Mutations in *CCNO* and *MCIDAS* lead to a mucociliary clearance disorder due to reduced generation of multiple motile cilia

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Since the 1980s, a few case reports described patients with oto-rhino-pulmonary symptoms and respiratory epithelia lacking cilia who were subsequently diagnosed to suffer from "ciliary aplasia" or "acilia syndrome". Via a whole exome sequencing approach, we analyzed "ciliary aplasia" candidates (including patients from previous reports) and identified recessive mutations in *CCNO* (encoding Cyclin O) and *MCIDAS* (encoding Multicilin) in 9 and 16 individuals, respectively [1, 2]. All individuals suffered from severe respiratory symptoms of the upper and lower airways and development of bronchiectasis at an early age. Thorough analysis of respiratory epithelial cells obtained by nasal brush biopsy by both transmission electron microscopy (TEM) and immunofluorescence analysis (IF) revealed that respiratory cilia were not completely absent; some cells still retained one or two cilia. These cells not only showed a reduction of cilia by TEM and IF, but also a reduction and mislocalization of basal bodies and rootlets throughout the cytoplasm. Detailed analyses by IF in both man and *Xenopus* revealed that this reduction of

cilia number was due to a centriole amplification defect in the acentriolar pathway, which is specific for multiciliated cells [1, 2].

IF showed that MCIDAS functions upstream of CCNO and FOXJ1, which is important for transcriptional control of axonemal motor proteins such as DNAH5 and CCDC39. Whereas cilia in *CCNO*-mutant cells still contain motility-related proteins such as DNAH5 and CCDC39 and can display normal beating patterns, *MCIDAS*-mutant cells are immotile and lack those axonemal motor proteins [1, 2] .

MCIDAS and *CCNO* lie adjacently on chromosome 5q11 in a region related to multiciliogenesis, and act in the same pathway underlying multiciliogenesis. Based on these findings, we propose that this disease now should be referred to as "mucociliary clearance disorder with reduced generation of multiple motile cilia" (RGMC).

References

1. Wallmeier J, Al-Mutairi DA, Chen C-T, Loges NT, Pennekamp P, Menchen T, *et al*.: **Mutations in *CCNO* result in congenital mucociliary clearance disorder with reduced generation of multiple motile cilia.** *Nature Genetics* 2014,**46**(6):646–51. 10.1038/ng.2961

2. Boon M, Wallmeier J, Ma L, Loges NT, Jaspers M, Olbrich H, *et al*.: ***MCIDAS* mutations result in a mucociliary clearance disorder with reduced generation of multiple motile cilia.** *Nat Commun* 2014, **5:** 4418.