## Phylogeny

The insulin receptor (INSR) is a member of the receptor tyrosine kinase (RTK) family (du2017acomprehensivesurvey pages 24-27, murthy2024insulinsignalingand pages 17-18). Based on the kinome classification by Manning et al., it belongs to the tyrosine kinase group and the insulin receptor (InsR) subfamily (aslanzadeh2024deepmutationalscanning pages 1-4, tatulian2015structuraldynamicsof pages 1-5). This subfamily includes the closely related paralogs, insulin-like growth factor 1 receptor (IGF1R) and insulin receptor-related receptor (INSRR), with which INSR shares structural and functional properties (du2017acomprehensivesurvey pages 24-27, murthy2024insulinsignalingand pages 17-18, tatulian2015structuraldynamicsof pages 1-5). INSR orthologs are conserved across metazoan and vertebrate species, indicating an essential role in metabolic regulation (du2017acomprehensivesurvey pages 24-27, tatulian2015structuraldynamicsof pages 1-5, aslanzadeh2024deepmutationalscanning pages 1-4).

## Reaction Catalyzed

The enzymatic reaction catalyzed by INSR is the ATP-dependent phosphorylation of protein tyrosine residues (du2017acomprehensivesurvey pages 24-27, murthy2024insulinsignalingand pages 17-18). The reaction is formally described as: ATP + [a protein-tyrosine] = ADP + [a protein-tyrosine phosphate] (du2017acomprehensivesurvey pages 24-27, tatulian2015structuraldynamicsof pages 1-5, murthy2024insulinsignalingand pages 17-18).

## Cofactor Requirements

The kinase activity of INSR is dependent on metal ion cofactors (tatulian2015structuraldynamicsof pages 14-16, aslanzadeh2024deepmutationalscanning pages 37-39). Specifically, Mg²⁺ is typically required to facilitate ATP binding and the phosphotransfer reaction (tatulian2015structuraldynamicsof pages 1-5, murthy2024insulinsignalingand pages 17-18).

## Substrate Specificity

INSR phosphorylates key intracellular substrates, including insulin receptor substrate (IRS) proteins and SHC (aslanzadeh2024deepmutationalscanning pages 37-39, murthy2024insulinsignalingand pages 17-18). Based on comprehensive profiling of the human tyrosine kinome, the INSR recognition motif “C-R-S-D-D-Y-M-P-M-S-P” has been identified (yaronbarir2024theintrinsicsubstrate pages 3-3). The consensus motif for INSR phosphorylation shows a strong preference for acidic residues, such as aspartate (D) and glutamate (E), at position -1 relative to the phosphorylated tyrosine (pY), and these residues are also prominent in proximal positions from -1 to +3 (yaronbarir2024theintrinsicsubstrate pages 16-17, yaronbarir2024theintrinsicsubstrate pages 3-3). Hydrophobic aliphatic residues like isoleucine (I) are generally favored at positions -1 and +3 (yaronbarir2024theintrinsicsubstrate pages 3-3). Favorable substrate patterns can also involve a phosphotyrosine at the +2 position (yaronbarir2024theintrinsicsubstrate pages 16-17). Conversely, serine (S) is disfavored at position -1, and basic or other phosphoresidues are generally disfavored near the phosphorylation site (yaronbarir2024theintrinsicsubstrate pages 16-17, yaronbarir2024theintrinsicsubstrate pages 3-3).

## Structure

INSR is a large (1382 residues), disulfide-linked glycoprotein that forms an (αβ)₂ heterotetrameric complex (du2017acomprehensivesurvey pages 24-27, du2017acomprehensivesurvey pages 27-29). It is synthesized as a single polypeptide pro-receptor that is cleaved to form the extracellular α-subunit and the transmembrane β-subunit (ardon2014sequencinganalysisof pages 3-4, du2017acomprehensivesurvey pages 27-29). The domain organization is as follows: - **Ectodomain**: Comprises the α-subunit and has a folded-over conformation responsible for insulin binding (aslanzadeh2024deepmutationalscanning pages 37-39, tatulian2015structuraldynamicsof pages 1-5). It consists of two leucine-rich repeat domains (L1, L2), a cysteine-rich region (CR), three fibronectin type III domains (FnIII-1, FnIII-2, FnIII-3), and the C-terminal α-helix (αCT) (du2017acomprehensivesurvey pages 27-29, tatulian2015structuraldynamicsof pages 7-9). The receptor is heavily N-glycosylated (du2017acomprehensivesurvey pages 24-27). - **Transmembrane (TM) Domain**: A single helix within each β-subunit that spans the plasma membrane (du2017acomprehensivesurvey pages 27-29). - **Intracellular Domain**: This region within the β-subunit contains a juxtamembrane (JM) domain and a bilobal tyrosine kinase (TK) domain (du2017acomprehensivesurvey pages 27-29, tatulian2015structuraldynamicsof pages 5-7). Key catalytic and regulatory features of the TK domain include: - **Activation Loop (A-loop)**: This flexible loop blocks the catalytic cleft in the inactive state (ye2017structureanddynamics pages 5-6). Tris-phosphorylation of tyrosines Y1158, Y1162, and Y1163 within this loop relieves autoinhibition, triggering full kinase activation (tatulian2015structuraldynamicsof pages 5-7, ye2017structureanddynamics pages 5-6). - **C-helix and Hydrophobic Spine**: These are conserved structural motifs essential for stabilizing the active conformation of the kinase domain and maintaining catalytic function (du2017acomprehensivesurvey pages 24-27, murthy2024insulinsignalingand pages 17-18, tatulian2015structuraldynamicsof pages 1-5).

## Regulation

INSR activity is regulated by ligand binding, post-translational modifications, and protein-protein interactions. - **Ligand Binding and Autophosphorylation**: Insulin binding to the ectodomain induces conformational changes that lead to trans-autophosphorylation of the β-subunits on specific tyrosine residues, which activates the kinase (aslanzadeh2024deepmutationalscanning pages 37-39, tatulian2015structuraldynamicsof pages 1-5). Key autophosphorylation sites are tyrosines Y1158, Y1162, and Y1163 in the activation loop (ye2017structureanddynamics pages 5-6, tatulian2015structuraldynamicsof pages 5-7). - **Dephosphorylation**: Protein tyrosine phosphatases, including PTP1B, SHP1, and SHP2, negatively regulate INSR signaling by dephosphorylating the receptor (murthy2024insulinsignalingand pages 17-18, ye2017structureanddynamics pages 8-9, aslanzadeh2024deepmutationalscanning pages 1-4). - **Ubiquitination**: This modification modulates receptor stability, internalization, and degradation, thereby regulating signal duration and intensity (du2017acomprehensivesurvey pages 24-27, murthy2024insulinsignalingand pages 17-18, tatulian2015structuraldynamicsof pages 1-5). - **Structural Regulation**: The juxtamembrane (JM) domain plays a dual regulatory role, acting as a cis-autoinhibitory and trans-activating element (du2017acomprehensivesurvey pages 27-29). Inhibitory adaptor proteins like Grb14 also negatively regulate the receptor (ye2017structureanddynamics pages 11-11).

## Function

INSR is broadly expressed, with critical roles in metabolism and growth regulation in tissues like liver, adipose tissue, and skeletal muscle (aslanzadeh2024deepmutationalscanning pages 37-39, unknownauthors2023identifyingsmallmolecule pages 23-27). Upon activation, INSR phosphorylates key substrates including the IRS protein family and SHC (aslanzadeh2024deepmutationalscanning pages 37-39, tatulian2015structuraldynamicsof pages 5-7). This initiates two main downstream signaling pathways: - **PI3K-AKT Pathway**: This pathway is responsible for the majority of insulin’s metabolic actions, including glucose uptake via GLUT4 translocation, as well as glycogen and lipid synthesis (aslanzadeh2024deepmutationalscanning pages 37-39, tatulian2015structuraldynamicsof pages 5-7, lukman2015harnessingstructuraldata pages 1-2). - **Ras-MAPK Pathway**: This pathway regulates gene expression and cooperates with the PI3K-AKT pathway to control cell growth and differentiation (aslanzadeh2024deepmutationalscanning pages 37-39, tatulian2015structuraldynamicsof pages 1-5). Key interacting partners that propagate the signal include adaptor proteins such as Grb2, which links the receptor to the Ras/MAPK pathway, and the phosphatase SHP2, which modulates insulin signaling cascades (du2017acomprehensivesurvey pages 24-27, murthy2024insulinsignalingand pages 17-18).

## Inhibitors

Experimental modulators of INSR have been described. Monoclonal antibodies have been developed that can activate mutant receptors (aslanzadeh2024deepmutationalscanning pages 37-39, aslanzadeh2024deepmutationalscanning pages 1-4). Small molecule activators and sensitizers, including S597, CG7 (ursolic acid), XMetA, TLK16998, and TLK19780, can enhance receptor autophosphorylation or kinase activity (ye2017structureanddynamics pages 8-9). The phosphatase inhibitor Morin acts indirectly to enhance receptor phosphorylation by inhibiting PTP1B (ye2017structureanddynamics pages 9-10).

## Other Comments

Mutations in the *INSR* gene are linked to severe inherited insulin resistance syndromes, including Donohue syndrome (leprechaunism) and Rabson–Mendenhall syndrome (ardon2014sequencinganalysisof pages 1-3, aslanzadeh2024deepmutationalscanning pages 37-39). The clinical severity of these syndromes often correlates with the level of residual receptor function, with some mutations severely impairing insulin binding or kinase activity (aslanzadeh2024deepmutationalscanning pages 1-4, ardon2014sequencinganalysisof pages 1-3). Dominant-negative mutations also contribute to severe insulin resistance (ardon2014sequencinganalysisof pages 1-3, aslanzadeh2024deepmutationalscanning pages 1-4). The receptor exists as two main isoforms, IR-A and IR-B, generated by alternative splicing of exon 11 (du2017acomprehensivesurvey pages 27-29, ardon2014sequencinganalysisof pages 3-4). These isoforms have differential functions; IR-B primarily mediates metabolic effects, while IR-A is linked to mitogenic signaling (du2017acomprehensivesurvey pages 27-29).

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