Phylogeny  
CaMKIγ (CAMK1G) belongs to the Ser/Thr eukaryotic protein kinase super-family, CAMK group, CaMKI subfamily (Unknown Authors, 2012, pp. 18-22). Human paralogues within this subfamily are CAMK1 (α), PNCK/CAMK1B (β), CAMK1D (δ) and CAMK1G (γ) (Brzozowski & Skelding, 2019, pp. 1-4). Orthologous proteins with verified coding sequences have been reported in Homo sapiens, Mus musculus, Rattus norvegicus, Danio rerio and Drosophila melanogaster (Ohmae et al., 2006, pp. 4-5). Kinase-domain phylogenies place CaMKIγ with other CaMKI isoforms and clearly separate the clade from CaMKII and CaMKIV branches (Ohmae et al., 2006, pp. 5-6).

Reaction Catalyzed  
ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (Unknown Authors, 2023, pp. 133-137).

Cofactor Requirements  
Mg²⁺ is required for catalysis; Mn²⁺ can substitute in standard CaMKI family assays (Brzozowski & Skelding, 2019, pp. 19-21).

Substrate Specificity  
Validated substrates include CREB1 at Ser133 (Ohmae et al., 2006, p. 1) and LIMK1 within the CaMKI–LIMK–cofilin pathway (Unknown Authors, 2012, pp. 42-48). Family-wide biochemical data indicate preference for basic residues N-terminal to the phospho-acceptor (Arg/Lys-X-X-Ser/Thr); no CaMKIγ-specific motif has been mapped (Unknown Authors, 2012, pp. 54-58).

Structure  
Residues 1-279 form the bilobal catalytic kinase domain containing canonical VAIK, HRD, DFG and APE motifs; residues 280-322 constitute an autoinhibitory/calmodulin-binding regulatory domain; residues 323-414 comprise a unique C-terminal extension ending in a CAAX prenylation motif (Unknown Authors, 2012, pp. 36-42, 54-58). Homology crystal structures of CaMKIα (PDB 1MRW) and CaMKIδ (PDB 4FG8) show the conserved fold and packing of the autoinhibitory helix (Unknown Authors, 2012, pp. 245-254). An AlphaFold model (AF-Q96NX5-F1) covers flexible regions including the CAAX tail (Unknown Authors, 2012, pp. 245-254). Thr177 in the activation loop (CaMKIδ numbering) is the CaMKK phosphorylation site; completion of hydrophobic regulatory and catalytic spines accompanies activation (Takemoto-Kimura et al., 2017, pp. 4-6; Unknown Authors, 2012, pp. 178-187).

Regulation  
• Phosphorylation – CaMKK1/2 phosphorylate Thr177 to enhance activity; PP2A and PP2B reverse this modification (Takemoto-Kimura et al., 2017, pp. 4-6, 16-18).  
• Ca²⁺/calmodulin – Ca²⁺/CaM binding to the regulatory domain displaces the autoinhibitory segment from the catalytic cleft (Unknown Authors, 2012, pp. 36-42).  
• Lipid modification – Prenylation of the C-terminal CAAX cysteine is required for Golgi and plasma-membrane localisation; loss of prenylation redistributes the kinase to the cytosol (Unknown Authors, 2012, pp. 36-42).

Function  
High mRNA and protein expression occur in limbic brain regions (central amygdala, bed nucleus of the stria terminalis, ventromedial hypothalamus, hippocampus, medial frontal cortex); peripheral expression is lower and largely neuronal (Piechota et al., 2022, pp. 4-6; Unknown Authors, 2012, pp. 42-48). Glucocorticoids and acute stress markedly up-regulate CAMK1G transcription in the central amygdala (Piechota et al., 2022, pp. 4-6). Upstream activators are Ca²⁺/CaM (binding) and CaMKK1/2 (phosphorylation) (Takemoto-Kimura et al., 2017, pp. 4-6). Downstream, CaMKIγ phosphorylates CREB1 to couple Ca²⁺ signals to gene expression (Ohmae et al., 2006, p. 1) and activates LIMK1 and ERK pathways to drive actin polymerisation and dendritic development (Unknown Authors, 2012, pp. 42-48). Physiologically, CaMKIγ modulates anxiety-like behaviour and conditioned fear; Camk1g knock-down mice show increased freezing and anxiety (Piechota et al., 2022, pp. 4-6). The kinase also promotes neuronal morphogenesis, including dendritic arborisation in an activity-dependent manner (Unknown Authors, 2012, pp. 42-48).

Other Comments  
Elevated CAMK1G expression correlates with poor prognosis in clear-cell renal carcinoma (Brzozowski & Skelding, 2019, pp. 23-24), and CAMK1G co-expression modules are enriched in schizophrenia transcriptomic datasets (Piechota et al., 2022, pp. 4-6).

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