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Structural Studies of the CELSR1 Extracellular Region Reveal a Compact Multidomain Module of thirteen Domains which Regulates Signaling

Sumit J. Bandekar,[1] Krassimira Garbett,[2] Szymon P. Kordon,[1] Tanner R. Shearer,[2] Ethan Dintzner,[1] Richard C. Sando,[2] and Demet Araç[1]

[1]University of Chicago; and [2]Vanderbilt University

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Cadherin EGF Laminin G seven-pass G-type receptors (CELSRs) are conserved members of the adhesion class of G protein-coupled receptors; they are essential for embryogenesis and neural development. CELSRs have large and enigmatic extracellular regions (ECRs) with nine cadherin repeats and a variety of adhesion domains which couple cell adhesion to receptor signaling. This paradigm regulates the development of planar cell polarity, including the closure of the neural tube during embryonic development. Despite numerous cell and animal studies, molecular details on CELSR proteins are sparsely available, precluding an integrative understanding of CELSR biology. Here, we report the 4.2 Å cryo-EM reconstruction of the CELSR1 ECR which enables unambiguous assignment of the 13 domains within the structure. These domains form a compact module mediated by robust and evolutionarily conserved interdomain interactions. This compact module provides a plethora of potential ligand binding sites for the various adhesion domains within the structure and hints at a model where the compact module could be pulled apart by robust mechanical force. We present biophysical evidence that the CELSR1 ECR forms an extended dimer in the presence of Ca^{2+}, which we propose represents the cadherin repeats dimerizing in a configuration similar to protocadherins. We employ cellular assays with full-length CELSR1 and truncation constructs to assess the adhesive and signaling functions of this protein. We assign the N-terminal CADH1-8 module as necessary for cell adhesion and we show the C-terminal CAHD9-GAIN module regulates signaling. Our work provides important molecular context to the literature on CELSR function and lays the groundwork for further elucidation of structure/function relationships in CELSRs.