Phylogeny  
• Orthologous genes have been cloned in Mus musculus, Rattus norvegicus, Oryctolagus cuniculus, Gallus gallus, Danio rerio and Xenopus laevis, demonstrating conservation across vertebrates (josso2003transductionpathwayof pages 2-3, howard2022molecularmechanismsof pages 1-2).  
• AMHR2 shares < 30 % sequence identity with the type-II receptors ACVR2A, ACVR2B, BMPR2 and TGFβR2, defining a distinct clade within the serine/threonine kinase receptor type-II (STKR-II) family (rak2019antimullerianhormonereceptor pages 3-5).  
• Sequence similarity to its closest paralogues is ~20 %, and the receptor has evolved as the only dedicated type-II receptor for a single TGF-β family ligand (AMH) (unknownauthors2022structuralandfunctional pages 80-83, hart2021structureofamh pages 1-1).  
• Structural and sequence analyses place AMHR2 in the STKR-II group of the human kinome (cate2022antimüllerianhormonesignal pages 6-8).

Reaction Catalyzed  
ATP + [type I receptor]-Ser/Thr → ADP + [type I receptor]-O-phospho-Ser/Thr (josso2003transductionpathwayof pages 2-3).

Cofactor Requirements  
Catalytic activity requires Mg²⁺ coordinated by the conserved HRD and DFG motifs of the kinase domain (howard2022molecularmechanismsof pages 1-2, cate2022antimüllerianhormonesignal pages 6-8).

Substrate Specificity  
• Direct substrates: BMP-type I receptors ALK2 (ACVR1), ALK3 (BMPR1A) and ALK6 (BMPR1B); phosphorylation of these receptors triggers Smad1/5/9 activation (unknownauthors2022structuralandfunctional pages 43-46, cate2022antimüllerianhormonesignal pages 6-8).  
• A linear consensus phosphorylation motif for AMHR2 has not been defined; no Johnson-2023 atlas entry is available (unknownauthors2022structuralandfunctional pages 43-46).

Structure  
• Domain organisation: signal peptide, 127-residue extracellular ligand-binding domain (three-finger toxin fold with five intramolecular disulfides), single transmembrane helix, and ~403-residue intracellular serine/threonine kinase domain (rak2019antimullerianhormonereceptor pages 3-5).  
• Extracellular complex: crystal structure of AMH bound to AMHR2 ECD at 2.6 Å (PDB 7L0J/7L0I) reveals a 933 Å² buried interface, a finger-1 loop extension unique to AMHR2, and a receptor shift of ~7.5 Å relative to Activin/BMP complexes (hart2021structureofamh pages 1-1, unknownauthors2022structuralandfunctional pages 73-76, unknownauthors2022structuralandfunctional pages 80-83).  
• Key contact elements include a Lys534AMH–Asp81/Glu84AMHR2 salt bridge and receptor residues Phe62, Met76, Asp81, Leu106 and Thr108; mutation of these sites substantially impairs signaling (unknownauthors2022structuralandfunctional pages 69-73, hart2020mutationalanalysisof pages 6-7).  
• Disulfide connectivity differs from other receptors by linking the finger 2/3 loop to finger 2, contributing to ligand specificity (unknownauthors2022structuralandfunctional pages 80-83).  
• Kinase domain: no crystal structure; sequence predicts a bilobal STKR-II fold with VAIK, HRD and DFG catalytic motifs, a regulatory C-helix, GS box and activation loop (cate2022antimüllerianhormonesignal pages 6-8). AlphaFold modelling supports this topology (howard2022molecularmechanismsof pages 1-2).

Regulation  
• Two N-glycosylation sites in the ECD facilitate proper folding (josso2003transductionpathwayof pages 2-3).  
• Proteolytic cleavage removing most of the ECD generates inactive oligomers retained in the endoplasmic reticulum (rak2019antimullerianhormonereceptor pages 3-5).  
• Alternative splicing yields at least three isoforms with divergent C-termini (rak2019antimullerianhormonereceptor pages 3-5).  
• Activation requires formation of a heterotetramer with ALK2/3/6; AMHR2 phosphorylates the GS loop of the type I receptor, which then autophosphorylates and recruits Smad substrates (cate2022antimüllerianhormonesignal pages 6-8).  
• SMURF family E3 ubiquitin ligases mediate ubiquitination and degradation of type-II receptors, likely restraining AMHR2 signaling amplitude (howard2022molecularmechanismsof pages 1-2).  
• Inhibitory Smads 6/7 attenuate downstream signaling (josso2003transductionpathwayof pages 2-3).

Function  
• Expression is largely restricted to reproductive tissues: fetal Sertoli cells, mesenchyme surrounding the Müllerian duct, and ovarian granulosa cells (unknownauthors2022structuralandfunctional pages 18-22, josso2003transductionpathwayof pages 2-3).  
• Male fetal development: AMHR2 mediates AMH-induced Müllerian duct regression (hart2021structureofamh pages 1-1).  
• Female ovary: signaling limits primordial follicle recruitment and modulates folliculogenesis (unknownauthors2022structuralandfunctional pages 69-73).  
• Canonical pathway: AMH binding → AMHR2 dimerisation with ALK2/3/6 → Smad1/5/9 phosphorylation → gene transcription (unknownauthors2022structuralandfunctional pages 43-46).  
• Non-canonical signaling: AMHR2 can activate NF-κB independently of Smads in certain cell types (rak2019antimullerianhormonereceptor pages 3-5).

Other Comments  
• Biallelic loss-of-function variants cause persistent Müllerian duct syndrome (PMDS); a recurrent 27-bp deletion in exon 10 and missense mutations at Met76 and Asp81 impair receptor function (rak2019antimullerianhormonereceptor pages 3-5, hart2020mutationalanalysisof pages 9-10).  
• Conservative substitutions M76V or D81E retain in-vitro signaling yet are reported in PMDS cohorts, indicating additional pathogenic mechanisms such as misfolding or trafficking defects (unknownauthors2022structuralandfunctional pages 46-50).  
• Reduced AMHR2 activity has been implicated in polycystic ovary syndrome (unknownauthors2022structuralandfunctional pages 69-73).

References

1. (hart2021structureofamh pages 1-1): Kaitlin N. Hart, William A. Stocker, Nicholas G. Nagykery, Kelly L. Walton, Craig A. Harrison, Patricia K. Donahoe, David Pépin, and Thomas B. Thompson. Structure of amh bound to amhr2 provides insight into a unique signaling pair in the tgf-β family. Proceedings of the National Academy of Sciences, Jun 2021. URL: https://doi.org/10.1073/pnas.2104809118, doi:10.1073/pnas.2104809118. This article has 51 citations.
2. (unknownauthors2022structuralandfunctional pages 43-46): Structural and Functional Studies of Anti-Müllerian Hormone (AMH) and its Receptor
3. (unknownauthors2022structuralandfunctional pages 69-73): Structural and Functional Studies of Anti-Müllerian Hormone (AMH) and its Receptor
4. (howard2022molecularmechanismsof pages 1-2): James A. Howard, Kaitlin N. Hart, and Thomas B. Thompson. Molecular mechanisms of amh signaling. Frontiers in Endocrinology, Jun 2022. URL: https://doi.org/10.3389/fendo.2022.927824, doi:10.3389/fendo.2022.927824. This article has 41 citations and is from a peer-reviewed journal.
5. (josso2003transductionpathwayof pages 2-3): Nathalie Josso and Nathalie di Clemente. Transduction pathway of anti-müllerian hormone, a sex-specific member of the tgf-β family. Trends in Endocrinology & Metabolism, 14:91-97, Mar 2003. URL: https://doi.org/10.1016/s1043-2760(03)00005-5, doi:10.1016/s1043-2760(03)00005-5. This article has 200 citations.
6. (rak2019antimullerianhormonereceptor pages 3-5): A. Ya. Rak, A. V. Trofimov, and A. M. Ischenko. Anti-mullerian hormone receptor type ii as a potential target for antineoplastic therapy. Biochemistry (Moscow), Supplement Series B: Biomedical Chemistry, 13:202-213, Jul 2019. URL: https://doi.org/10.1134/s1990750819030053, doi:10.1134/s1990750819030053. This article has 3 citations.
7. (unknownauthors2022structuralandfunctional pages 18-22): Structural and Functional Studies of Anti-Müllerian Hormone (AMH) and its Receptor
8. (unknownauthors2022structuralandfunctional pages 46-50): Structural and Functional Studies of Anti-Müllerian Hormone (AMH) and its Receptor
9. (cate2022antimüllerianhormonesignal pages 6-8): Richard L. Cate. Anti-müllerian hormone signal transduction involved in müllerian duct regression. Frontiers in Endocrinology, Jun 2022. URL: https://doi.org/10.3389/fendo.2022.905324, doi:10.3389/fendo.2022.905324. This article has 19 citations and is from a peer-reviewed journal.
10. (hart2020mutationalanalysisof pages 6-7): Kaitlin N Hart, David Pépin, Magdalena Czepnik, Patricia K Donahoe, and Thomas B Thompson. Mutational analysis of the putative anti-müllerian hormone (amh) binding interface on its type ii receptor, amhr2. Endocrinology, Apr 2020. URL: https://doi.org/10.1210/endocr/bqaa066, doi:10.1210/endocr/bqaa066. This article has 18 citations and is from a domain leading peer-reviewed journal.
11. (hart2020mutationalanalysisof pages 9-10): Kaitlin N Hart, David Pépin, Magdalena Czepnik, Patricia K Donahoe, and Thomas B Thompson. Mutational analysis of the putative anti-müllerian hormone (amh) binding interface on its type ii receptor, amhr2. Endocrinology, Apr 2020. URL: https://doi.org/10.1210/endocr/bqaa066, doi:10.1210/endocr/bqaa066. This article has 18 citations and is from a domain leading peer-reviewed journal.
12. (unknownauthors2022structuralandfunctional pages 73-76): Structural and Functional Studies of Anti-Müllerian Hormone (AMH) and its Receptor
13. (unknownauthors2022structuralandfunctional pages 80-83): Structural and Functional Studies of Anti-Müllerian Hormone (AMH) and its Receptor