GENETIC DIAGNOSIS OF HEREDITARY RECURRENT FEVER (HRFs)

Hereditary recurrent fevers (HRFs) are a heterogenous group of diseases sharing various clinical symptoms with periodic recurrent fever attacks as the most common. Familial Mediterranean Fever (FMF), in particular, is the most common among autoinflammatory diseases, and it is caused by mutations in the *MEFV* gene on chromosome 16. FMF is relatively rare in Europe and US, but it is quite common in populations of the Mediterranean basin and middle eastern origin. In this area the incidence of the disease can reach 1/200-1/1000 with the prevalence of healthy carriers as high as 1 in 5 among Armenian.

In Italy, data from the Eurofever registry for autoinflammatory diseases indicate FMF as a rare disease, with an estimated overall prevalence of 1 in 60,000 people, and most of patients living in Southern regions of the country (in particular Sicily, Calabria, and Apulia).

FMF shares with other hereditary recurrent fevers symptoms such as periodic fever episodes and serositis mostly developing in the abdomen, chest and joints. The responsible gene, *MEFV*, encodes for a 781 amino acids protein, named pyrin, which plays a fundamental role in the assembly of a specific inflammasome. The pyrin inflammasome is usually activated in response to either pathogen- or damage- associated molecular patterns, ultimately leading to the release of inflammatory cytokines IL-1ß and IL-18. Mutated *MEFV,* however, can trigger pathogenic recurrent inflammation mediated by antigen-independent activation of the innate immune system.

Genetic diagnosis is based on a thorough collection of clinical history in patients, and once a HRFs diagnosis is suspected, next-generation-sequencing (NGS) multi-gene panels are commonly used to confirm the clinical diagnosis with a positive genetic test. In the Laboratory of Medical Genetics at Policlinico di Bari, the gene testing actually uses a four gene panel (*MEFV*, *NLRP3*, *TNFRSF1A*, *MVK*) and gene testing is preceded and followed by genetic counselling. During genetic counselling, the description of the gene test, the possible outcomes and their consequences are detailed to patients. In the post-test counselling in case of a positive gene test the identified variant interpretation and its putative association with the disease is communicated to patients. The combination of gene testing and clinical history is fundamental to confirm diagnosis and to help in tailoring follow-up of HRFs patients.