Brief report

Mutations at the *C*-terminus of CDC42 cause distinct hematopoietic and autoinflammatory disorders

Simona Coppola, PhD,[a]* Antonella Insalaco, MD,[b]* Erika Zara, MSc,[c,d] Martina Di Rocco, PhD,[e,f] Denise Pires Marafon, MD,[b] Francesca Spadaro, PhD,[g] Luca Pannone, PhD,[c] Luciapia Farina, MSc,[b] Luca Pasquini, PhD,[g] Simone Martinelli, PhD,[e] Fabrizio De Benedetti, MD, PhD,[b]‡ and Marco Tartaglia, PhD[c]‡ *Rome, Italy*

Background: Pathogenic missense variants in cell division control protein 42 (*CDC42*) differentially affect protein function, causing a clinically wide phenotypic spectrum variably affecting neurodevelopment, hematopoiesis, and immune response. More recently, 3 variants at the *C*-terminus of CDC42 were proposed to similarly impact protein function and cause a novel autoinflammatory disorder.

Objectives: We sought to clinically and functionally classify these variants to improve patient management.

Methods: Comparative analysis of the available clinical data and medical history of patients was performed. *In vitro* and *in vivo* studies were carried out to functionally characterize individual variants.

Results: Differently from what had previously been observed for the p.R186C change causing neonatal-onset cytopenia, autoinflammation, and recurrent hemophagocytic lymphohistiocytosis, p.C188Y and p.*192Cext*24 promoted accelerated protein degradation. Unprenylated CDC42^{C188Y} did not behave as a membrane-bound protein, whereas the residual CDC42^{*192Cext*24} mutant replicated the CDC42^{R186C} behavior, being targeted to the Golgi apparatus in a palmitoylation-dependent manner. Assessment of *in vitro* polarized migration and development in *Caenorhabditis elegans* documented a loss-of-function behavior of the p.C188Y and p.*192Cext*24 variants. Consistently, the 3 pathogenic variants were associated with different clinical presentations, with dysmorphisms, severity, and age of onset of cytopenia and extent of autoinflammation representing major differences.

Conclusions: Pathogenic variants at the CDC42 *C*-terminus differently impact protein stability, localization, and function, and cause different diseases, with p.R186C specifically associated with neonatal-onset pancytopenia and severe autoinflammation/hemophagocytic lymphohistiocytosis requiring emapalumab and bone marrow transplantation, and p.C188Y and p.*192Cext*24 causing anakinra-sensitive autoinflammation. (J Allergy Clin Immunol 2022;150:223-8.)

Key words: *CDC42, NOCARH syndrome, autoinflammation, HLH, MAS, cytopenia, anakinra, emapalumab, palmitoylation, Golgi apparatus*

INTRODUCTION

Cell division control protein 42 (CDC42) belongs to the Rho family of small monomeric guanosine triphosphate hydrolases. It orchestrates several cellular processes, including cell division, polarity, and migration, and controls development and physiology of various systems, including the nervous, immune, and hematopoietic ones.[1,2] CDC42 function is regulated by reversible localization of the protein at the cytoplasmic leaflet of the plasma membrane and other intracellular membranes, which is mediated by geranyl-geranylation, a carboxy-terminal (*C*-terminal) post-translational lipidation at Cys,[188] and CDC42 binding to multiple regulatory proteins. Pathogenic missense *CDC42* variants differently impacting protein function have been reported to cause a wide spectrum of neurodevelopmental phenotypes with variable hematopoietic dysfunction.[3-7] More recently, in 4 pediatric patients, we identified a *de novo* missense mutation (p.R186C) at the *C*-terminus to uniquely affect CDC42 localization and cause a distinctive condition termed NOCARH (Neonatal-Onset Cytopenia, Autoinflammation, and Recurrent Hemophagocytic lymphohistiocytosis [HLH]).[8] In NOCARH, the immunologic and hematopoietic involvement may occur early in life without

From [a]the National Centre Rare Diseases, Istituto Superiore di Sanità, [b]the Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, [c]the Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, IRCCS, [d]the Department of Biology and Biotechnology "Charles Darwin," "Sapienza" University of Rome, [e]the Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, [f]the Department of Human Neuroscience, "Sapienza" University of Rome, and [g]Core Facilities, Istituto Superiore di Sanità, Rome.

*These authors equally contributed to this study.

‡These authors jointly coordinated this study.

This work was supported, in part, by grants from the Italian Ministry of Health (Ricerca Corrente 2019-2021 to F.D.B. and M.T. and grant no. 5x1000 to M.T.), Associazione Italiana per la Ricerca sul Cancro (AIRC; grant no. IG 21614 to M.T.), Italian Ministry of Research (grant no. FOE 2019 to M.T.), Fondazione Bambino Gesù (Vite Coraggiose to M.T.), and Istituto Superiore di Sanità (Bando Ricerca Indipendente ISS 2020-2022-ISS20-39c812dd2b3c to S.C.).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 13, 2021; revised December 27, 2021; accepted for publication January 18, 2022.

Available online February 12, 2022.

Corresponding author: Fabrizio De Benedetti, MD, PhD, Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome 00146, Italy. E-mail: fabrizio.debenedetti@opbg.net. Or: Marco Tartaglia, PhD, Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome 00146, Italy. E-mail: marco.tartaglia@opbg.net.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2022.01.024

Abbreviations used

CDC42: Cell division control protein 42
C-terminal/-terminus: Carboxy-terminal/-terminus
HLH: Hemophagocytic lymphohistiocytosis
HSCT: Hematopoiestic stem cell transplantation
LoF: Loss of function
NOCARH: Neonatal-Onset Cytopenia, Autoinflammation, and Recurrent Hemophagocytic lymphohistiocytosis
WT: Wild-type

evidence of neurodevelopmental defects. Our original finding was confirmed by other reports documenting the peculiar functional impact and clinical features associated with the p.R186C substitution.[8-11] Independently, Gernez et al[12] described inflammatory and hematological phenotypes of 4 patients heterozygous for 3 variants affecting the CDC42 *C*-terminus (p.R186C, p.C188Y, and p.*192Cext*24).[12]

Here, we analyze the functional and clinical impact of those variants, providing evidence that they are functionally and clinically distinct.

RESULTS AND DISCUSSION

We previously showed that CDC42^{R186C} is geranylgeranylated at Cys^{188} within the *C*-terminal canonical cysteine (C), aliphatic amino acid (A), any amino acid (X) motif.[8,9] This mutant is also aberrantly palmitoylated, resulting in Golgi-selective membrane trapping.[8,9] In striking contrast, both p.*192Cext*24 and p.C188Y impair CDC42 geranylgeranylation by altering the *C*-terminal cysteine (C), aliphatic amino acid (A), any amino acid (X) motif. No additional lipid modifications were predicted at the CDC42^{C188Y} *C*-terminus (GPS-Lipid, http://lipid.biocuckoo.org/webserver.php), whereas palmitoylation at 3 sites (Cys^{188}, Cys^{192}, and Cys^{200}) was anticipated for the CDC42^{*192Cext*24} mutant (GPS-Palm, http://gpspalm.biocuckoo.cn/download.php) (Fig 1, *A*). Given the role of lipidation in controlling CDC42 targeting to cellular compartments,[13] both mutants were predicted to be mislocalized. Immunofluorescence analysis on COS1 cells transiently transfected to express wild-type (WT) CDC42 or each mutant confirmed proper distribution of CDC42^{WT} in cytosol and membranes, and the Golgi-restricted localization of palmitoylated CDC42^{R186C} (Fig 1, *B*, left). As expected, Golgi sequestration of CDC42^{R186C} was reverted by treatment with 2-bromopalmitate, a general inhibitor of protein palmitoylation. This subcellular relocation of CDC42^{R186C} resembled the WT protein localization, consistent with a proper prenylation (Fig 1, *B*, right). In line with the lack of lipidation at the *C*-terminus, the CDC42^{C188Y} mutant did not show any significant targeting to intracellular membranes and was characterized by an aberrant massive nuclear localization (Fig 1, *B*). Differently, CDC42^{*192Cext*24} accumulated in the Golgi similarly to CDC42^{R186C}. Golgi targeting of this mutant was dependent on palmitoylation, as demonstrated by treating cells with 2-bromopalmitate treatment (Fig 1, *B*, right). Similar to CDC42^{C188Y}, lack of lipidation in 2-bromopalmitate–treated CDC42^{*192Cext*24} was associated with nuclear translocation, confirming the peculiar mislocalization resulting from impaired prenylation. To identify the cysteine residue(s) at the CDC42^{*192Cext*24} *C*-terminus serving as substrate(s) for palmitoylation, a set of amino acid substitutions (C188G, C192G, and C200G) or a combination of them (C188G+C192G, C188G+C200G, and C192G+C200G) was introduced, and the subcellular localization of these mutants was assessed in COS1 cells (Fig 1, *C*). As shown, the 3 residues variably contributed to Golgi sequestration, with Cys^{188} playing a minor role in this process. These data indicate that 2 palmitoylation modifications are mandatory for Golgi targeting of CDC42^{*192Cext*24}. Overall, these findings demonstrate a substantially diverse behavior of CDC42^{C188Y} compared with CDC42^{*192Cext*24} and CDC42^{R186C}.

Then we assessed whether p.C188Y and p.*192Cext*24 affect protein expression/stability by western blot analysis using lysates of transiently transfected COS1 cells in the absence and presence of the protein synthesis inhibitor cycloheximide and the proteasome inhibitor MG132 (Fig 2, *A*). As we previously showed, p.R186C did not affect protein levels.[6] In contrast, substantially reduced levels of both p.C188Y and p.*192Cext*24 mutants were observed, with a barely detectable expression of CDC42^{*192Cext*24}. Treatment with MG132 rescued levels of cycloheximide-treated proteins, indicating accelerated proteasomal degradation. Overall, these data documented a disruptive impact of p.*192Cext*24 and p.C188Y on protein stability, supporting their distinct functional behavior compared with CDC42^{R186C}. The occurrence of accelerated protein degradation in CDC42^{C188Y} and CDC42^{*192Cext*24} strongly pointed to a loss-of-function (LoF) effect as the underlying mechanism of action for both mutations.

Previous functional characterization of the NOCARH-associated CDC42^{R186C} protein documented its hypomorphic behavior in terms of polarized migration in NIH3T3 cells and developmental processes controlling *Caenorhabditis elegans* vulval development.[8] We used the 2 experimental systems to compare the behavior of the p.C188Y and p.*192Cext*24 variants. Wound healing assay in transiently transfected NIH3T3 cells documented LoF of both p.C188Y and p.*192Cext*24 (Fig 2, B; see Fig E1 and Videos E1-E5 in this article's Online Repository at www.jacionline.org). Consistently, *C elegans* lines ubiquitously overexpressing *CDC-42*^{C188Y} under the control of a heat-shock–inducible promoter displayed a severe reduction in the prevalence of both protruding vulva and multivulva phenotypes compared with animals overexpressing the WT protein or the CDC-42^{R186C} mutant (Fig 2, *C*). The p.*192Cext*24 variant was not modeled in this system because the *C*-terminal tail of the protein differs substantially between the 2 species. These data support a severe hypomorphic effect of p.C188Y on Wiskott–Aldrich Syndrome protein (WASP) signaling mediating vulval morphogenesis and complete LoF on RAS/mitogen-activated protein kinase signaling controlling vulval induction.[5] Taken together, our findings demonstrate a definite difference in the functional consequences of the 3 *C*-terminal CDC42 variants (Table I).

Analysis of the available clinical data from the literature and intramural clinical records indicates that the 3 *CDC42* variants are associated with distinct clinical phenotypes (Table II), mirroring the collected functional observations. Although only 2 subjects among the 9 patients heterozygous for p.R186C were reported to have minor facial dysmorfism,[12] this feature was observed in all individuals carrying the p.C188Y and p.*192Cext*24 variants.[12] Polymorphic erythematous skin rash was documented in

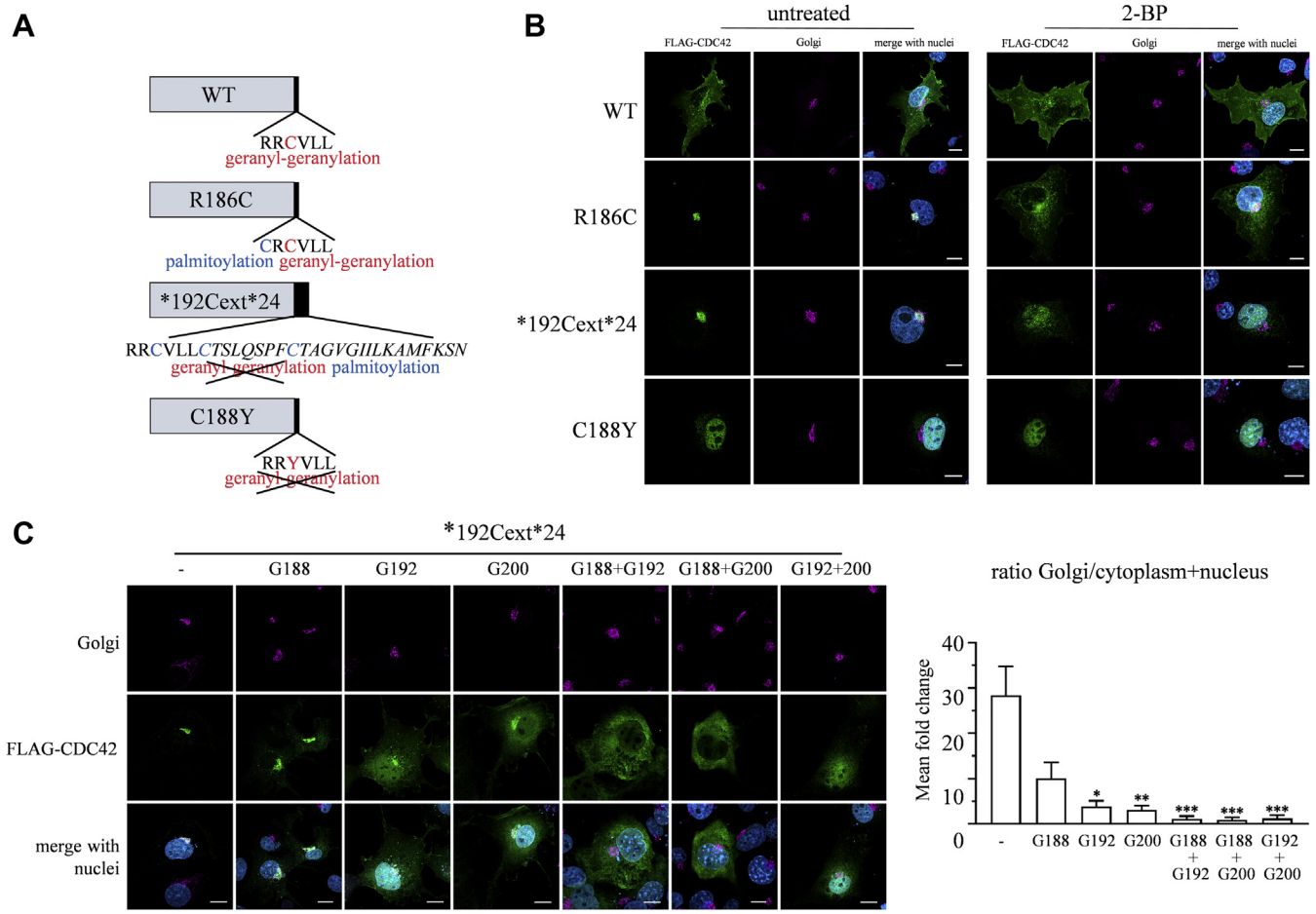

FIG 1. Pathogenic *C*-terminal CDC42 variants differently impact protein lipidation and localization. **A,** *In silico* prediction of *C*-terminus lipidation in disease-causing $CDC42^{R186C}$, $CDC42^{*192Cext*24}$, and $CDC42^{C188Y}$ proteins. **B,** Subcellular localization of CDC42 proteins in untreated (*left*) and 2-BP–treated (*right*) transfected COS1 cells. **C,** Single and double substitutions of cysteine residues in $CDC42^{*192Cext*24}$ impair Golgi-restricted localization. Scale bars, 10 μm. *2-BP,* 2-Bromopalmitate.

all patients with p.R186C and in none of those carrying the other variants. In p.R186C heterozygous patients, rash did not appear to be clinically relevant with the exception of a single subject showing a severe psoriasiform dermatitis that did not improve after hematopoiestic stem cell transplantation (HSCT).[9] Considering the hematological involvement, severe neonatal-onset trilinear pancytopenia was reported as the predominant feature of all patients carrying p.R186C.[8-12] In contrast, neutropenia was not reported in patients carrying p.C188Y or p.*192Cext*24, and anemia and thrombocytopenia appear to occur later in life in individuals heterozygous for the p.C188Y substitution. Notably, the patient with p.*192Cext*24 presented with neonatal-onset anemia and thrombocytopenia, and subsequently developed a transfusion-dependent thrombocytopenia, for a few months only, showing an intermediate phenotype. Remarkably, although treatment with the IL-1 inhibitor anakinra was used in most patients carrying *C*-terminal variants (9 of 12), thrombocytopenia and anemia improved only in patients carrying the p.C188Y or p.*192Cext*24 changes.[12] No effect or marginal effect of anakinra, even at high dose, on thrombocytopenia and anemia was reported in patients with the p.R186C variant (Fig 3, *A*), with the exception of 1 of the p.R186C-affected patients.[12] Neutropenia was found in all patients carrying the p.R186C variant, and persisted despite high-dose anakinra and G-CSF (Fig 3, *B*). Thus, among the pathogenic CDC42 variants, p.R186C is unique in causing neonatal-onset severe trilineage dyshematopoiesis, possibly due to decreased content of hematopoietic progenitor cells.[8] Cytopenias in these individuals persisted despite therapy with anakinra that, on the other hand, partially controlled systemic inflammation.

Because HLH is a key severe feature in several of these patients, we searched for clinical and laboratory data fulfilling the 2 sets of available criteria for HLH/macrophage activation syndrome (HLH 2004 criteria and the macrophage activation syndrome in systemic juvenile idiopathic arthritis criteria),[14,15] or for statements from the authors that at least 1 of these sets of criteria was fulfilled. In 5 of 9 patients heterozygous for the p.R186C substitution, the above conditions were met and HLH was reported as present.

In the remaining 4 patients, data were not sufficient to demonstrate fulfillment of the criteria. In contrast, among the 3 patients with p.C188Y or p.*192Cext*24, HLH was reported only in 1 subject with apparent response to anakinra.

Death occurred in 5 of the p.R186C-carrying patients, mostly while being prepared for HSCT. No information on survival for 1 early-onset apparently severe subject was reported.[10] One

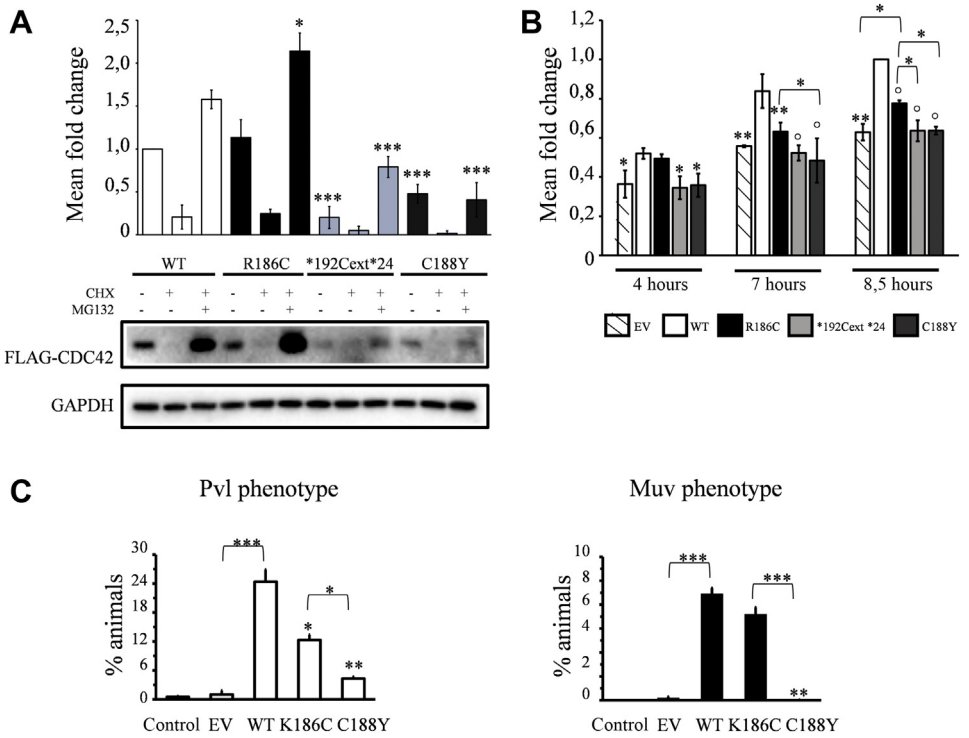

FIG 2. Pathogenic CDC42 variants variably affect protein function. **A,** CDC42^{*192Cext*24} and CDC42^{C188Y} undergo accelerated degradation via proteasome. **B,** CDC42^{*192Cext*24} and CDC42^{C188Y} abolish polarized migration in NIH3T3 cells. Migration-fold changes were calculated with respect to cells overexpressing WT CDC42 at 8.5 hours after scratch. **C,** CDC42^{C188Y} affects vulval development in *Caenorhabditis elegans*. *GAPDH,* Glyceraldehyde-3-phosphate dehydrogenase.

TABLE I. Distinctive functional features associated with *C*-terminal variants of CDC42

Functional feature	R186C	C188Y	*192Cext*24
Protein function			
Prenylation	Yes	No (predicted)	No (predicted)
Palmitoylation	Yes	No	Yes
Accelerated degradation	No	Yes	Yes
Mislocalization	Golgi-restricted	Nuclear/cytoplasmic	Golgi-restricted
Cell function			
Polarized migration	Reduced	Loss	Loss
Vulval development (*Caenorhabditis elegans*)			
Muv phenotype	Slightly reduced	Absent	No data available
Pvl phenotype	Reduced	Strongly reduced	No data available

Muv, Multivulva phenotype; *Pvl*, protruding vulva phenotype.

survivor was described with apparently mild disease responsive to anakinra,[12] and 1 with early-onset severe disease that led to successful HSCT at age 24 months.[9] One of our patients survived: a very severe HLH flare was successfully treated with the IFN-γ inhibitor emapalumab, and subsequently HSCT.[8] IFN-γ neutralization did not revert cytopenias that were corrected only by HSCT, consistently with the impact of p.R186C on hematopoietic progenitor cells.[8]

Overall, multiple lines of evidence indicate that the identified mutations involving the *C*-terminal tail of CDC42 are functionally and clinically different. First, *in vitro* and *in vivo* data support the view that the 3 variants differently perturb CDC42 function, having variable consequences on lipidation, stability, subcellular localization, and intracellular signaling. Second, they result in different clinical phenotypes with different presentations, onset, and severity of cytopenias and response to therapeutic IL-1 targeting. In particular, efficacy of IL-1 inhibition in individuals with unprenylated CDC42 is in agreement with previous reports, indicating that prenylation defects of Rab family guanosine triphosphate hydrolases in patients homozygous for LoF mutations of the gene encoding the mevalonate kinase are causative of an IL-1–dependent autoinflammatory disease.[16,17] In the patients with unprenylated CDC42, anemia and thrombocytopenia appear to be dependent on inflammation because they are reverted by IL-1 inhibition. In contrast, in patients with p.R186C, cytopenia is in general not responsive to IL-1 inhibition. Available data suggest that the p.R186C substitution triggers overactivation of several inflammatory pathways with increased production of IL-1, IL-6, TNF, IL-18, IFN-γ, and CXCL9.[8,9,12] IL-1 overproduction appears to

TABLE II. Distinctive clinical features associated with variants affecting the CDC42 *C*-terminus

Feature	R186C	C188Y	*192C*24
Reported patients	9 (references 8-11)	2 (reference 12)	1 (reference 12)
Facial dysmorphisms	1 (mild, not further specified) 1 (mild, low-set ears, mild arched palate)	Yes (frontal bossing, hypertelorism, depressed nasal bridge in 1; frontal bossing, macrocephaly, thin sparse hair, and depressed nasal bridge in 1)	Yes (frontal bossing)
Neonatal-onset pancytopenia	Yes	No	No
Trasfusion-dependent anemia	Yes	Yes	Yes
Response to IL-1 inhibition*	No	Yes	Yes
Thrombocytopenia	Yes, severe	1 (mild)	Yes, severe
Response to IL-1 inhibition*	No	Yes	Yes
Neutropenia	Yes, severe	Not reported	Not reported
Response to IL-1 inhibition*	No		
Myelofibrosis (MF)	Yes, in 2	Absent	Absent
Acute myeloid leukemia	Yes, in 1	Absent	Absent
Skin polymorphic erythematous rash	Yes	No	No
Additional skin manifestations	Psoriasiform erythroderma in 1 case	Nodular lesions in 1 case, macular lesions in 1 case	Macular and purpuric rash
Autoinflammation	Yes	Yes	Yes
Response to IL-1 inhibition*	Partial†	Complete	Complete
HLH syndrome‡	Yes in 5	Yes in 1 patient	No
Response to IL-1 inhibition	Yes in 1 No in 4	Yes in 1 patient	
HSCT	Performed in 3 cases, survived and cured (2 cases)	Not performed	Not performed

All mutations were *de novo* except for 2 siblings who inherited a paternal mosaicism.[10]

CRP, C-reactive protein; *MAS*, macrophage activation syndrome; *sJIA*, systemic juvenile idiopathic arthritis.

*Six patients heterozygous for the R186C amino acid substitution and all subjects carrying the other variants were treated with the IL-1 inhibitor anakinra.

†Response judged on the basis of available data (fever, rash, CRP, and glucocorticoid dose).

‡We considered as having HLH those patients in which fulfillment of the HLH-2004 criteria and/or the MAS in sJIA criteria was reported. Insufficient data for the other 4 patients (ie, lack of absolute values related to laboratory workflow) do not allow to assess fulfillment of HLH criteria.

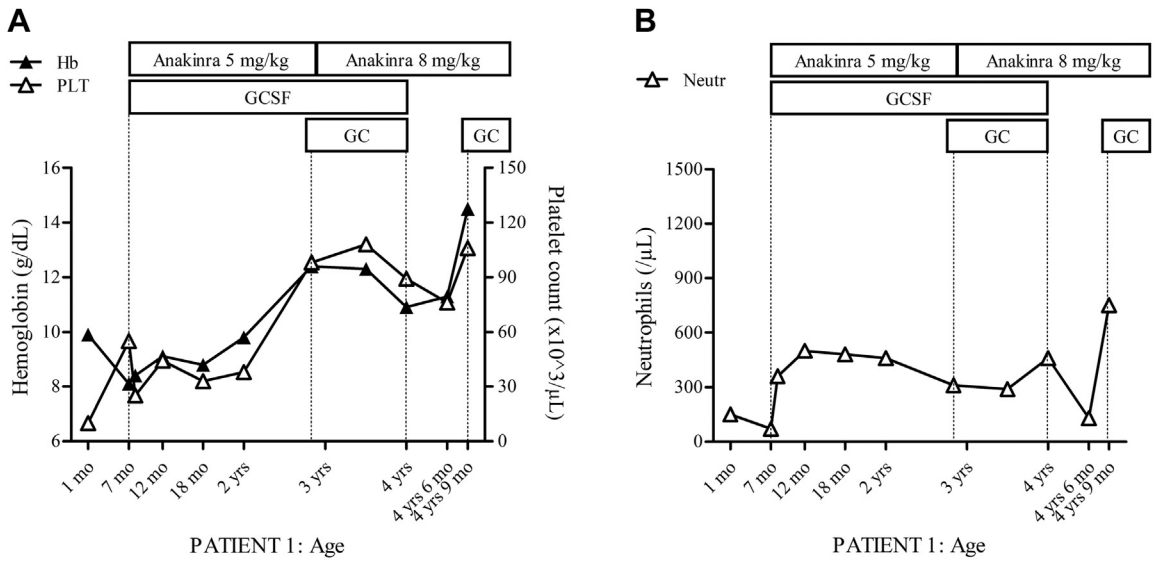

FIG 3. Impact of different treatments on cytopenia in the long-term survivor affected subject harboring the p.R186C variant. **A,** Hemoglobin and platelet counts. **B**, Neutrophil counts. Full clinical information of the subject is reported in Lam et al[8] (patient 1). *Hb*, Hemoglobulin; *Plt*, platelet.

be responsible for some of the autoinflammatory features; overproduction of IL-18 drives IFN-γ and HLH, which may be fatal.[8] HSCT should be considered ideally when the disease is controlled, because it may lead to resolution of inflammation, cytopenia, and absence of HLH recurrence.

We thank Serenella Venanzi (Istituto Superiore di Sanità, Rome) and Claudia Compagnucci (Ospedale Pediatrico Bambino Gesù, Rome) for skillful technical assistance. *C elegans* strains were provided by the *Caenorhabditis* Genetics Center (CGC), which is funded by the National Institutes of Health Office of Research Infrastructure Programs (grant no. P40 OD010440). We also thank WormBase.

Key messages

- **p.R186C results in an aberrantly palmitoylated CDC42 protein constitutively targeted to the Golgi. The associated disorder, NOCARH syndrome, is characterized by neonatal-onset pancytopenia and HLH, and requires treatment with emapalumab (IFN-γ–blocking antibody) to manage HLH flares, and bone marrow transplantation for full recovery.**
- **p.C188Y impairs CDC42 geranyl-geranylation and causes accelerated protein degradation and impaired membrane translocation. This mutant is associated with an autoinflammatory condition responsive to anakinra.**
- **p.*192Cext*24 impairs CDC42 geranyl-geranylation and causes accelerated CDC42 degradation. The residual protein is aberrantly palmitoylated and targeted to the Golgi. The associated condition is characterized by neonatal-onset anemia and thrombocytopenia, and autoinflammation responsive to anakinra.**

REFERENCES

1. Heasman SJ, Ridley AJ. Mammalian Rho GTPases: new insights into their functions from in vivo studies. Nat Rev Mol Cell Biol 2008;9:690-701.
2. Melendez J, Grogg M, Zheng Y. Signaling role of Cdc42 in regulating mammalian physiology. J Biol Chem 2011;286:2375-81.
3. Takenouchi T, Kosaki R, Niizuma T, Hata K, Kosaki K. Macrothrombocytopenia and developmental delay with a de novo CDC42 mutation: yet another locus for thrombocytopenia and developmental delay. Am J Med Genet A 2015;167A:2822-5.
4. Takenouchi T, Okamoto N, Ida S, Uehara T, Kosaki K. Further evidence of a mutation in CDC42 as a cause of a recognizable syndromic form of thrombocytopenia. Am J Med Genet A 2016;170A:852-5.
5. 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;102:309-20.
6. Asiri A, Alwadaani D, Umair M, Alhamoudi KM, Almuhanna MH, Nasir A, et al. Pancytopenia, recurrent infection, poor wound healing, heterotopia of the brain probably associated with a candidate novel de novo CDC42 gene defect: expanding the molecular and phenotypic spectrum. Genes 2021;12:294.
7. Szczawinska-Poplonyk A, Ploski R, Bernatowska E, Pac M. A novel CDC42 mutation in an 11-year old child manifesting as syndromic immunodeficiency, autoinflammation, hemophagocytic lymphohistiocytosis, and malignancy: a case report. Front Immunol 2021;11:318.
8. Lam MT, Coppola S, Krumbach OHF, Prencipe G, Insalaco A, Cifaldi C, et al. A novel disorder involving dyshematopoiesis, inflammation, and HLH due to aberrant CDC42 function. J Exp Med 2019;216:2778-99.
9. Bekhouche B, Tourville A, Ravichandran Y, Tacine R, Abrami L, Dussiot M, et al. A toxic palmitoylation of Cdc42 enhances NF-κB signaling and drives a severe autoinflammatory syndrome. J Allergy Clin Immunol 2020;146:1201-4.e8.
10. He T, Huang Y, Ling J, Yang J. A new patient with NOCARH syndrome due to CDC42 defect. J Clin Immunol 2020;40:571-5.
11. Verboon JM, Mahmut D, Kim AR, Nakamura M, Abdulhay NJ, Nandakumar SK, et al. Infantile myelofibrosis and myeloproliferation with CDC42 dysfunction. J Clin Immunol 2020;40:554-66.
12. 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-1β inhibition. J Allergy Clin Immunol 2019;144:1122-5.e6.
13. Nishimura A, Linder ME. Identification of a novel prenyl and palmitoyl modification at the CaaX motif of Cdc42 that regulates RhoGDI binding. Mol Cell Biol 2013;33:1417-29.
14. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
15. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, et al, Paediatric Rheumatology International Trials Organisation; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Histiocyte Society. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481-9.
16. Park YH, Wood G, Kastner DL, Chae JJ. Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. Nat Immunol 2016;17:914-21.
17. De Benedetti F, Gattorno M, Anton J, Ben-Chetrit E, Frenkel J, Hoffman HM, et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. N Engl J Med 2018;378:1908-19.