

0/144 alleles, p 0.002) has no clear explanation and may reflect some bias in the selection of the control groups in the two studies. In any case, we should be prepared for the new challenges of genetic diagnostics in patients with periodic fever syndromes, while novel techniques are making more affordable the sequencing of multiple candidate genes (3). In particular, the relative frequency of possible low-penetrance genetic variants associated with auto-inflammation in the population should raise the question whether some cases of periodic fever actually have a multifactorial rather than a monogenic cause (4, 5).

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Competing interests: none declared.

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The role of the F402L allele in the NLRP12-autoinflammatory disorder

reply to:
F402L variant in NLRP12 in subjects with undiagnosed periodic fevers and in healthy controls

De Pieri *et al.*

Sirs,

De Pieri *et al.* (1) published a letter to the editor in response to our case series presenting NLRP12 gene variants associated with a NLRP12-autoinflammatory disorder (NLRP12-AD) phenotype (2). In particular, they commented on the role of the F402L variant stating that, though there was a trend towards an increased frequency of the F402L allele in subjects suffering from recurrent fevers, the clinical relevance of this variant could not be determined (1).

Although F402L mutation frequencies did not show a statistically significant difference between patients presenting with recurrent fevers and healthy controls, the proportion of subjects carrying the F402L variant was rather higher among the former than among the latter (18.6% and 11.7%, respectively) (1). In addition, since the F402L variant shows a high frequency (up to 5%) also in databases that report sequence variations from the general population, the gap with patients analysed by De Pieri *et al.* is even more evident.

In order to better understand the pathogenic role of the F402L variant, we have evaluated a further cohort of 31 patients presenting with NLRP12-AD-like manifestations as well as 35 patients with recurrent fevers as sole clinical manifestations. Five patients (16.12%) with NLRP12-AD phenotype and eight subjects (28.5%) with recurrent fevers were heterozygous for the missense variant p.F402L, respectively. Strikingly, there was no statistically significant difference between the groups ($p=0.496$), but percentage of patients carrying the F402L variant was higher among those without NLRP12-like phenotype.

Among the two different nucleotide variants (rs199985574:c.1204C>T; rs34971363:c.1206C>G) reported to give the same F402L amino acid change, all our patients were carriers of the rs34971363 (c.1206C>G, p.F402L) variant.

De Pieri *et al.* also identified a different prevalence of the F402L mutation compared to our study involving a very similar population. Like them, we cannot explain this difference apart from the result of an un-

identified bias or, less probably, a stochastic event.

For these reasons, in agreement with De Pieri *et al.*, a definite association between the F402L variant and NLRP12-AD cannot be actually confirmed.

In this regard, we wonder whether NLRP12-AD-like patients that we have previously described as carrying the F402L mutation (2) were just casual carriers. However, clinical and laboratory response to IL-1 inhibition could represent an Ariadne's thread to disentangle functional mutations and occasional findings in such patients. Finally, De Pieri *et al.*'s comment on whether some cases carrying low-penetrance mutations and presenting with periodic fever actually have a multifactorial rather than a monogenic cause could represent an interesting food for thought. However, we add that – looking a bit further into the future – evaluating the role of epigenetic mechanisms and alterations in such patients, as well as in those affected with other monogenic autoinflammatory disorders, may be even more intriguing (3, 4).

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