



A CDC42 Stop-loss Mutation in a Patient with Relapsing Polychondritis and Autoinflammation

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To the Editor,

Cell division control protein 42 homolog (CDC42) is one of the most well-studied members of the Rho GTPase family. Rho GTPases have a critical role in a wide variety of pivotal cellular functions like rearrangement of the actin cytoskeleton, cell polarity, cell motility, vesicle trafficking, cell cycle regulation, transcription activation, and migration [1]. Mutations in *CDC42* are associated with a clinically heterogeneous group of phenotypes, including growth retardation, neurodevelopmental anomalies, cardiac malformations, immune dysregulation, and hematological disturbances (Table S1) [2]. Martinelli and colleagues classified the *CDC42* variants in three groups based on their position in the *CDC42* structure and their functional characterization. Recently, variants in the C-terminal region of *CDC42* have been described, which make up a fourth group of mutations. These mutations cause an autoinflammatory syndrome characterized by neonatal onset of fever, rashes, and cytopenias ultimately leading to secondary hemophagocytic lymphohistiocytosis (HLH) in a significant number of patients.

We report the oldest patient with a known pathogenic mutation in *CDC42* diagnosed with relapsing polychondritis (RP) and autoinflammation, who succumbed at the age of 55 from multiorgan failure. At age 42, she presented to the clinical immunological department with short stature resembling achondroplasia (height of 134 cm), subtle dysmorphic

features (round face with flat profile, mild upslanting of her palpebral fissures, and a wide nasal tip), hepatosplenomegaly, subglottic stenosis, scleritis, and inflammation of both auricles. From childhood onwards, she suffered from recurrent infections including multiple pneumonias and an episode of viral meningitis. She worked as an artist and had a clinical history of asthma and progressive bilateral sensorineural deafness since early adulthood. Neurologically, she was completely normal and brain MRI showed no structural abnormalities. Immunoglobulin screening at the time of presentation showed an isolated IgM deficiency (<0.3 g/L; ref 0.45–2.3 g/L) with normal IgG and elevated IgA (3.9–22.0 g/L; ref 0.76–3.91 g/L). Other laboratory evaluations revealed an increased ESR and CRP, mild anemia, and slightly elevated liver enzymes. Auto-immune serological tests were negative. No thrombocytopenia or leukopenia were observed; however, there was a slight decrease of B-cells (0.07×10^9 ; ref $0.1\text{--}0.4 \times 10^9$) and NK-cells (0.02×10^9 ; ref $0.1\text{--}0.4 \times 10^9$). Bone marrow biopsy revealed hypercellularity with trilineage hematopoiesis interpreted as reactive changes. Over time, she was admitted multiple times for pneumonias and treated with antibiotics. She was diagnosed as RP and suspected from an immunodeficiency. She was treated with glucocorticosteroids and IgG maintenance therapy. When she was 44, a partial jejunum resection was performed after she suffered from acute abdominal pain due to intestinal necrotizing vasculitis. At age 55, she was admitted with acute abdominal pain from a suspected ileus. During admission, she worsened and died due to hemodynamic instability and pulmonary hypertension; additionally, during autopsy, a persistent foramen ovale was found.

Because of the complex nature and severity of the disease, WES was performed on whole blood DNA of the patient after informed consent was obtained. Analysis revealed a heterozygous stop-loss mutation (NM_001039802, c.576A > C; p.*192Cys*24, gnomAD frequency, never observed) in *CDC42* (Fig. 1b), which causes an abnormal

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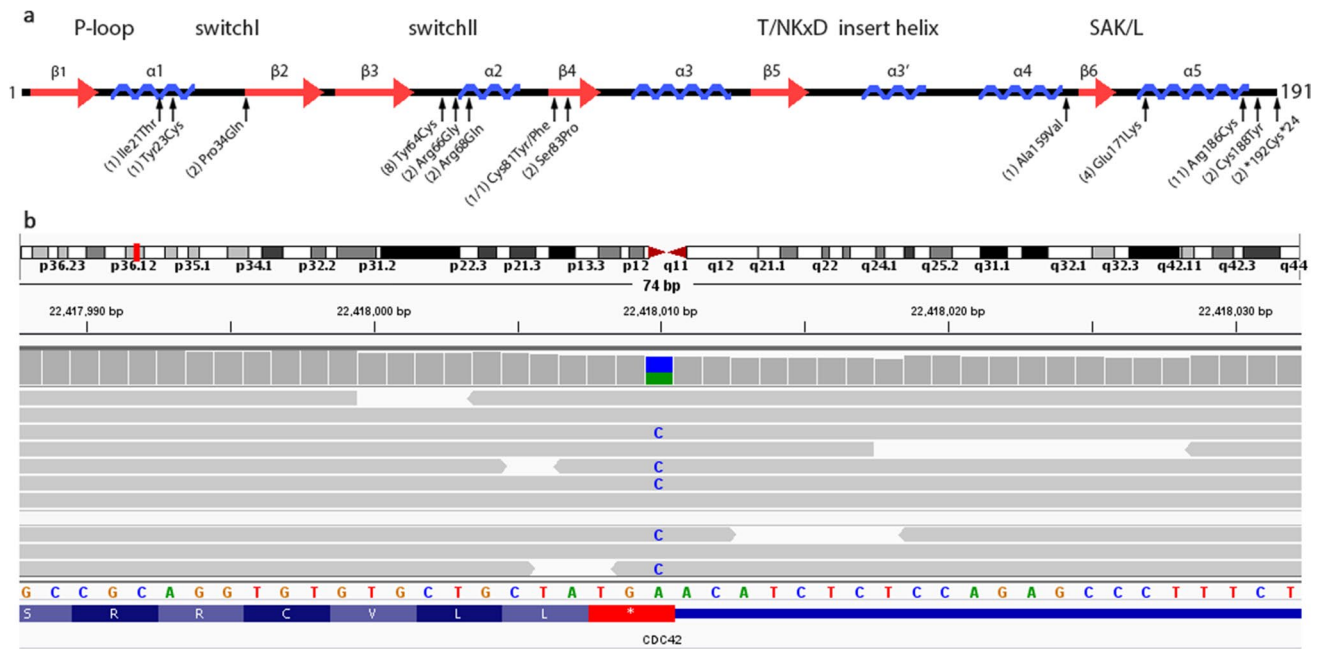


Fig. 1 a Schematic representation of the secondary structure (α -helices and β -strands) of *CDC42* and the positions of known disease-causing *CDC42* mutations and their reported frequency. The variant reported here (c.576A>C; p.*192Cys*24) is included in this

figure. **b** The heterozygous c.576A>C mutation at the final codon of *CDC42* results in read-through of the stop codon and adds 24 amino acids to the C-terminus of the *CDC42* protein

addition of 24 amino acids to the *CDC42* protein. The specific mutation we found was previously described in a patient with neonatal-onset multisystem inflammatory disease (NOMID), an IL-1-mediated autoinflammatory disease [3]. Recently, functional analysis of this particular mutation showed impaired geranyl-geranylation resulting in Golgi-restricted mislocalization of the mutant protein, hyperactivation of the pyrin inflammasome, and subsequent accelerated proteasomal degradation [4, 5]. Moreover, we also found extremely rare and severe truncating heterozygous mutations in *PANX3* (NM_052959 c.765delC; p.V255fs, gnomAD frequency 3.98×10^{-6}) and *JDP2* (NM_001135049 c.476dupC; p.T159fs, gnomAD frequency 4.00×10^{-6}), which both play a role in cartilage and bone development. Unfortunately, her parents were already deceased at the time of these findings, so we could not determine the de novo status of these mutations. However, we performed Sanger sequencing in her immunologically healthy sister for the observed variants and all were absent. Therefore, we could not rule out a contributing and modifying role for these rare variants.

RP is a rare progressive inflammatory disorder that affects the cartilaginous tissue throughout the body. It is characterized as an episodic immune-mediated condition most often affecting the ears, nose, joints, and respiratory tract, but it can also have systemic and ocular manifestations. The exact etiology and pathogenesis remain elusive, partly because of the rareness and heterogeneity of the condition. However,

there is evidence for a cell-mediated autoimmune reaction and autoantibodies matrix proteins like type II, IX, and XI collagen or matrilin-1 and cartilage oligomeric matrix proteins (COMP). Recently, somatic mutations in the X-linked gene *UBA1* have been associated with chondritis. Moreover, RP is associated with several immunologic and hematologic conditions, suggesting an underlying immunologic mechanism.

Currently, at least 39 patients have been described in literature with mutations in *CDC42* (Fig. 1 and Table S1). A broad spectrum of clinical phenotypes is associated with these variants. Patients can be roughly categorized into four groups based on the pathogenic mutation. Most pathogenic *CDC42* mutations have been investigated functionally, showing a disrupted protein function of *CDC42*, including impaired binding between *CDC42* and its regulators and effectors, hyperactivity of nucleotide exchange resulting in increased *CDC42* signaling, and aberrant palmitoylation and geranyl-geranylation leading to mislocalization of *CDC42* (reviewed in [1]). These specific consequences likely do account for the variable clinical phenotypes associated with *CDC42* variants. Our patient harbored the p.*192Cys*24 mutation in the C-terminal of *CDC42*. She presented with systemic autoinflammatory disease, a characteristic finding of C-terminal mutations. Similar to other patients, she also presented with short stature, recurrent infections, hepatosplenomegaly, and transaminitis. However, unlike

other patients with C-terminal mutations, her disease was not neonatal onset nor did we observe severe cytopenias. Differences in phenotype may be explained by the level of detailed phenotypic description of patients, the occurrence of rare variants in additional genes that can modify the clinical phenotype and the age of disease presentation. However, despite an intricate genotype–phenotype relationship, some intragroup variability is also observed as highlighted by this and other cases [2].

CDC42 is critical for cytoskeletal rearrangement, which affects cell mobility and migration. Cell motility is driven by cytokines and chemokines and is essential for the immune system to adequately respond to pathogens. Moreover, an impaired actin cytoskeleton also reduces the ability of immune cells to adequately invaginate the plasma membrane necessary for endocytosis, phagocytosis, and formation of the immunological synapse. Mutations and defects in genes that play a role in actin cytoskeleton rearrangement have been described in primary immunodeficiencies such as *WASP* and *DOCK8*. Complete aberration of *CDC42* is lethal suggesting a crucial role of *CDC42* in normal development. Unfortunately, mammalian models carrying heterozygous *CDC42* mutations are still lacking; however, knock-out models of *Cdc42* have been studied intensively. Interestingly, *Cdc42*-deficient mice demonstrated the critical function of *Cdc42* for normal morphogenesis and functioning of many organ systems including the immune, cardiac, and nervous systems as well as the cartilaginous tissue.

In conclusion, we present an adult female with RP, autoinflammation, and recurrent infections in whom genetic analysis revealed describe a stop-loss mutation in *CDC42*. The phenotype showed similarities to the other reported patients with C-terminal *CDC42* mutations, but unlike those, she did not present at neonatal age, nor did she suffer from severe cytopenias and life-threatening inflammation during childhood. Mutations in the C-terminal region of *CDC42*, therefore, do not necessarily cause severe neonatal-onset inflammation, but can cause later-onset, longstanding systemic autoinflammation and necrotizing vasculitis. This particular clinical phenotype expands the growing spectrum of disease caused by *CDC42* mutations.

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Author Contribution All authors contributed to the study conception, design, and writing. Rogier van Wijck, Martin van Hagen, and Paul van Daele wrote the case report. Rogier van Wijck, Sigrid Swagemakers,

and Peter van der Spek performed WES analysis and interpretation. The first draft of the manuscript was written by Rogier van Wijck and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval Informed consent was obtained from all individual participants included in the study. Genetic analysis was performed on whole exome sequencing data generated to acquire a diagnosis. Therefore, approval by a Medical Ethics Committee was not necessary.

Competing Interests The authors declare no competing interests.

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References

1. El Masri R, Delon J. RHO GTPases: from new partners to complex immune syndromes. *Nat Rev Immunol.* 2021;21(8):499–513.
2. Martinelli S, Krumbach OHF, Pantaleoni F, Coppola S, Amin E, Pannone L, et al. Functional dysregulation of *CDC42* causes diverse developmental phenotypes. *Am J Hum Genet.* 2018;102(2):309–20.
3. Gernez Y, de Jesus AA, Alsaleem H, Macaubas C, Roy A, Lovell D, et al. Severe autoinflammation in 4 patients with C-terminal variants in cell division control protein 42 homolog (*CDC42*) successfully treated with IL-1beta inhibition. *J Allergy Clin Immunol.* 2019;144(4):1122–5.e6.
4. Coppola S, Insalaco A, Zara E, Di Rocco M, Marafon DP, Spadaro F, et al. Mutations at the C-terminus of *CDC42* cause distinct hematopoietic and autoinflammatory disorders. *J Allergy Clin Immunol.* 2022;150(1):223–8.
5. Nishitani-Isa M, Mukai K, Honda Y, Nihira H, Tanaka T, Shibata H, et al. Trapping of *CDC42* C-terminal variants in the Golgi drives pyrin inflammasome hyperactivation. *J Exp Med.* 2022;219(6):e20211889.

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