OR2-002 - The risk of FMF in MEFV heterozygotes

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder due to *MEFV* mutations and one of the most frequent Mediterranean genetic diseases. The observation of many heterozygous patients in whom a second mutated allele was excluded led to propose that heterozygosity could be causal; however, this might often be coincidental due to the very high rate of mutations in Mediterranean populations.

Objectives

To better delineate the pathogenicity of heterozygosity in order to help genetic counselling and better manage the disease.

Methods

Complementary statistical approaches were used: estimation of FMF prevalence at population levels, genotype comparison in siblings from 63 familial forms, and genotype study in 557 patients from four Mediterranean populations.

Results

At population level, we did not observe any contribution of heterozygosity to the disease prevalence. In affected siblings of patients carrying two *MEFV* mutations, 92% carry two mutated alleles whereas 4% are heterozygous with typical FMF diagnosis. We also demonstrated statistically that patients are more prone to be heterozygous than healthy individuals, as shown by the higher ratio heterozygous carriers/non carriers in patients ($p<10^{-7}$ - $p<0.003$). The risk for heterozygotes to develop FMF was estimated between $2.1x10^{-3}$ and $5.8x10^{-3}$ and the relative risk, as compared to individuals carrying no *MEFV* mutation, between 6.3 and 8.1.

Conclusion

This is the first statistical demonstration that heterozygosity is not responsible for classical Mendelian FMF, but constitutes a susceptibility factor for clinically-similar complex conditions. We also provide a first estimate of the risk for heterozygotes to develop FMF.

Disclosure of interest

None declared.

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