Phylogeny  
AMHR2 is conserved across vertebrates; orthologues are present in mouse, rat, rabbit, chicken, zebrafish and Xenopus (Josso & di Clemente, 2003; Howard et al., 2022). Within the serine/threonine kinase receptor type-II (STKR-II) family it forms a distinct, low-identity (< 30 %) clade relative to ACVR2A/B, BMPR2 and TGFβR2 (Rak et al., 2019). Sequence identity to its closest paralogues is ~20 %, and AMHR2 is the only dedicated type-II receptor for a single TGF-β ligand (AMH) (Hart et al., 2021; Unknown Authors, 2022, pp. 80-83). Kinome analyses classify it in the STKR-II subgroup of the human kinome (Cate, 2022).

Reaction Catalyzed  
ATP + [type I receptor]-Ser/Thr ⇌ ADP + [type I receptor]-O-phospho-Ser/Thr (Josso & di Clemente, 2003).

Cofactor Requirements  
Mg²⁺, coordinated by the canonical HRD and DFG motifs of the kinase domain (Howard et al., 2022; Cate, 2022).

Substrate Specificity  
Direct substrates are the BMP-type I receptors ALK2/ACVR1, ALK3/BMPR1A and ALK6/BMPR1B; phosphorylation of their GS loops initiates Smad1/5/9 signalling (Unknown Authors, 2022, pp. 43-46; Cate, 2022). No linear consensus phosphorylation motif has yet been defined and the Johnson-2023 kinase atlas contains no entry for AMHR2 (Unknown Authors, 2022, pp. 43-46).

Structure  
Signal peptide → 127-residue extracellular domain (three-finger toxin fold with five disulfides) → single transmembrane helix → ~403-residue intracellular serine/threonine kinase domain (Rak et al., 2019).  
Extracellular complex: 2.6 Å crystal structure of AMH-bound AMHR2 ECD (PDB 7L0J/7L0I) shows a 933 Å² interface, a finger-1 loop unique to AMHR2 and a ~7.5 Å receptor shift relative to Activin/BMP complexes (Hart et al., 2021; Unknown Authors, 2022, pp. 73-76, 80-83). Key contacts include Lys534\_AMH with Asp81/Glu84\_AMHR2 and receptor residues Phe62, Met76, Asp81, Leu106, Thr108; mutations at these sites weaken signalling (Unknown Authors, 2022, pp. 69-73; Hart et al., 2020, pp. 6-7). Disulfide connectivity links the finger-2/3 loop to finger-2, contributing to ligand selectivity (Unknown Authors, 2022, pp. 80-83).  
Kinase domain: no experimental structure; sequence and AlphaFold models predict the canonical bilobal STKR-II fold with VAIK, HRD, DFG catalytic motifs, C-helix, GS box and activation loop (Cate, 2022; Howard et al., 2022).

Regulation  
• Two N-glycosylation sites in the ECD support correct folding (Josso & di Clemente, 2003).  
• Proteolytic removal of most of the ECD yields inactive oligomers retained in the ER (Rak et al., 2019).  
• Alternative splicing produces at least three C-terminally divergent isoforms (Rak et al., 2019).  
• Ligand activation requires a heterotetramer with ALK2/3/6; AMHR2 phosphorylates the type I receptor GS loop, which then autophosphorylates and recruits Smad substrates (Cate, 2022).  
• SMURF E3 ubiquitin ligases ubiquitinate type-II receptors, limiting signal amplitude (Howard et al., 2022).  
• Inhibitory Smads 6/7 dampen downstream signalling (Josso & di Clemente, 2003).

Function  
Expression is largely confined to reproductive tissues—fetal Sertoli cells, the mesenchyme surrounding the Müllerian duct, and ovarian granulosa cells (Unknown Authors, 2022, pp. 18-22; Josso & di Clemente, 2003).  
• Male embryos: mediates AMH-driven Müllerian duct regression (Hart et al., 2021).  
• Female ovary: restricts primordial follicle recruitment and modulates folliculogenesis (Unknown Authors, 2022, pp. 69-73).  
• Canonical pathway: AMH → AMHR2 + ALK2/3/6 → Smad1/5/9 phosphorylation → gene transcription (Unknown Authors, 2022, pp. 43-46).  
• Non-canonical pathway: AMHR2 can activate NF-κB independently of Smads in some contexts (Rak et al., 2019).

Other Comments  
Biallelic loss-of-function variants cause persistent Müllerian duct syndrome; a recurrent 27-bp exon-10 deletion and missense mutations (e.g., Met76, Asp81) abolish signalling (Rak et al., 2019; Hart et al., 2020, pp. 9-10). Conservative substitutions (M76V, D81E) retain in-vitro activity yet are found in PMDS patients, implying misfolding or trafficking defects (Unknown Authors, 2022, pp. 46-50). Reduced AMHR2 activity has also been linked to polycystic ovary syndrome (Unknown Authors, 2022, pp. 69-73).

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