1. Phylogeny  
   AMHR2, also designated as MISR2, is a member of the transforming growth factor‐β (TGF‐β) receptor superfamily and is classified as a type II transmembrane serine/threonine kinase receptor. Orthologs of AMHR2 exist widely in vertebrates, with well‐characterized forms reported in mammals such as human, mouse, and canine, as well as in teleost fishes including medaka, Nile tilapia, and ayu. This receptor occupies a unique evolutionary niche in that it binds specifically to Anti‐Müllerian hormone (AMH) and mediates its effects on sexual differentiation and reproductive development. Although it shares structural and catalytic features with other TGF‐β type II receptors, AMHR2 is distinguished by its exclusive ligand specificity for AMH, reflecting an evolutionary adaptation in the gonadal differentiation pathway (hart2021structureofamh pages 1-1, mullen2019amhandamhr2 pages 1-2, nakamoto2021aylinkedantimüllerian pages 15-17).
2. Reaction Catalyzed  
   AMHR2 functions as the initiating component of a receptor complex in which, upon binding of its ligand AMH, it phosphorylates associated type I receptors. The catalytic process involves the transfer of a phosphate group from ATP to specific serine/threonine residues within the GS domain of type I receptors. In brief, the reaction proceeds as follows:  
     ATP + [Type I receptor]-L-serine/threonine → ADP + [Type I receptor]-L-serine/threonine-phosphate + H⁺  
   This phosphorylation event is essential to trigger downstream SMAD-mediated transcriptional regulation (hart2021structureofamh pages 1-1, mullen2019amhandamhr2 pages 2-3).
3. Cofactor Requirements  
   The kinase activity of AMHR2, as with most serine/threonine kinases, is dependent on the presence of Mg²⁺ ions. The Mg²⁺ cofactor is required for optimal ATP binding and proper positioning of the phosphate group for transfer, thereby facilitating the phosphorylation reaction (hart2021structureofamh pages 1-1).
4. Substrate Specificity  
   AMHR2 exhibits a high degree of substrate specificity in that its kinase activity is directed toward the phosphorylation of type I receptors, including ALK2, ALK3, and ALK6, within the receptor complex. Upon formation of the heterotetrameric complex following AMH binding, AMHR2 phosphorylates the GS domain of these type I receptors, which in turn become activated to phosphorylate receptor-regulated SMAD proteins. Although a detailed consensus phosphorylation motif for the type I receptor substrates has not been explicitly defined in the literature available here, the substrate specificity of AMHR2 is inherent to its role in TGF‐β signaling (hart2021structureofamh pages 3-5, mullen2019amhandamhr2 pages 2-3).
5. Structure  
   AMHR2 is a modular transmembrane protein composed of three distinct domains. The extracellular domain (ECD) adopts a three-finger toxin fold that is characteristic of TGF‐β type II receptors. In this structure, an extended finger 1 loop plays a critical role in binding to the convex knuckle region of AMH; hydrophobic interactions and salt bridges formed by residues in the finger 1 and the finger 2/3 loop ensure high-affinity and specific ligand binding (hart2021structureofamh pages 3-5, hart2021structureofamh pages 7-8). Following the ECD, AMHR2 contains a single transmembrane helix that anchors the receptor to the cell membrane. The intracellular domain is a serine/threonine kinase, organized into a bilobal kinase fold with a smaller N-terminal domain predominantly composed of β-strands and a larger C-terminal domain rich in α-helices. This classical kinase structure encompasses an activation loop and other conserved motifs essential for catalytic activity. Notably, the kinase domain of AMHR2 is constitutively active, although receptor signaling is regulated by ligand-induced receptor complex formation (hart2021structureofamh pages 1-1, hart2021structureofamh pages 5-7).
6. Regulation  
   Regulation of AMHR2 occurs at multiple levels. At the transcriptional level, the expression of AMHR2 is controlled by key transcription factors implicated in sexual differentiation, such as SOX9 and steroidogenic factor 1 (SF1), ensuring that the receptor is expressed in the appropriate tissues during critical developmental windows. Post-transcriptionally, alternative splicing results in isoforms of AMHR2; some splice variants lack essential exons required for ligand binding or kinase activity and may function as dominant-negative inhibitors. Ligand binding itself induces clustering and conformational changes within the receptor complex, thereby triggering the phosphorylation of type I receptors. Despite the intrinsic kinase activity of the receptor, full signal propagation requires the assembly of the heterotetrameric receptor complex, which serves as an additional regulatory checkpoint (mullen2019amhandamhr2 pages 3-4, hart2021structureofamh pages 1-1).
7. Function  
   AMHR2 is the dedicated receptor for Anti-Müllerian hormone (AMH) and plays a critical role in reproductive biology. In males, the AMH-AMHR2 signaling axis is essential during embryogenesis for the regression of the Müllerian ducts, thereby preventing the development of female reproductive tract structures. In females, AMHR2 contributes to the regulation of folliculogenesis by inhibiting the recruitment of primordial follicles and modulating follicle sensitivity to gonadotropins. Beyond its classic roles in gonadal differentiation, AMHR2 is also expressed in extragonadal tissues, including certain regions of the central nervous system, where it has been implicated in the regulation of gonadotropin-releasing hormone (GnRH) neuron activity. Functional studies in genetic models have demonstrated that loss-of-function mutations in AMHR2 lead to Persistent Müllerian Duct Syndrome (PMDS), characterized by the retention of Müllerian derivatives in genetic males, and underscore the receptor’s pivotal role in sexual differentiation and reproductive function (hart2021structureofamh pages 1-1, mullen2019amhandamhr2 pages 1-2, nakamoto2021aylinkedantimüllerian pages 20-22).
8. Other Comments  
   Mutations in AMHR2 are strongly associated with reproductive disorders. In particular, loss-of-function mutations causing premature truncation or misfolding of AMHR2 result in Persistent Müllerian Duct Syndrome (PMDS) in humans and animal models. For instance, in certain canine breeds, a nonsense mutation in AMHR2 leads to the retention of female reproductive tract structures in genetically male individuals, often accompanied by cryptorchidism. Although no specific inhibitors of AMHR2 have yet been widely adopted in clinical practice, detailed structural insights from the AMH–AMHR2 complex have provided a basis for exploring therapeutic strategies aimed at modulating receptor activity in disorders characterized by dysregulated AMH signaling, such as polycystic ovary syndrome (PCOS) and certain forms of infertility (mullen2019amhandamhr2 pages 8-9, nakamoto2021aylinkedantimüllerian pages 20-22, hart2021structureofamh pages 8-9).
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