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

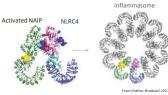
Farah Diab¹*, Camille Louvrier ¹.²*, Marc Fabre ³, Mira Rabbaa ¹, Aphrodite Daskalopoulou ¹, Eman Assrawi ¹, Rahma Mani ¹, Quentin Brandao ¹, Romain Levergeois ², Angela Arenas Garcia ¹, Florence Dastot Le Moal ², William Piterboth ², Frédéric Lézot ¹,

¹ Sorbonne Université, Inserm, Childhood Genetic Diseases Laboratory, Hôpital Armand-Trousseau, 75012 Paris, France. ² Département de Génétique Médicale, Assistance Publique-Hôpitaux de Paris (APHP), Hôpital Armand-Trousseau, 75012 Paris, France. ³ Service de Médecine interne, Maladies infectieuses et Hématologie, Centre Hospitalier Pierre Oudot, Bourgoin-Jallieu, France. * These authors contributed equally

Introduction

Autoinflammatory diseases (AIDs) usually emerge in childhood, characterized by fever episodes that resolve spontaneously. They often entail inflammation affecting the skin, serosa (like the peritoneum, pericardium, and meninges), and synovium (joints). The pathophysiology of AIDs is intricate, involving innate immune components such as inflammasomes—complexes of multiple proteins crucial for initiating the inflammatory process.

The NLRC4-NAIP inflammasome is composed of NLRC4, which acts as an adaptor protein and is recruited by NAIP. Upon the recognition of bacterial elements, this inflammasome utilizes the adaptor protein ASC (apoptotic speck protein containing a CARD) to recruit the caspase-1 protease. Caspase-1 then cleaves the pro-interleukins (pro-IL1b and pro-IL18), resulting in the production of their active forms (IL1b and IL18) and the initiation of the inflammatory response.



Germline variants in NLRC4 leading to gain-of-function are associated with NLRC4-associated autoinflammatory disease (NLRC4-AID), an autosomal dominant disorder that may involve 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

This study sought to evaluate functional impact of a NLRC4 somatic mosaic variation identified in a patient presenting with an autoinflammatory disease and to characterize the related disease phenotype.

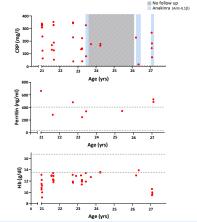
Methods

- 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 NFkB pathway activity.

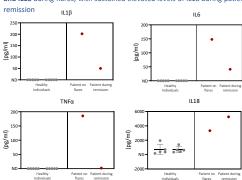
Results

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

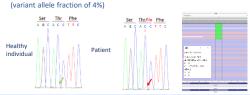
- severe inflammatory crises characterized primarily by fever. arthralgia and abdominal pain
- elevated C-reactive protein levels accompanied by anemia and leukocytosis
- moderate hyperferritinemia



Increased plasma levels of the pro-inflammatory cytokines IL1B, TNF α , IL6 and IL18 during flares, with sustained elevated levels of IL18 during patient's

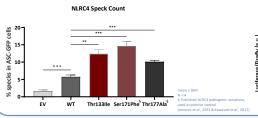


Identification of a mosaic c.398C>T. p.(Thr133Ile) NLRC4 variation (variant allele fraction of 4%)

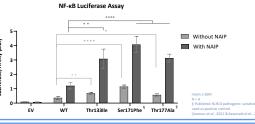


Functional Analyses

The p.Thr133Ile NLRC4 variation induced increased inflammasome activation



The p.Thr133Ile NLRC4 variation activated the NFkB pathway



Conclusion

This study identified a novel mosaic variation of NLRC4 in an adult patient exhibiting both an autoinflammatory disease and chronic psychosis. Functional investigations demonstrated that the identified variation had a pathogenic gain-of-function effect 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 repea





