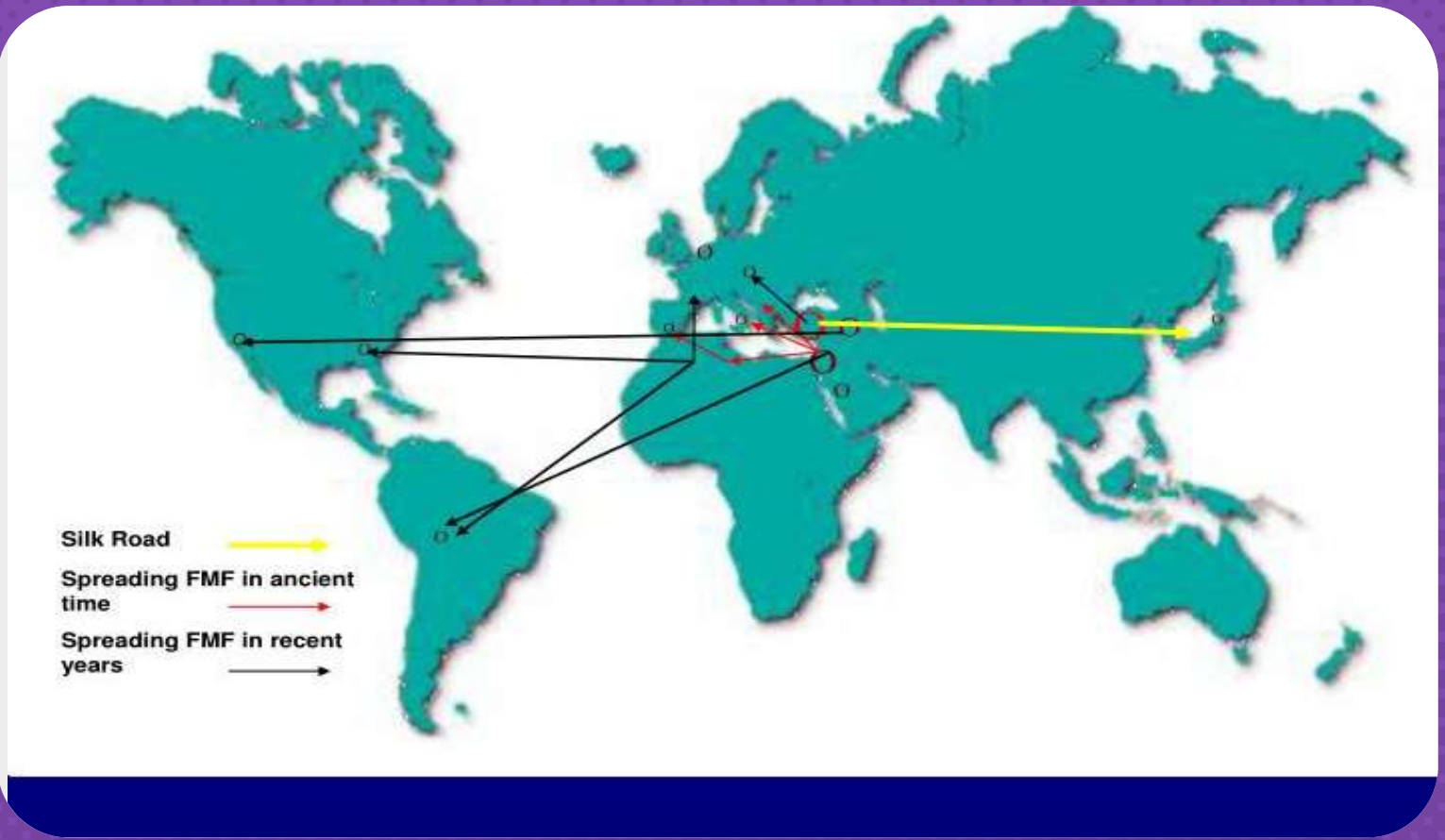
PATTERN OF INHERITANCE

- Autosomal recessive trait

- FMF is most prevalent in individuals of:
  - Sephardic Jewish (1 in 6 – 8)
  - Armenian (1 in 7)
  - Ashkenazi (1 in 12)
  - Turkish
  - Arab descent



Epidemiology



Clinical Manifestations

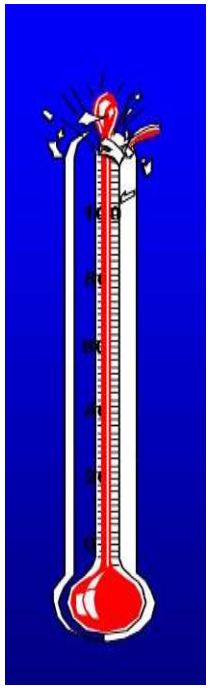
- Consists of inflammation involving the **peritoneum**, **pleura**, **joints**, or **skin**, sometimes **in combination**.
- The first clinical episode usually occurs **during childhood or adolescence** (with 90% of patients having had onset **by age 20 years old**).
- FMF attacks last between 12 and 72 hours.
- Between episodes, patients usually feel completely well and remain so for a few days to a few months

Clinical Manifestations

- In children, **fever may be the only sign** of FMF, although other symptoms generally develop progressively with time
- The attacks **vary** not only between patients but also between episodes in a given affected individual
- The **exact mechanism** of triggering periodic attacks in FMF is **unclear**, with patients often noting menstruation or stress associated with the onset of an attack

Recurrent fever

- one of the most constant characteristics of FMF and is present **in almost all cases** during attacks
- In the majority of FMF patients, the temperature rises from 38° to 40°C. although **mild attacks** may be accompanied by a subfebrile temperature (37.5° to 38°C).
- Typically, the duration of the fever is brief, **lasting between 12 hours and three days**
- Fever may be the first and only symptom of FMF, especially in **toddlers**

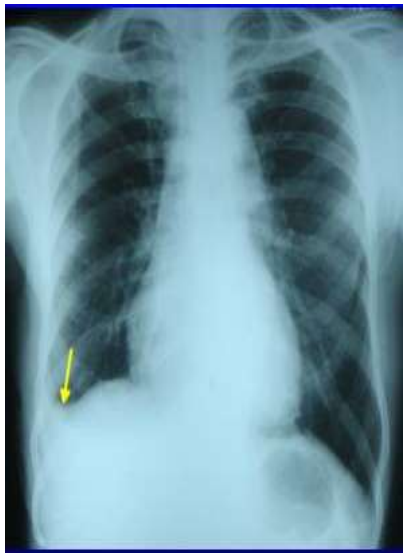


Abdominal symptoms

- Often accompany the fever and range from mild discomfort and distention to severe pain with rigidity.
- **Constipation** is more common than **diarrhea**, and in extreme cases, peristalsis may cease and result in paralytic ileus
- Pain can be generalized or focused in a quadrant, sometimes mimicking acute appendicitis.
- Since the **cause** of the abdominal pain is **inflammation of the peritoneum**, signs of peritonitis such as guarding, rebound tenderness, rigidity, and an adynamic ileus are often present

Pleural symptoms

- Chest pain may be due to **inflammation of the pleura** or **referred pain** from subdiaphragmatic inflammation
- Pleural inflammation typically manifests as **unilateral chest pain**, that is worse with inspiration or coughing
- Less commonly, a small effusion, friction rub, or atelectasis may be present
- Episodes usually **resolve within three days**, but may last up to one week with pleuritis.



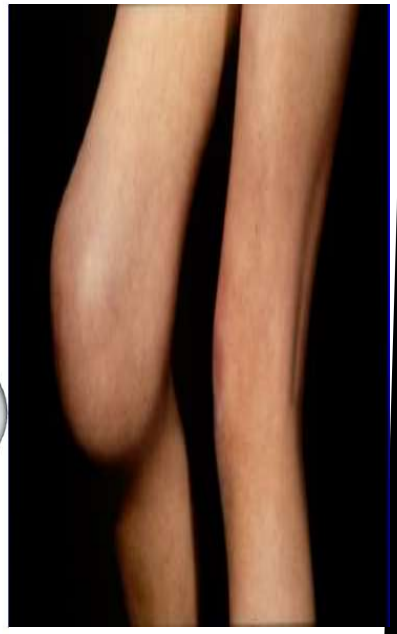
Joint manifestations

Are common and **are sometimes the first sign** of the disease in children

Arthralgia occurs more frequently than **arthritis**.

Arthritis in adults usually is **monoarticular**, although children may have involvement of several joints, symmetrically or asymmetrically. with pain and large effusions.

Synovial aspirates from joints are **sterile** but may demonstrate leukocyte counts as high as 100,000/ mm3.



Muscular symptoms

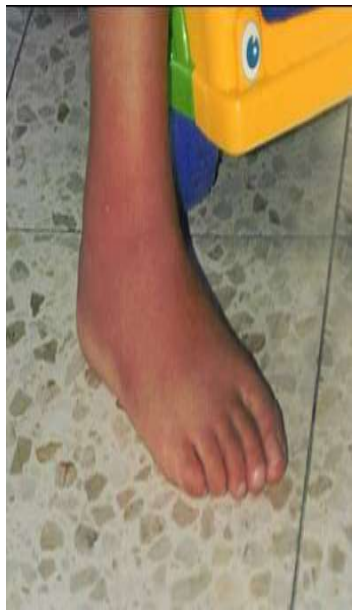
- Muscle pain is a classical manifestation of FMF and occurs **in about 20% of patients.**
- Usually the pain is **not severe**, appears in the **lower extremities** after physical exertion (mostly in the evenings), lasts from a few hours to 2 or 3 days,and subsides with rest
- Treatment with nonsteroidal antiinflammatory drugs (NSAIDs) may be needed

Muscular symptoms

- Protracted febrile myalgia is an uncommon dramatic manifestation of FMF
- requires treatment with corticosteroids.
- It is important to differentiate colchicine–induced myopathy, a rare side effect, from an attack of prolonged febrile myalgia, an even rarer disease manifestation.
- Fever, high erythrocyte sedimentation rate (ESR), normal creatine
- kinase (CK) levels, and the evidence of inflammatory myopathy on electromyogram (EMG)
- rule out colchicine as a likely causative factor

Cutaneous findings

- Are less common than serosal or synovial involvement (reported in **12 to 40 percent** of FMF patients
- Most commonly, there is an erysipeloid erythematous rash on the **dorsum of the foot**, **ankle**, or **lower leg**
- The lesion is typically 10 to 35 cm2 in area, **tender**, **raised**, and **erythematous**
- The rash may occur **alone** or **in conjunction with other manifestations**
- Recovery is **spontaneous** and does not require antibiotics



Less common findings

- episodes of **unilateral acute scrotal pain** in prepubescent boys
- diverse cutaneous manifestations including **Henoch–Schönlein purpura** (IgA vasculitis)

- Rarely, **pericarditis** is observed
- Bechet disease, polyarteritis nodosa, microscopic polyarteritis, glomerulonephritis, and inflammatory bowel disease may occur more frequently in FMF patients than in the general population.

- The M694V mutation in MEFV is a known independent risk factor for **Bechet disease** and **ankylosing spondylitis**

Laboratory Investigations

- During attacks, concentrations of acute phase reactants such as **C-reactive protein** (CRP), **serum amyloid A** (SAA), and **complement** increase. **Leukocytosis** and an increased **ESR** are also commonly observed.
- **Serum homocysteine** and **lipoprotein(a)** concentrations are often increased in individuals with FMF during attack-free periods
- The continuous elevation of these acute phase serum proteins during and even between attacks predisposes to
- the development of AA systemic amyloidosis, the most serious sequela of FMF

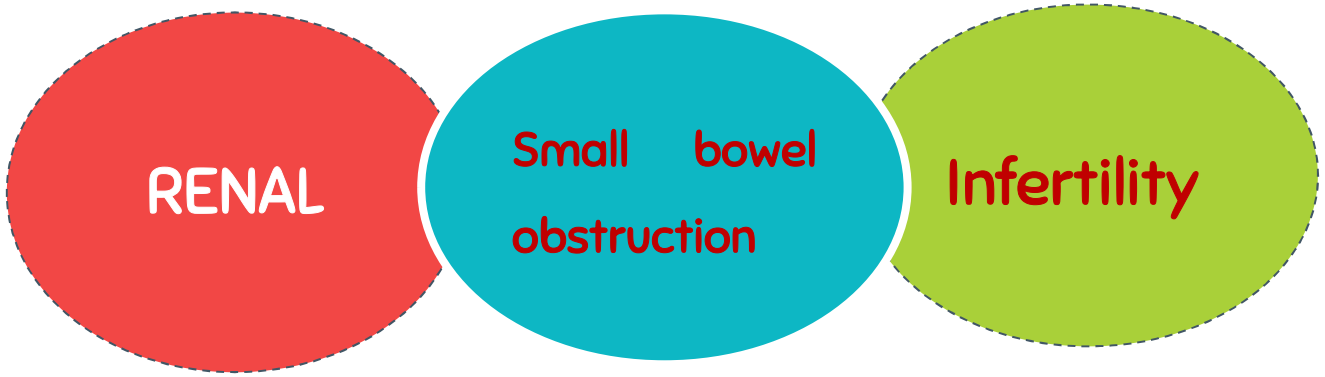
Most serious sequela of FMF

Systemic (AA) amyloidosis

Systemic (AA) amyloidosis

- SAA deposition occurs in **several organs**, including the gastrointestinal tract, spleen, kidneys, adrenals, thyroid, and lungs, but usually not the tongue, peripheral nerves, or heart
- The risk of amyloidosis increases with a *positive family history* of this complication…..
  - **male sex, the α/α genotype at the SAA1 locus**, and **poor compliance with colchicine therapy**.
  - **homozygosity for the M694V mutation** also predisposes patients to amyloidosis, to *arthritis,and to erysipeloid erythema*.
  - For reasons not clear, the **country of origin** influences the phenotype of FMF and is a key risk factor for amyloidosis in FMF, with a *decreased incidence* of amyloidosis in patients **living in the United State**

LONG-TERM COMPLICATIONS



LONG-TERM COMPLICATIONS

Renal

- An early indicator of impaired renal function is **microalbuminuria**, and periodic urinalyses are an important part of continuing care for FMF patients.
- After proteinuria occurs, amyloidosis can be **confirmed by biopsy of the kidney or rectum.**
- Although kidney biopsy is more sensitive, abdominal fat pad or rectal biopsy are preferred because they are safer and less invasive

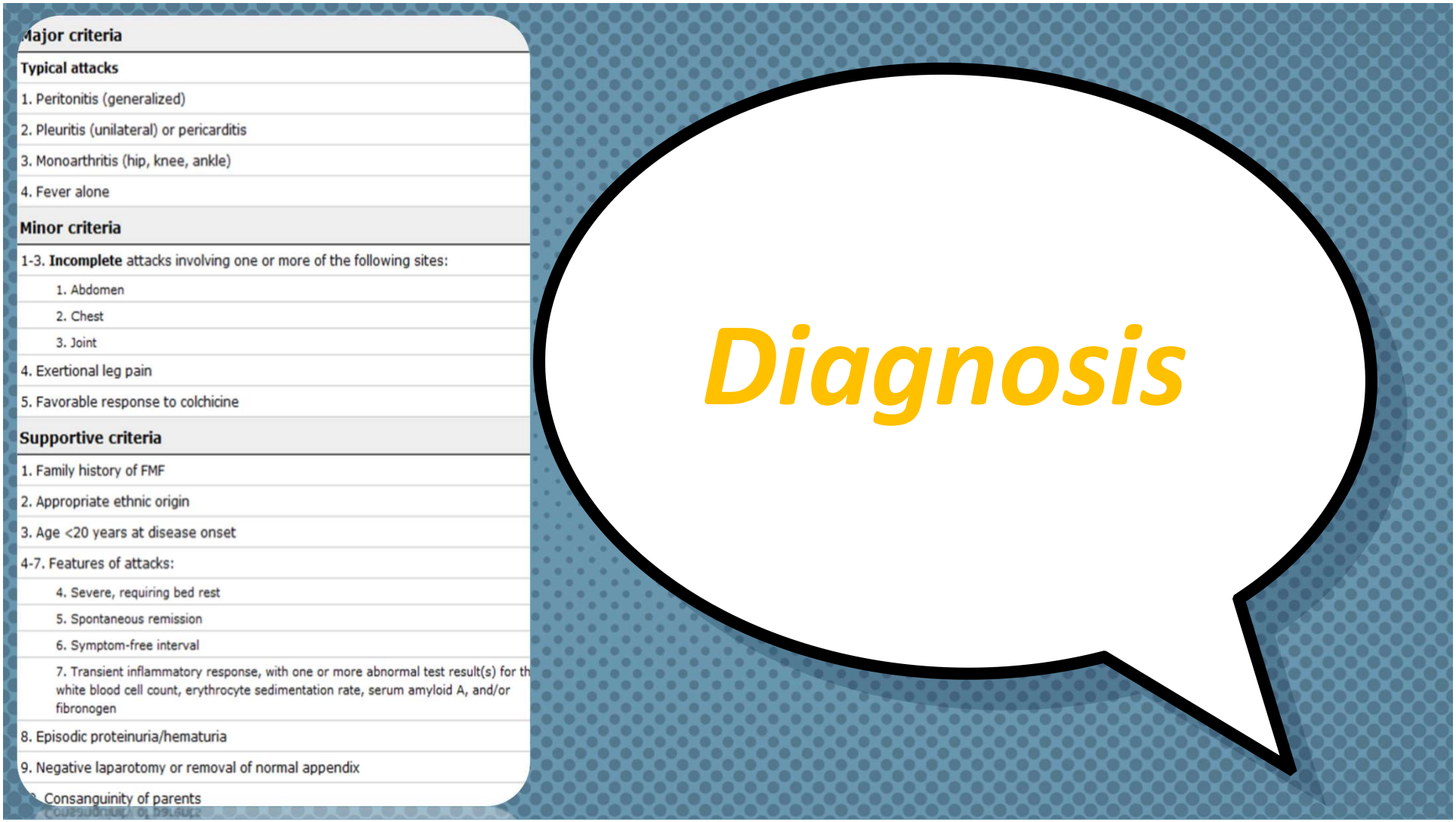
LONG-TERM COMPLICATIONS

Small bowel obstruction

- Recurrent attacks of peritonitis may lead to **adhesions** and small bowel obstruction
- Treatment with **colchicine**, which controls the FMF attacks, is also effective in preventing the development of peritoneal adhesions.

Infertility

- In the pre-colchicine era, **pelvic adhesions** and **fallopian tube obstruction** led to mechanical infertility in female patients
- In men, fertility may be decreased due to azoospermia from testicular amyloidosis or impairment in sperm penetration

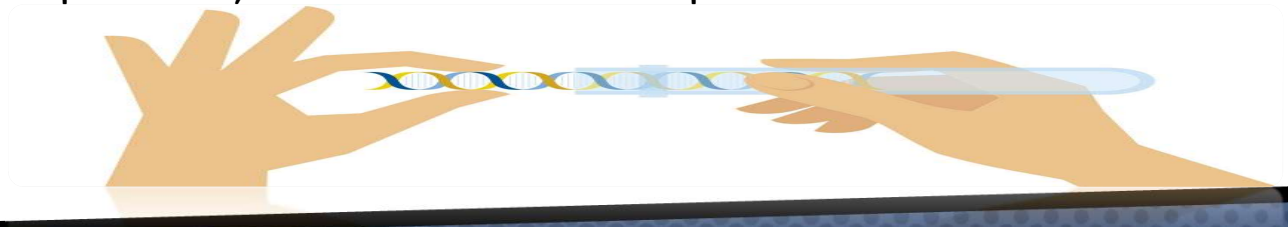

Major criteria
Typical attacks
1. Peritonitis (generalized)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
Minor criteria
1-3. Incomplete attacks involving one or more of the following sites:
1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
5. Favorable response to colchicine
Supportive criteria
1. Family history of FMF
2. Appropriate ethnic origin
3. Age <20 years 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 one or more abnormal test result(s) for th
white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or
fibronogen
8. Episodic proteinuria/hematuria
9. Negative laparotomy or removal of normal appendix
Consanguinity of parents
Diagnosis

Diagnosis

- The clinical diagnosis of FMF is **based on the presence of short (12 to 72 hours), recurrent (three or more) febrile episodes**, with abdominal, chest, joint, or skin manifestations and no discernible infectious cause

- Appropriate ethnicity, positive family history, onset before the age of 20 years old, and a favorable response to colchicine also support the diagnosis.

- Genetic testing has become a valuable adjunct to clinical diagnosis, particularly in North America and Europ



Diagnosis

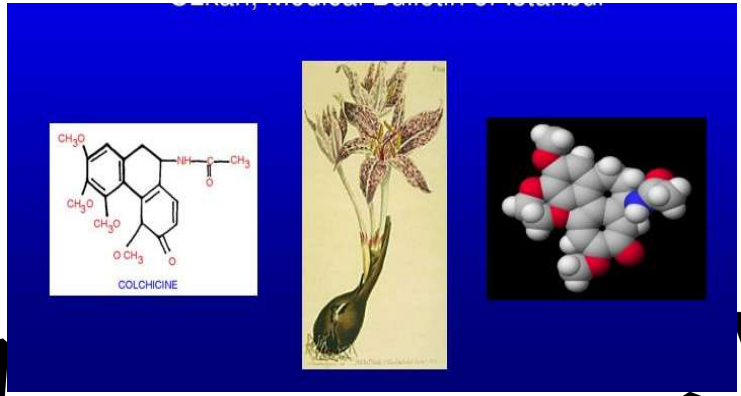
- More than 300 variants have been described in *MEFV* but only about 10% are known or considered likely to be pathogenic.
- The majority of FMF-associated mutations are missense changes clustered in exon 10, which encodes the C-terminal B30.2 domain of the pyrin protein.
- The most common mutations are the substitutions of valine or isoleucine for methionine at position 694 (**M694V and M694I**, respectively), the substitution of isoleucine for methionine at residue **680 (M680I)**, and the substitution of alanine for valine at position **726 (V726A).**
- Exon 2 of *MEFV* includes a number of missense substitutions that are variously considered to be functional polymorphisms or mild mutations
- the most notable of which is the substitution of glutamine for glutamic acid at **residue 148 (E148Q)**

Diagnosis

- Some rare mutations appear to cause clinically typical FMF, inherited in a multigeneration dominant fashion.
- whereas approximately 30% of patients with clinical signs of FMF have only one demonstrable mutation.
- Mutations at S208 and S242 block pyrin phosphorylation,leading to a dominantly inherited chronic inflammatory condition termed pyrin–associated autoinflammation with neutrophilic dermatosis(PAAND)
- The clinical and ethnic spectra of FMF have definitely expanded with the availability of genetic testing
- suggesting that a combination of clinical evaluation and genetic testing for selected patients is the most sensible diagnostic approach

Treatment

COLCHICINE



Treatment

- Colchicine therapy is highly effective for most patients in preventing febrile episodes and systemic amyloidosis.
- **Daily therapy** is generally more effective in controlling the attacks of FMF than intermittent treatment at the time of attacks,
- daily therapy has the important added benefit of reducing the subclinical inflammation between episodes that potentially leads to amyloidosis.

Treatment

- Colchicine is general safe in childrenal,though colchicine pharmacokinetics may differ in younger patients, and doses adjusted for body weight may be greater in children than those used in adults.
- The recommended adult colchicine dose is **1.2 to 1.8 mg/day** given by mouth.
- Dosage should be started as low as possible (**one–half of a 0.6–mg tablet** once daily in children) and slowly increased, titrating to maximize efficacy and minimize side effects, but usually not exceeding **1.8 mg/day** in single or divided doses.

Adverse effect

A gradual increase in dose often prevents or lessens diarrhea, the most common adverse effect. Some patients develop *lactose intolerance* because of colchicine, and a lactose-free diet may help control gastrointestinal symptoms.

In children with FMF, development of myopathy with progressive *proximal muscle weakness* and generalized myalgia is rarely observed on regular dosage

Adverse effect

- Bone marrow alterations (hemolytic or aplastic anemia, pancytopenia, neutropenia, and thrombocytopenia) have been reported in cases of acute intoxication but are rarely observed in the usual doses given orally.

- Toxicity is more common with intravenous therapy. and when given together with other drugs that are metabolized by CYP3A4, such as erythromycin and cimetidine.

Adverse effects of Colchicine

Therapeutic oral doses:

cramping abdominal pain, hyperperistalsis, diarrhea and vomiting.

Overdoses:

cholera-like syndrome, dehydration, shock and acute renal failure.

Toxic doses:

alopecia, bone marrow failure, hepatocellular failure, D.I.C, epileptic seizures, coma and death.

Treatment

- Based on the role of pyrin, the FMF protein, in IL-1 activation, IL-1 inhibitors have been increasingly used in FMF patients who are unresponsive to or cannot tolerate therapeutic doses of colchicine.
- *canakinumab*, a monoclonal antibody targeting human IL-1β,
- was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of *colchicine-unresponsive or colchicine-intolerant FMF*

prognosis

- When diagnosed and treated early, the prognosis for FMF is excellent.
- For those patients who develop amyloidosis, intensive treatment to normalize acute phase reactants may arrest the progression of amyloidosis and even reduce the extent of deposits over an extended period of time
- Studies have confirmed little difference in patient and graft survival between FMF and control kidney transplant recipients.
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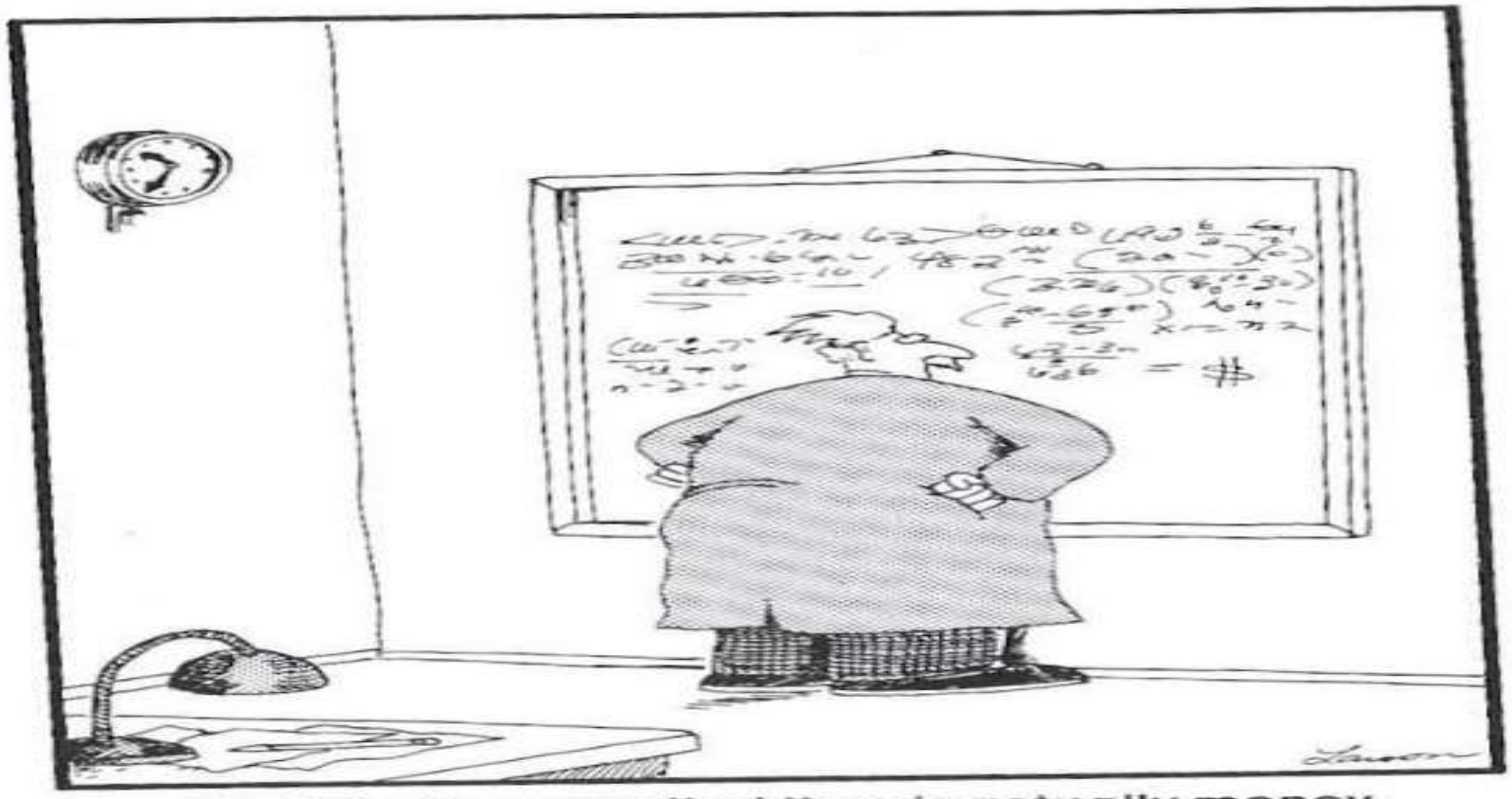

Einstein discovers that time is actually money.


THANK YOU
FOR YOUR
ATTENTION