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Late-onset expression of an autoinflammatory disease: Identification and functional characterization of a mosaic variant in *NLRC4*

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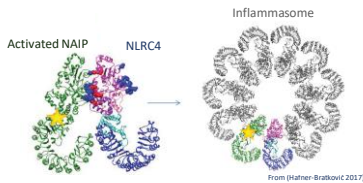
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Introduction

NLRC4 acts as an adaptor protein that is recruited by NAIP to initiate the formation of the *NLRC4*-NAIP inflammasome upon recognition of bacterial elements.

The *NLRC4*-NAIP inflammasome requires the adaptor protein ASC (apoptotic speck protein containing a CARD) to recruit the caspase-1 protease, which cleaves the pro-interleukins (pro-IL1 β and pro-IL18), resulting in the production of their active forms (IL1 β and IL18) and triggering the inflammatory response.

NLRC4 gain-of-function germline variants are implicated in *NLRC4*-associated autoinflammatory disease (*NLRC4*-AID), an autosomal dominant disorder that may include severe neonatal enterocolitis or macrophage activation syndrome (MAS). To date, only four mosaic and 15 germline pathogenic variations in the *NLRC4* gene have been reported in *NLRC4*-AID patients.



Objectives

The aim of this study was to evaluate the functional impact of a *NLRC4* somatic mosaic variation identified in a patient presenting with an autoinflammatory disease and to describe the related disease phenotype.

Methods

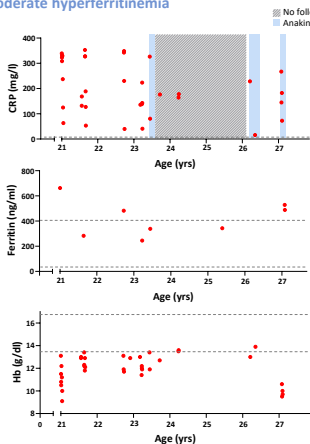
- An autoinflammatory diseases gene panel (1100X) was used to analyze the patient's leukocyte DNA.
- Plasma levels of pro-inflammatory cytokines (IL1 β , IL6, TNF α and IL18) were measured by ELISA.
- NLRC4* constructs, whether wild type or mutant, were overexpressed in HEK293T cells co-expressing the inflammasome components ASC and caspase-1.
- Activation of the *NLRC4*-NAIP inflammasome was assessed by measuring the apoptotic speck aggregates (insoluble ASC oligomers) and NF κ B pathway activity.

Results

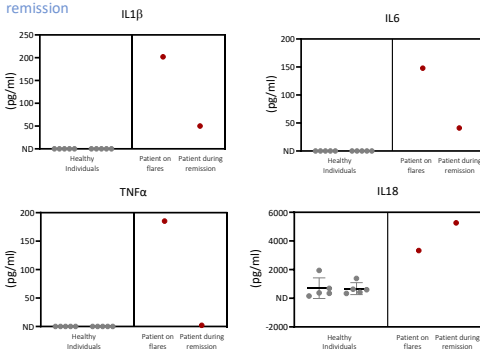
Clinical Features

The patient is a 28-year-old man with a chronic psychosis since the age of 18 who has been experiencing:

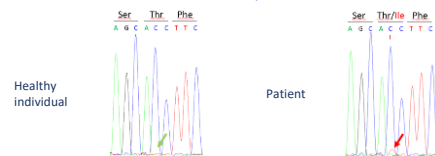
- severe inflammatory crises characterized primarily by fever, arthralgia and abdominal pain
- elevated C-reactive protein levels accompanied by anemia and leukocytosis
- moderate hyperferritinemia



Increased plasma levels of the pro-inflammatory cytokines IL1 β , TNF α , IL6 and IL18 during flares, with sustained elevated levels of IL18 during patient's remission



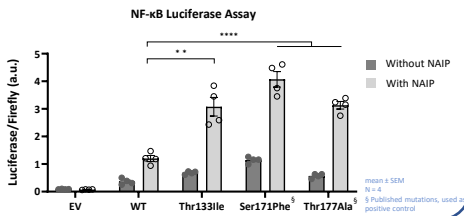
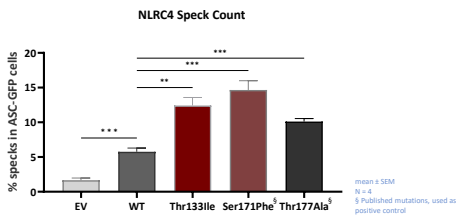
Identification of a mosaic c.398C>T, p.(Thr133Ile) *NLRC4* variation (variant allele fraction of 5%)



Functional Analyses

The p.Thr133Ile *NLRC4* variation induced increased inflammasome activation

The p.Thr133Ile *NLRC4* variant activated the NF κ B pathway



Conclusion

In this study, we identified a novel mosaic variation of *NLRC4* in an adult patient with an autoinflammatory disease. Functional studies demonstrated the gain-of-function pathogenic effect of the identified variation on inflammation.

Abbreviations: CARD, caspase recruitment domain; CRP, C-reactive protein; EV, Empty Vector; Hb, hemoglobin; NAIP, nucleotide-binding leucine-rich repeat family apoptosis inhibitory protein; *NLRC4*, nucleotide-binding leucine-rich repeat family CARD domain containing 4; WT, Wild-type.