The role of E148Q in FMF

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Familial Mediterranean Fever (FMF)

Acute attacks of fever accompanied by:

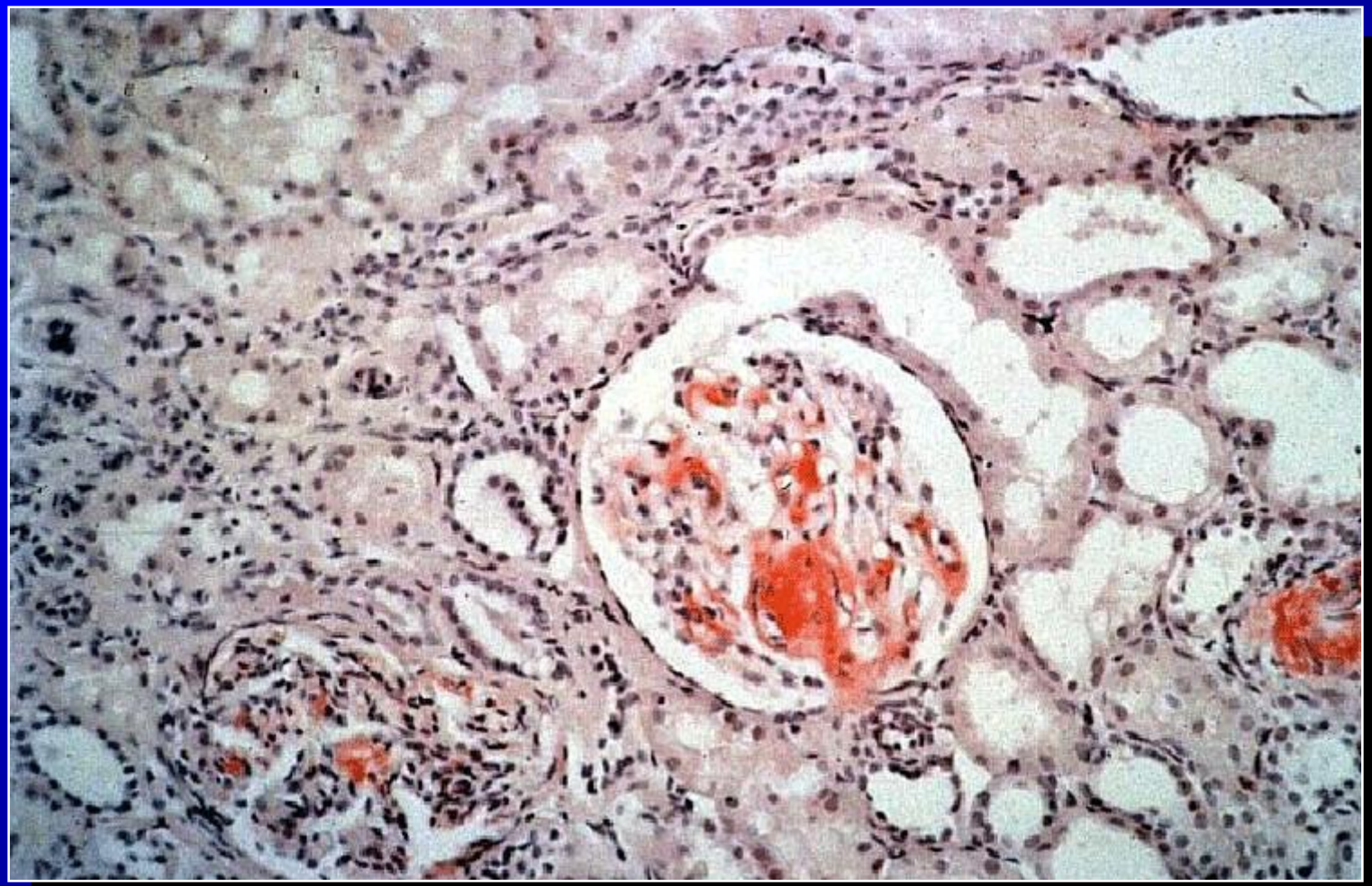
- **Peritonitis**
- **Pleuritis**
- **Arthritis**
- **Erysipelas like erythema**

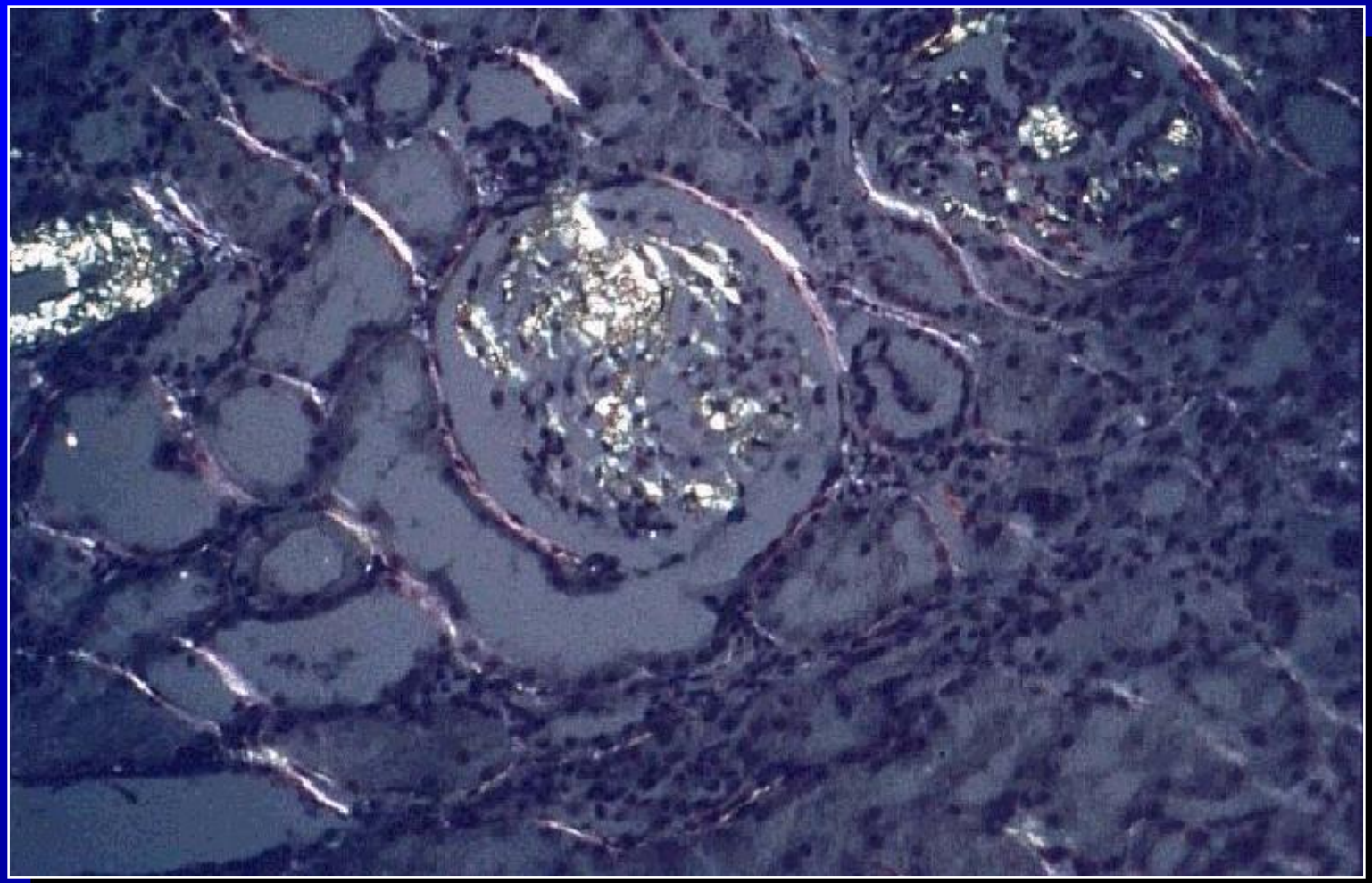
Frequency of Attacks

From twice a week to once every couple of years

Precipitating Factors

Infections, trauma, physical activity, menstrual period, mental stress, unknown factors





Disease Distribution

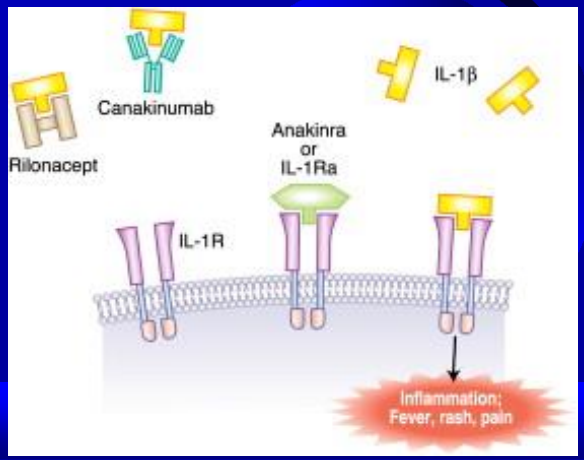
- North African Jews
- Iraqi Jews
- Armenians
- Turks
- Middle eastern Arabs
- Ashkenazi Jews

- **The disease is one of the most common Mendelian disorder in world**
- **Hundreds of thousands of FMF patients world wide**
- **The disease is by far the most common Mendelian disorder in Israel with more than 15,000 patients**

Colchicine Treatment

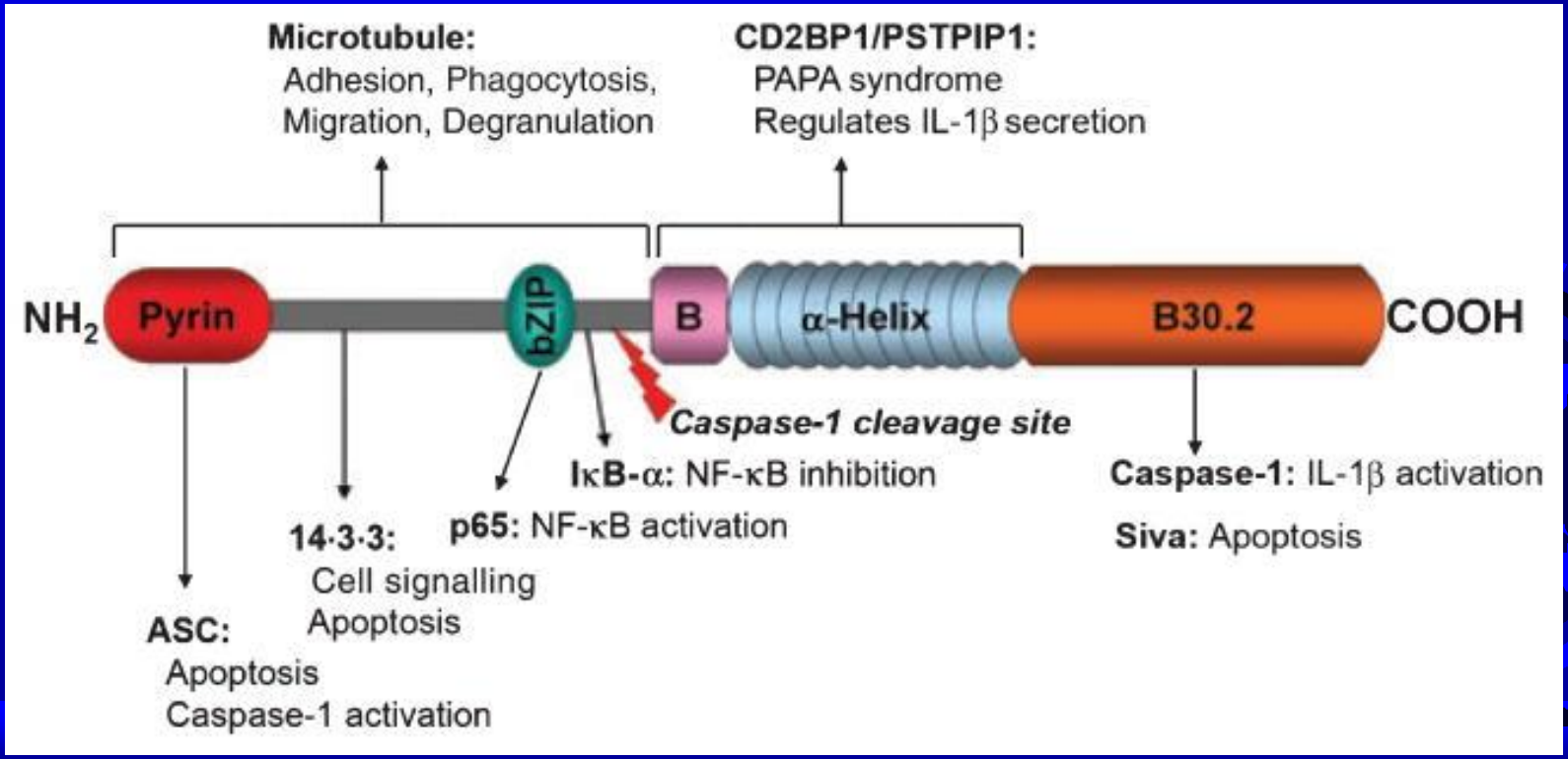
- Until the mid 70's - no effective treatment
  Prophylactic colchicine first introduced

- Patients resistant to colchicine treated today with Il-1 Inhibitors



The FMF Gene (MEFV)

- mRNA-3700 bp long
- Encodes a 781 amino acid protein (Pyrin)



FMF patients with a single mutation

Mutation analysis in FMF patients reveal:

- **60-65% two mutations**
- **20-25% one mutation**
- **5-10% no mutations**

The most common single mutation genotype found is M694V/null

MEFV Mutations

- M694V
- V726A
- E148Q
- E167D
- P369S
- M680I
- M694I
- K695R
- A744S
- V704I
- G687E
- T267I
- F479L
- I692Del
- R42W
- E230K
- E148V
- L110P
- R408Q
- I591T
- R761H
- Y688X
- T681I
- M680L
- S675N
- R653H
- M640Del

E148Q In FMF a Mutation or a Polymorphism ?

- In the Far East carrier rate of 25% in control samples.
- No difference in the frequency of this variant between cohorts of patients and controls

One of the most common ways to differentiate between a mutation and a polymorphism is to assess its frequency in patients vs. controls

	Patients (Zaks 2003)	Healthy Controls
E148Q	58	163
--------	766	2639
Total	824	2802
	7.04%	5.81%

PV=0.2280

	Patients (Zaks 2003)	Healthy Controls
V726A	122	141
--------	702	3877
Total	824	4018
	14.8%	3.5%

PV=0.0001

No functional assay For FMF mutations

IN-FEVERS DATA BASE

E148Q is defined as a variant of unknown significance (VOUS)

(http://fmf.igh.cnrs.fr/infevers)

Through out the years

We all shared the feeling that E148Q has a functional effect but the game changing evidence was missing

Penetrance

$$\frac{\text{No. of symptomatic patients with a given genotype}}{\text{Total no. of individuals with that genotype}}$$

Full Penetrance = 1.0

What is the penetrance of the disease in patients with the M694V/E148Q genotype

What is the penetrance of the disease in patients with the M694V/null genotype

Compare

the penetrance of

M694V/E148Q

to the penetrance of M694V/null

Aim:

To determine the penetrance of the M694V/null and M694V/E148Q genotypes in adult FMF patients.

Functional role for E148Q in the disease

Calculating penetrance

1. Direct calculation: Genotype 100,000 individuals, look for the M694V/E148Q and M694V/null genotypes and see how many of them have FMF.

2. Indirect relative penetrance calculation

Methods

Find a population group in which FMF and these 2 mutations are very prevalent.

Assess the allele frequencies of these two variants in a large control group.

Calculate the expected frequencies of the M69V/M694V, M694V/null and M694V/E148Q genotypes.

Construct a cohort of at least 100 consecutive FMF patients who came for genetic analysis, all belonging that population group.

Assuming a penetrance of 100% for the M694V/M694V genotype:

The ratio between the calculated frequencies of the 3 genotypes and the actual frequencies of these 3 genotypes obtained from the patient cohort will be used to determine the penetrance of M694V/null and M694V/E148Q.

North African Jewish population (NAJ)

We shall assess the carrier rates for M694V and E148Q in NAJ from three previous studies (over 500 controls).

The expected frequencies of the M69V/M694V, M694V/null and M694V/E148Q genotypes were calculated.

We will construct a cohort of at least 100 consecutive patients with FMF, all of NAJ decent who came for genetic analysis.

The ratio between the calculated frequencies of the 3 genotypes and the actual frequency obtained from the patient cohort was used to determine the penetrance of M694V/null and M694V/E148Q.


The End