The role of E148Q in FMF

Elon Pras
Institute of Human Genetics
Sheba Medical Center
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
<table>
<thead>
<tr>
<th>MEFV Mutations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M694V</td>
<td>K695R</td>
</tr>
<tr>
<td>V726A</td>
<td>A744S</td>
</tr>
<tr>
<td>E148Q</td>
<td>V704I</td>
</tr>
<tr>
<td>E167D</td>
<td>G687E</td>
</tr>
<tr>
<td>P369S</td>
<td>T267I</td>
</tr>
<tr>
<td>M680I</td>
<td>F479L</td>
</tr>
<tr>
<td>M694I</td>
<td>I692Del</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
E148Q in FMF: a Mutation or a Polymorphism?

- In the Far East, the carrier rate is 25% in control samples.
- No difference in the frequency of this variant between 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.
<table>
<thead>
<tr>
<th></th>
<th>Patients (Zaks 2003)</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E148Q</strong></td>
<td>58</td>
<td>163</td>
</tr>
<tr>
<td><strong>---------</strong></td>
<td>766</td>
<td>2639</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>824</td>
<td>2802</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>7.04%</th>
<th>5.81%</th>
</tr>
</thead>
</table>

**PV = 0.2280**
<table>
<thead>
<tr>
<th></th>
<th>Patients (Zaks 2003)</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>V726A</td>
<td>122</td>
<td>141</td>
</tr>
<tr>
<td>V726A</td>
<td>702</td>
<td>3877</td>
</tr>
<tr>
<td>Total</td>
<td>824</td>
<td>4018</td>
</tr>
<tr>
<td>%</td>
<td>14.8%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

$PV=0.0001$
No functional assay For FMF mutations
E148Q is defined as a variant of unknown significance (VOUS)
Through out the years

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

No. of symptomatic patients with a given genotype
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.