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The growing spectrum of human diseases caused by inherited *CDC42* mutations

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Abstract

Several recent studies provide valuable new information that expands the spectrum of human disease associated with mutations in *CDC42*.

CDC42, an intracellular member of the Rho-family GTPases, is a key regulator of cell polarity that is highly conserved among eukaryotes (reviewed in (1)). By regulating the assembly of actin cytoskeletal structures in a temporal-spatial manner, *CDC42*, along with RAC and RHO A, controls cell shape and cell movement. In this way, *CDC42* plays an important role in migration and directed functions, processes that are integral for embryonic development, hematopoiesis or immune system function. *CDC42* also influences other functions such as cell growth and proliferation through effects on multiple downstream cell signaling pathways, via actin-based platforms and/or direct interactions of *CDC42* with other effectors.

As a GTPase, *CDC42* functions as an intracellular molecular switch. It cycles between two forms – an active form when bound to GTP, and an inactive form when bound to GDP – subject to complex regulation by GTPase Activation Proteins (GAPs), Guanine Exchange Factors (GEFs), and Guanine Dissociation Inhibitors (GDIs). When activated, *CDC42* undergoes a conformational change that enables it to associate with membranes and to interact with effector molecules, which in turn undergo their own conformational changes to exert downstream biochemical functions.

To understand how *CDC42* biologically functions, much work had been done using cell lines that express dominantly negative or constitutively active mutants. However, these mutants can exert non-specific effects by binding guanine nucleotide exchange factors that not only affect *CDC42* but also other Rho-family GTPases. Physiological studies using mice

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rendered genetically deficient in Cdc42 have been limited by embryonic lethality. However, mice rendered conditionally deficient for Cdc42 revealed its requirement for proper tissue morphogenesis and functioning, including effects on the cardiac, nervous, hematopoietic, and immune systems.

Clues provided by studies in mutant mice were soon followed by the identification of humans with inherited *CDC42* mutations. From 2015 onwards, the first patients were reported to have a *de-novo* heterozygous missense mutation in *CDC42* at p.Tyr64Cys, associated with a constellation of features termed Takenouchi-Kosaki syndrome, which includes dysmorphism, developmental delay, macrothrombocytopenia, and in one case immunodeficiency (2–4). In 2018, Martinelli and colleagues reported 15 more patients with *de-novo* heterozygous missense mutations in *CDC42*, several of which were recurrent (5). Disease characteristics shared by the patients included poor growth, facial dysmorphism, neuro-developmental abnormalities, and malformations of the heart, and non-specific hematological and immune aberrations.

More recently, widespread use of whole exome sequencing in patients with complex or severe conditions has led to discoveries that heterogeneous disease phenotypes can be associated with mutations in the same gene. Along this line, Lam and colleagues recently reported four patients with recurrent *de-novo* heterozygous missense mutations in *CDC42* at p.Arg186Cys, a variant not previously associated with Takenouchi-Kosaki syndrome (6). These patients had a different disease, termed NOCARH for neonatal-onset cytopenia with dyshematopoiesis, autoinflammation, rash, and hemophagocytic lymphohistiocytosis (HLH). The pathogenic hallmark of HLH is defective NK cell cytotoxicity in the context of other hyperactive immune responses. Indeed, defects in NK cell cytotoxicity, migration, and conjugate formation, as well as overproduction of proinflammatory cytokines, were all observed in NOCARH. Importantly, these observations help to explain why most of the patients showed some improvement after treatment with IL-1 and/or IFN- γ antagonists. Furthermore, they explain why HSCT, which is the treatment of choice for HLH, cured disease in the one patient who underwent this procedure.

Additionally, similar clinical findings were reported in four other patients who had a severe neonatal autoinflammatory disease, including HLH / macrophage activation syndrome. Gernez and colleagues found similar *de-novo* heterozygous missense mutations nearby in the C-terminal region of *CDC42*, and observed that these patients also improved after treatment with IL-1 receptor antagonists (7).

More recently, including in this and an earlier issue of the *Journal of Clinical Immunology*, five reports add to the rapidly expanding body of knowledge about this fascinating new disease. The first, by Bucciol and colleagues, describes the oldest patient so far reported, who at 26 years was found to have Takenouchi-Kosaki syndrome with the usual p.Tyr64Cys mutation in a conserved domain of *CDC42* required for its GTPase activity (8). Surprisingly, the patient also had systemic autoinflammation previously associated with NOCARH and other C-terminal region mutations, as well as recurrent severe infections leading to bronchiectasis and death from sepsis. Several new features were observed including myelofibrosis, pulmonary hemorrhage, and vascular malformations. The second, by He and

Yuan, described a patient with the p.Arg186Cys mutation, dysmorphism, and NOCARH along with elevated serum IgE and a possible mild protein allergy [cite ref when accepted]. The third, by Bekhouhe and colleagues, described another patient with the p.Arg186Cys mutation and similar findings including elevated serum IgE, but who continued to have difficulties despite HSCT or IL-1 antagonists (9). Thus, these cases potentially add to the phenotypic spectrum but opens questions regarding genotype-phenotype correlations of CDC42 as well as the potential for other clinical or secondary influences.

The fourth report, by Verboon and colleagues, describes two additional siblings with a shared heterozygous p.Arg186Cys mutation, inherited via paternal germline mosaicism [in press, cite ref when published]. Both patients presented with congenital pancytopenia and myelofibrosis, with one dying of complications after HSCT and the other dying after progressing to acute myeloid leukemia in infancy. This distinct phenotype, and the demonstration that the mutation exerts deleterious effects on the function of hematopoietic stem and progenitor cells, led the authors to explore the possibility of CDC42 dysfunction more broadly. Intriguingly, they saw a correlation with decreased CDC42 expression in the bone marrow in other cases of primary myelofibrosis, suggesting the importance of this common pathway in disease pathogenesis. Finally, a fifth report recently described a child with a novel *de-novo* heterozygous p.Cys81Tyr mutation, who had syndromic immunodeficiency, autoinflammation, HLH, and Hodgkin's lymphoma, illustrating again that the broad phenotypic spectrum of this disease includes malignancy (10).

Together these five recent studies provide valuable new information that expands the spectrum of human disease associated with mutations in *CDC42*. However, they also raise other interesting questions: As more patients are identified, can they shed new light into genotype-phenotype relationships? If so, what are the specific molecular perturbations that can explain how different mutations give rise to the different clinical presentations? At present, most of the severe immunologic syndrome presentations stem predominantly from variation at residue 186. There is strong biochemical basis for how this variation impacts CDC42 biology as the variant is abnormally palmitoylated, which causes inappropriate CDC42 localization with protein retention at the Golgi complex. However, more detailed studies of the other variants are needed to elucidate how they lead to an immunological/ autoinflammatory disease, and why some patients with the same variants might fail to do so. Finally, do either germline or somatic mutations in *CDC42* underlie some forms of myelofibrosis or leukemia, and can modulating CDC42 activity be used therapeutically for these conditions? Clearly, there is much more to be learned from patients about how CDC42 functions physiologically in humans.

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