Structure of the endosomal Commander complex mutated in Ritscher-Schinzel syndrome: combining crystallography, cryoEM and AlphaFold2


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Keywords: Membrane trafficking, protein complex structure

The Commander complex is required for endosomal recycling of diverse transmembrane cargos and is mutated in Ritscher-Schinzel syndrome. It comprises two subassemblies: Retriever composed of VPS35L, VPS26C and VPS29, and the CCC complex which contains twelve subunits: COMMD1-COMMD10 and the coiled-coil domain-containing (CCDC) proteins CCDC22 and CCDC93. Combining X-ray crystallography, electron cryomicroscopy and in silico predictions we have assembled a complete structural model of Commander [1]. Retriever is distantly related to the endosomal Retromer complex but has unique features preventing the shared VPS29 subunit from interacting with Retromer-associated factors. The COMMD proteins form a distinctive hetero-decameric ring stabilised by extensive interactions with CCDC22 and CCDC93. These adopt a coiled-coil structure that connects the CCC and Retriever assemblies and recruits a sixteenth subunit, DENND10, to form the complete Commander complex. The structure allows mapping of disease-causing mutations and reveals the molecular features required for the function of this evolutionarily conserved trafficking machinery.

Figure 1. Structure of the sixteen subunit Commander protein complex.