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First report of *MEFV* duplication in FMF patient

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Introduction

Familial mediterranean fever (FMF) is a rare monogenic disease and the prototype of autoinflammatory disorders. It is caused by mutations in the *MEFV* gene and is autosomal recessively inherited. Most mutations are missense substitutions, small deletions are quite rare, and only three nonsense mutation has been described (http://fmf.igh.cnrs.fr/ISSAID/infevers/). Large rearrangements have been searched for in the frame of a collaborative project including 216 patients but were not identified.

Objectives

We report here the first case of *MEFV* duplication in a FMF patient.

Patients and methods

The proband is a 21 years-old woman who presented with classical FMF phenotype: recurrent fever, arthralgia, and abdominal pain with vomiting. Attacks lasted three days and biological inflammation was documented with elevated C-reactive protein. Her father is Armenian and her mother Malagasy, and both are asymptomatic. We performed Sanger analysis (ABI3130x, Life Technologies) of the *MEFV* gene, quantitative polymerase chain reaction (qPCR) (LighCycler, Roche) and deep-sequencing (Nextera Rapid Capture, Illumina) (MiSeq, Illumina). Microsatellite analysis (ABI3130x, Life Technologies) was also performed.

Results

We identified a well-known severe mutation: p.Met694Val, and a controversial variant: p.Glu148Gln. Parental testing confirmed that the variants were non-allelic. Sanger sequencing displayed unbalanced ratio of the mutated and wild type alleles. Mosaicism was excluded because all polymorphisms were found at the same 1:2 ratio. DNA contamination was ruled out through microsatellite analysis. We thus suspected a gene micro-rearrangement. qPCR and deep-sequencing revealed a heterozygous duplication of the entire wild *MEFV* gene. The two surrounding genes (*NAA60* and *OR1F1*) were not duplicated demonstrating that this rearrangement was confined to the *MEFV* region. qPCR analysis showed that the duplication was inherited from the mother.

Conclusion

We report here the first FMF patient with 1/3 dose of p.Met694Val. Interestingly, the patient's phenotype seemed not to be impacted by the "dilution" of the pathological variants.

Consent to publish

Written informated consent for publication of their clinical details was obtained from the patient/parent/guardian/relative of the patient.

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