Genetic Findings from a Multigene Panel for Autoinflammatory Disease

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Introduction

Systemic autoinflammatory diseases (AIDs) are disorders resulting from inappropriate activation of the innate immune system. While 4 genes (*MEFV*, *NLRPS*, *TNFRSF1A*, *MVK*) explain most clinical diagnoses, recent use of expanded genetic testing panels has identified numerous monogenic AIDs[1], as well as somatic VEXAS syndrome, an adult-onset inflammatory condition primarily affecting males[2]. To further investigate the utility of genetic testing for patients with AIDs, we performed a retrospective analysis of results from a next-generation sequencing (NGS) multigene panel test.

Methods

A retrospective review of patients who underwent panel testing at Blueprint Genetics was performed. Testing included sequence and copy number variants (CNVs) analyses of up to 47 genes associated with AIDs by NGS data from a clinically validated assay. The patient sex, age, and clinical history were collected from the test requisition. Variant classification was performed applying a modified variant classification scheme of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP). A positive result was defined as the identification of a pathogenic (P) or likely pathogenic (LP) variant(s) consistent with the patient's reported phenotype and with associated disease inheritance.

Results

In total, deidentified test results from 912 consecutive patients were included for analysis. The median age at testing was 20 years (ranging from 3 months to 84 years) and 57% (n=517) of patients were female. A positive result was identified in 7% (n=61) of patients, including 71 (P/LP) variants (28 unique) from 10 different genes. Most variants were missense (n=68), but frameshift (n=2) and inframe deletion (n=1) variants were also identified. The 4 most common genes (*MEFV* n=37, *NLRP3* n=9, *MVK* n=5, and *TNFRSF1A* n=3) accounted for 88.5% of positive results. Additional positive results were observed in *TNFAIP3*, *NOD2*, *PSTPIP1*, *TMEM173*, *IL36RN*, and a mosaic variant in *UBA1*.

Among patients with *MEFV* variants, 21 (57%) had only a single pathogenic variant, 14 (38%) had 2 pathogenic variants, and 2 (5%) had a pathogenic variant and a variant of uncertain significance (phase unknown). The average age at testing was slightly older for patients with 1 pathogenic variant versus 2 (27.5 vs 21.4 years; p=0.169). The most common *MEFV* variant was NM_000243.2 c.2040G>C (p.M694V), which accounted for 57% of all heterozygotes. Other single *MEFV* variants observed included c.2230G>T (p.A744S), n=4; c.2040G>C (p.M680I), n=3; and c.2082G>A (p.M694I), n=2. All patients had documented symptoms associated with Familial Mediterranean Fever (FMF), including 1 adult patient with renal amyloidosis.

7% of patients undergoing next generation sequencing (NGS) panel testing for a systemic autoinflammatory disease indication received a positive result

Demographic	Number of individuals (n=912)	% of the cohort
Female sex	517	57%
Male sex	395	43%
Pediatric (0-17yrs)	408	45%
Adult (≥18yrs)	504	55%

Table 1. Patient demographics

Gene	MOI	% of total diagnoses
MEFV	AD/AR	61% (37/61)
NLRP3	AD	15% (9/61)
MVK	AR	8% (5/61)
TNFRSF1A	AD	5% (3/61)
TNFAIP3	AD	3% (2/61)
NOD2	AD	1.6% (1/61)
PSTPIP1	AD	1.6% (1/61)
TMEM173	AD/AR	1.6% (1/61)
IL36RN	AR	1.6% (1/61)
UBA1 mosaic variant	XL	1.6% (1/61)

Table 2. Genes with diagnostic findings in 101/404 cases and the associated mode of inheritance mode (MOI). AD – autosomal dominant; AR – autosomal recessive; XL – X-linked

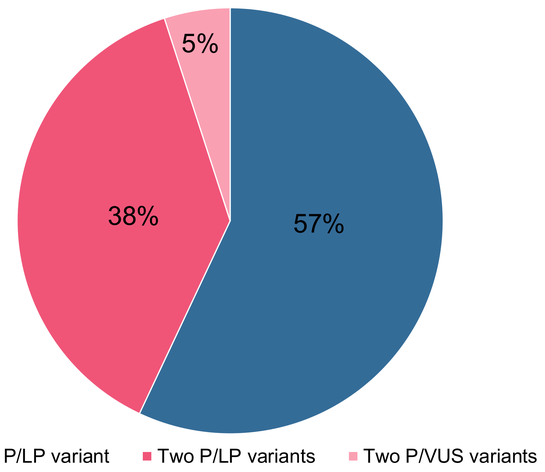

Figure 1: Proportion of *MEFV* variants identified in 61 patients. P – pathogenic; LP – Likely Pathogenic; VUS – Variant of uncertain Significance

Conclusions

- Seven percent of patients in our cohort received a positive result, the majority of which were in historically common genes (*MEFV*, *NLRP3*, *MVK*, and *TNFRSF1A*).
- 6 positive results (11.5%) were in other genes, all of which may inform treatment decisions.
- Single *MEFV* pathogenic variants accounted for over half (57%) of positive results for patients with FMF, which supports mounting evidence for AD FMF.
- This data supports the use of a multiple-gene panel for patients with suspected AIDs and for identifying heterozygous MEFV variants in symptomatic patients with FMF.

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Conflict of interest statement: All authors are employed by Blueprint Genetics.

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