

Familial mediterranean fever: An unusual disease enlightening the inflammation biology

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Familial Mediterranean fever (FMF) is an unusual and rare disease. In this disease paroxysms of fever lasting for few days coupled with inflammation of serous membranes such as peritoneal, pericard pleural, synovial and meningeal coverings are inflamed. Some of patients develop inflammation related amyloidosis (AA amyloidosis) with all its attendant consequences.^[1] Although the disease is now known for almost more than a century in the limited geographical areas of middle eastern countries, Turkey and Egypt. Sporadically this disease has been described from many parts of the world.^[2] The biology of the disease is only being understood for last two decades^[3] and the mutations of the disease causing gene are being increasingly identified and reported regularly in an international database.^[4]

Though the inflammatory nature of the disease was understood yet absence of any specific infecting agent, autoantibodies (some similarity of this disease with acute presentation of systemic lupus erythematosus and other autoimmune diseases exist), T-cell dysregulation and apparent absence of the complement system activation baffled the investigators with the disease. However,

serosal inflammatory fluids in this condition is studied with neutrophils as it's inflammatory components and in all probability neutrophils in synovial fluid lead to use of colchicine as a relieving agent for this condition with striking result in the same way as it is used for acute gouty arthritis. Colchicine is also used for prevention of this attack.^[1] In the present issue of the journal Al-Haggag *et al.*^[5] from Mansoura University, Egypt has reported phenotype – genotype correlation of four most common genetic mutations (M680I, M694I, M694V and V726A) of pyrin gene. His team used amplification refractory mutation system – polymerase chain reaction as the detection system for these mutations. They used a different set of clinical criteria, than usual, Tel Hashomer Criteria^[6] to diagnose FMF.^[7] Though this applied criteria worked well for patients with typical clinical feature in a limited geographical area, the criteria seems nonspecific and may not be useful for sporadic cases or elsewhere in the world.

Detection of a candidate gene for FMF at 16p13.3^[8] is one of the land mark discoveries of the present time. The gene called pyrin (Marenostim) is an important component of an organic platform complex called “inflammosome” [Figure 1]. In this disease activation of inflammosome occurs via activating mutation of pyrin leading to inappropriate secretion of IL-1 β .

The findings for Mansoura University is interesting, their clinical cohort consists of 282 male and 144 female patients, in some of their cases 3-5 members were clustered around a single family, hence all these cases were not unrelated. Consanguinity rate in this group

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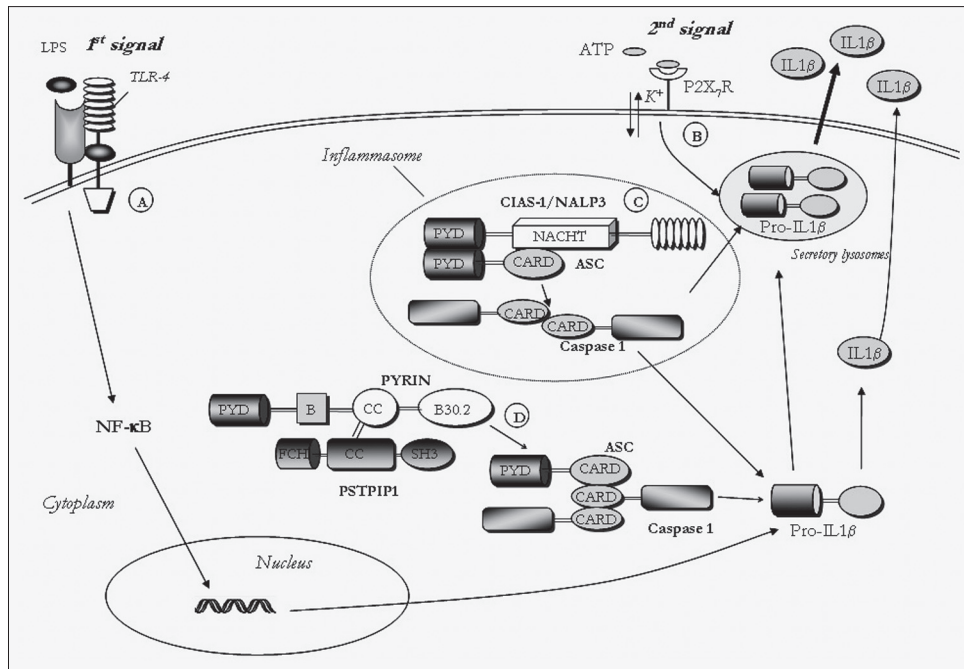


Figure 1: Pathway showing formation of inflammasome

goes up as high as 89.2%. 521/852 (64.67%) studied alleles showed one of the mutations showing that the new clinical criteria has picked up a large number of FMF patients in that region. And the most common allele (302/882 i.e., 35.4%) M694V is also known to be the most amyloidogenic.^[8] Other three alleles that is, M694 I, V726 A and M680I were found in frequencies of 10.7%, 7.9%, and 7.2%, respectively.

Familial Mediterranean fever is an autosomal recessive disorder hence majority of the cases should have shown homozygosity or double heterozygosity of the mutant allele, however in this study it is seen in 95 cases only (190 affected alleles) leading to a suspicion that several uncharacterized mutations of FMF might have been missed in this study. Majority of the mutations of FMF across the world has been shown to be concentrated around exon 10 and exon 2 of pyrin gene.^[9] The investigators would do well to sequence at least these 2 exons so that additional mutations of FMF from this area could be unraveled. Some work from this geographical area has been reported by other authors.^[10] As the gene frequency for FMF reaches very high in defined geographical areas^[11] there is a real risk that other paroxysmal and prolonged fever for being misdiagnosed as FMF, if only fever and genetic composition of FMF gene is

taken into account. However, most of the time FMF patients show extreme sensitivity to colchicine and colchicine test is an important diagnostic parameter for FMF and this will help us to discriminate several other paroxysmal fever syndromes from FMF^[1] that is, tumor necrosis factor receptor associated periodic syndrome (TNFRSF1A/12p13 – autosomal dominant inheritance), hyper immunoglobulinemia D syndrome (mevalonate kinase mutation/12q24 – autosomal recessive inheritance) Muckle–Wells Syndrome and neonatal onset multisystem inflammatory disease are associated with mutation in NLRP3/1q. 44 gene also called cryopyrin gene.

Being a genetic disorder, majority of the patients present before 10 years of age. However, there is a small group of patients who may present with amyloidosis as their first presentation between fourth and sixth decade of life.

Whenever we face a genetic disorder, one question, which needs to be answered is whether this genetic testing should be done in other family members with the disease to detect the homozygosity or carrier status of the mutated disease? Genetic testing of the mutated individuals is not advised in this disease because of low penetrance of the gene. We still do not know why the penetrance of the gene is low? Are there strong epistatic

factors, which are trans to this gene for low penetrance of the gene or is this gene susceptible to epigenetic or SiRNA/MiRNA based control? This needs to be worked out. Finally, India and China are vast countries, together they constitute 40% population of the world, but very few genuine cases of FMF have been reported from this part of the world.^[12] Are we missing some of these patients? If so from where should we start looking for such patients? Obviously we have to apply the clinical criteria as is applied to FMF elsewhere. Amyloidosis disease in the younger population may be another group where we should look for mutation in pyrin gene. This gene is not a big gene and at least sequencing of exon 10 and exon 2 of the gene in well selected cohort will not be difficult. Moreover, there could be other causes of periodic fever in India.^[13] The registry of FMF developed by Al-Haggar *et al.* of Mansoura University, Egypt will go a long way in helping us to sort out many riddles associated with FMF and if this cohort can be followed up for a long time then natural history of the disease can be more firmly established.

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