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Autoinflammatory Diseases: Germline vs. Somatic Mosaic Variations

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Introduction

Systemic autoinflammatory diseases (SAIDs) consist in a growing group of disorders characterized by clinical and biological inflammation. To date, more than 50 SAID genes, encoding key components of the innate immune system have been implicated in the pathophysiology of SAIDs. The best known autosomal dominant SAIDs, NLRP3-AIDs (or cryopyrin-associated periodic syndromes) and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), are due to germline variations in *NLRP3* and *TNFRSF1A*, respectively. Recently, the role of mosaic variations in these genes has emerged.

Objectives

This study aims to assess the contribution of somatic mosaic variations in SAID genes and describe the associated disease phenotypes.

Methods

We analyzed leukocyte DNAs from patients collected between 2018 and 2023 using a SAID gene panel (NGS = 800X). We then reviewed all mosaic variations in SAID genes recorded in PubMed and *Infervers* databases.

Results

NLRP3-AIDs

During the period of 2018-2023, we have identified 10 pathogenic variations in the *NLRP3* gene (Figure 1) including:

- 8 different mosaic variations in 11 independent patients
- 2 different germline variations in 3 independent patients.

A total of 34 mosaic and 88 germline *NLRP3* variations have been reported in the literature to date (Figure 1).

Clinically, *NLRP3* mosaic variations are associated with various *NLRP3*-AID phenotypes ranging from late-onset urticaria in the context of MWS to CINCA.

NLRP3 (cryopyrin)

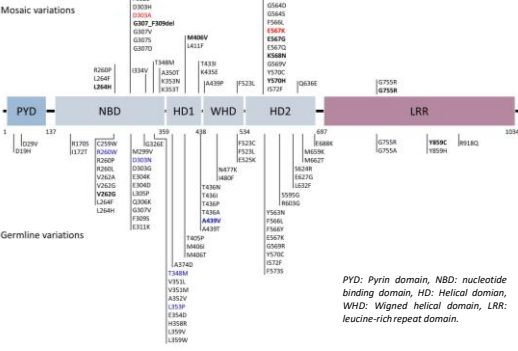


Figure 1. The *NLRP3* pathogenic variations reported to date (in red the recurrent mosaic variations, in blue the recurrent germline variations, and in bold the variations identified in this study). Our results indicate that the mosaic variations are located in two mutational hotspots (Figure 1, red arrows).

TRAPS

We identified two different mosaic variations (C59R, R97_L100del) in the *TNFRSF1A* gene in three independent TRAPS patients. Only three mosaic missense variations have been reported in the literature so far, while more than 100 germline variations have been reported since 1982 when TRAPS was first described.

Of the 5 *TNFRSF1A* mosaic variations identified, 4 are located in a small region of the cysteine-rich domain (CRD) 2, and one involves a cysteine residue of the CRD1 domain (Figure 3).

To date, no difference in disease severity has been observed between the germline and the mosaic variations.

Other SAIDs

Mosaic and germline variations have been reported in other SAID genes, such as *NLR4* (n=4 and n=15), *NOD2* (n=2 and n=35), *STING1* (n=2 and n=13), and *JAK1* (n=1 and n=4), respectively. However, due to the limited number of patients with mosaic variations in these genes, genotype/phenotype correlation studies are currently precluded. Noteworthy, most of the mosaic variations identified in SAID genes are widely distributed in various tissues.

Conclusions

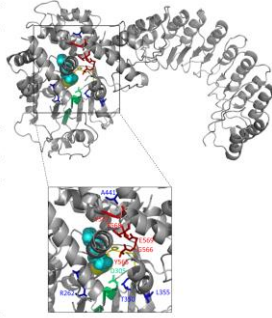
This study emphasizes the high frequency of somatic mosaic variations in NLRP3-AIDs. The phenotypic spectrum of NLRP3-AIDs appears to be related to both the germline/mosaic status and the localization in cryopyrin of the underlying variations.

Mosaic variations in the *NLRP3*, *TNFRSF1A*, and *NLR4* genes can cause symptoms even when present at very low allele frequencies (below 5%). Furthermore, misdiagnosis may occur due to the low allele frequency of mosaic variations.

Most frequent NLRP3 mutations

Germline mutations	CpG dimer	Patients' phenotype	Reported in mosaic state
T309M	Yes	MWS – CINCA (n=30)	No
K237R	Yes	FCAS – MWS (n=23)	No
L305S	Yes	FCAS/MWS – MWS – CINCA (n=43)	No
L355P	No	FCAS (n=17)	No
A443Y	Yes	FCAS – MWS – CINCA (n=3)	No

Mosaic mutations	CpG dimer	Patients' phenotype	Reported in germinal state
E588R	Yes	MWS – CINCA (n=10)	CINCA (n=1)
E586G	No	CINCA (n=1)	No
E586G	No	MWS (n=1)	No
Y585C	No	MWS – CINCA (n=4)	No
E335R	No	CINCA (n=4)	No
D355A	No	MWS (n=3)	No
F568I	No	CINCA (n=3)	CINCA (n=1)
G566D	No	MWS (n=2)	No
G565S	No	CINCA (n=3)	No
H727S	No	MWS – CINCA (n=2)	No
Y727S	No	CINCA (n=1)	CINCA (n=5)



Highlight of the five most frequently mutated aminoacids in mosaic state (in red), in germline state (in blue) and in both mosaic and germline state (in green). Cyan: adenosine di-Phosphate (ADP); yellow: Walker A motif; green: Walker B motif.

Figure 2. Localization in the 3D structure of *NLRP3* of the most frequently reported pathogenic (mosaic and germline) variations. CINCA: chronic infantile neurological, cutaneous and articular syndrome, FCAS: familial cold autoinflammatory syndrome, MWS: Muckle-Wells syndrome

The most frequent germline variations were not found in the mosaic state suggesting that they may be lead to minimal or no symptoms in the mosaic state.

Conversely, the most frequent mosaic variations were rarely reported in the heterozygous state, suggesting that *NLRP3* variations found exclusively in the mosaic state may be incompatible with life if present in the germinal state (Figure 2).

TNFRSF1A

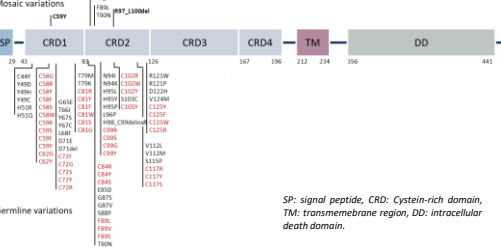


Figure 3. The *TNFRSF1A* pathogenic variations reported to date (in red the recurrent variations and in bold the variations identified in this study).