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OR7-002 – Pyrin 577 mutations in dominant autoinflammation

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Introduction

Autoinflammatory disorders are disorders of the innate immune system. Standard genetic testing provided no correct diagnosis in a female patient from a non-consanguineous family of British descent with a colchicine-responsive autosomal dominant periodic fever syndrome.

Objectives

We aimed to unravel the genetic cause of the symptoms in this family.

Methods

Whole exome sequencing was used to screen for novel sequence variants, which were validated by direct Sanger sequencing. Ex-vivo stimulations with peripheral blood mononuclear cells were done to study the functional consequences of the mutation. mRNA and cytokine levels were measured by q-PCR and ELISA, respectively.

Results

Whole exome sequencing revealed a novel missense sequence variant, not seen in around 6800 controls, mapping to exon 8 of the *MEFV* gene (c.1730C>A; p.T577N), co-segregating perfectly with disease in this family. Other mutations at the same amino acid (c.1730C>G; p.T577S; c.1729A>T; p.T577S) were found in a family of Turkish descent, with autosomal dominant inheritance of FMF-like phenotype, and a Dutch patient, respectively. Moreover, a mutation (c.1729A>G; p.T577A) was detected in 2 Dutch siblings, suffering from episodes of inflammation of varying severity not resembling FMF. PBMCs from one patient of the index family revealed increased basal IL-1β mRNA levels and cytokine responses after LPS stimulation. Responses normalized under colchicine treatment.

Conclusion

Heterozygous mutations at amino acid position 577 of pyrin can induce an autosomal dominant autoinflammatory syndrome. This suggests that T577, located in front of the C-terminal B30.2/SPRY domain, is crucial for pyrin function.

Disclosure of interest

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