The Cohen syndrome-associated protein COH1 is a novel, giant Golgi matrix protein required for Golgi integrity

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Mutations in COH1 (VPS13B) cause autosomal recessive Cohen syndrome, which is mainly characterized by mental retardation, postnatal microcephaly, pigmentary retinopathy, and intermittent neutropenia. However, the biochemical characteristics, cellular localization, or functional role of the encoded protein COH1 (3997aa) have so far not been addressed. Our cell biological analysis showed strong co-localization of COH1 with the cis-Golgi marker protein GM130, which was preserved even upon chemical disruption of the Golgi architecture. Further biochemical analysis showed that COH1 is a peripheral membrane protein similar to its remote homologue, Vps13p in yeast. Vps13p has been found to regulate anterograde and retrograde vesicular transport of transmembrane proteins between the prevacuolar compartment and the trans-Golgi network. Accordingly, we found that loss of COH1 upon RNAi impairs the ability of the Golgi ribbon to (re)assemble and thus induces fragmentation into ministacks. Furthermore, COH1 regulates the formation of Golgi-derived membrane tubules consistent with its possible function in intracellular membrane traffic. In summary, our study identifies COH1 as a Golgi matrix protein required for maintaining Golgi integrity and function. We suggest that our results provide an improved insight into the molecular function of COH1 in Golgi membrane traffic, which in the future may help to unravel its role in brain development, neuronal function, and general pathology in patients with Cohen syndrome.