Divide to conquer: Deciphering the interaction landscape of whirlin, an Usher syndrome protein.

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Whirlin is a scaffold protein whose mutations cause hereditary hearing loss, retinitis pigmentosa and Usher syndrome, the most common cause of combined deafness and blindness.[1] Despite its medical relevance, how whirlin functions and fails in disease remain largely unknown, a bottleneck for development of gene therapies. Moreover, although previous studies have confined whirlin research to hearing and blindness, several clinical reports mention the *WHRN/DFNB31* gene in pathologies other than sensory disorders. This argues that whirlin acts as a ubiquitous membrane scaffold whose full biological role has been underestimated.

Our work combines structural biology and biochemistry together with cross-sectoral collaborations with the aim to uncover the full functional and interaction profile of whirlin.

Result 1: Our genetic analysis of Usher patients reveals that missense variations in whirlin cluster in unexpected protein regions: N-terminal region and PDZ domain extensions. This aligns with my earlier demonstration that structural extensions of PDZ domains critically modulate their folding and binding[2,3] and with the inter-domain allostery characterised in the PDZ1–PDZ2 supramodule of whirlin.[4,5]

Result 2: Following genetic analysis and using a divide and conquer approach, we resolved the role of each domain in this multidomain protein and its supramodular organisation. Our results provide evidence that whirlin's capacity to organise distinct protein complexes at multiple submembrane locations depends on its ability to (i) engage diverse protein partners, (ii) anchor to the plasma membrane via phosphoinositide interactions (iii) oligomerise and create multivalent scaffolds, and (iv) nucleate condensates through liquid-liquid phase separation.[6]

Result 3: We have generated the first full expression landscape of whirlin in the human body. We report that whirlin is almost ubiquitously expressed, with enrichment in specific epithelial cells, arguing that this usher protein might in fact be a universal scaffold in key tissues for absorption and secretion.

Together, these findings reframe whirlin from a sensory-cell protein to a ubiquitous membrane scaffold with broad and largely unexplored roles in human biology, and establish a molecular foundation for understanding how its dysfunction drives disease with direct implications for the development of precision medicine in Usher syndrome and beyond.

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