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NextGen sequencing (NGS) panel for hereditary recurrent fevers: mutation spectrum, novel mutations, and evidence for re-classification of common variants based on analysis of >3000 cases from North America

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Aim

Hereditary recurrent fevers (HRF) are genetically heterogeneous and often present a diagnostic challenge. To aid in molecular diagnosis, we developed and utilized a 7-gene NGS panel for HRF.

Methods

The HRF panel includes *MEFV*, *MVK*, *NLRP3*, *TNFRSF1A*, *PSTPIP1*, *LPIN2* and *ELANE*, which are associated with familial Mediterranean fever (FMF), hyper-IgD syndrome, cryopyrin-associated periodic syndrome, tumor necrosis factor receptor-associated periodic syndrome (TRAPS), pyogenic sterile arthritis-pyoderma gangrenosum and acne syndrome, Majeed syndrome, and cyclic/severe congenital neutropenia, respectively. It utilizes a multiplex PCR approach, followed by NGS on HiSeq 2000/2500 instruments, and variant analysis using a custom-developed analysis pipeline.

Results

Using this NGS panel, 3,248 individuals with suspected HRF were tested in our diagnostic laboratory. In this largely North American population, the majority of pathogenic/ likely pathogenic variants (PV/LPV) were identified in the *MEFV* gene (66.6%; n=187), followed by *MVK* (14.6%; n=41), *NLRP3* (8.9%; n=25), *TNFRSF1A* (3.6%; n=10), *PSTPIP1* (2.5%; n=7), *ELANE* (2.1%; n=6), and *LPIN2* (1.7%; n=5). Sixty percent of PV/LPV were recurrent mutations in *MEFV* (M680I, M694V, K695R, V726A), *MVK* (I268T and V377I) and *NLRP3* (R490K). The remainder were low-frequency or unique PV/LPV. Co-occurrence of pathogenic variants in 2 different genes was only observed in 2 families. Novel PV/LPV were identified in 5 genes, including *LPIN* associated with Majeed syndrome. Originally reported as pathogenic, the genetic contribution of several common variants to HRF remains unclear, including *MEFV*-E148Q and *TNFRSF1A*-P75L. In our cohort, both variants co-occurred with definite pathogenic mutations in *MEFV* or another fever-associated gene. While their minor allele frequency (MAF) in affected individuals was higher than in our exome sequencing controls (*MEFV*-E148Q: 2.8% vs. 1.9%; *TNFRSF1A*-P75L: 0.6% vs. 0.3%), numerous healthy individuals were homozygous for either variant. Newly available population data (1000 Genomes, ESP and ExAC) revealed a MAF for p.E148Q as high as 30% in Asians, and 10% for p.P75L in African individuals, including a large number of homozygotes (p.E148Q: 701/7768; p.P75L: 20/2775), which exceeds by far the prevalence of FMF and TRAPS in these populations.

Conclusions

Our 7-gene NGS results represent the largest molecular-diagnostic dataset for HRF in the North American population, revealing mutation distribution and novel PV/LPV. We provide new evidence to reconsider the clinical significance of *MEFV*-E148Q and *TNFRSF1A*-P75L and propose these are population-specific polymorphisms that are unlikely to contribute to FMF or TRAPS. Our study underscores the utility of large datasets from

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diverse ethnic populations in clarifying the clinical significance of common HRF variants.

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