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## (#38060 P163) 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 *Infevers* 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.

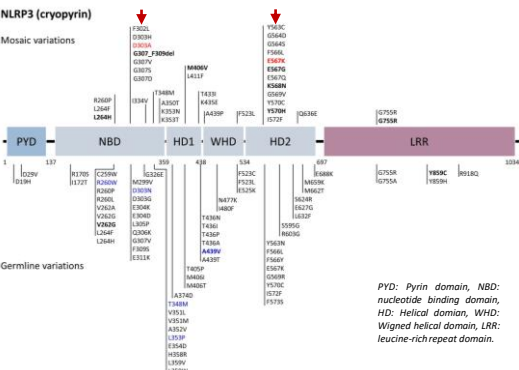


Figure 1. The *NLRP3* pathogenic variations reported to date (in red the recurrent mosaic variations, in blue the recurrent germline variations, and in bold the variations identified in this study).

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 *NLRP4* (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 germinal/mosaic status and the localization in cryopyrin of the underlying variations.

Mosaic variations in the *NLRP3*, *TNFRSF1A*, and *NLRP4* 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	CqG dimer	Patient's phenotype	Reported in mosaic state
T350M	Yes	MWS - CINCA (n=30)	No
R262W	Yes	FCAS - MWS (n=23)	No
G305N	Yes	FCAS/MWS - MWS - CINCA (n=31)	No
L355P	No	FCAS (n=17)	No
A443V	Yes	FCAS - MWS - CINCA (n=13)	No

Mosaic mutations	CqG dimer	Patient's phenotype	Reported in germinal state
E169R	Yes	MWS - CINCA (n=10)	CINCA (n=1)
E169G	No	CINCA (n=1)	No
E169Q	No	MWS (n=1)	No
V95C	No	MWS - CINCA (n=4)	No
G301H	No	CINCA (n=4)	No
G302S	No	MWS (n=1)	No
F98L	No	CINCA (n=3)	CINCA (n=1)
G166D	No	MWS (n=2)	No
G166S	No	CINCA (n=1)	No
V172C	No	CINCA (n=2)	CINCA (n=5)
V172W	No	CINCA (n=1)	No

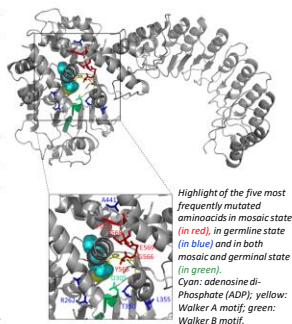


Figure 2. Localization in the 3D structure of *NLRP3* of the most frequently reported pathogenic (mosaic and germline) variations. CINCA: chronic infantile neurological, cutaneous and articular syndrome, FCAS: familial cold autoinflammatory syndrome, MWS: Muckle-Wells syndrome

The most frequent germline variations were not found in the mosaic state suggesting that they may 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

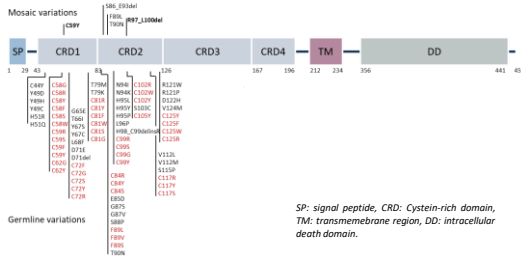


Figure 3. The *TNFRSF1A* pathogenic variations reported to date (in red the recurrent variations and in bold the variations identified in this study).