HCN4: Hyperpolarization-activated Cyclic Nucleotide-gated Channel 4

Gene: HCN4 **Chromosomal location:** 15q24.1 **Channel type:** Non-selective cation channel **Ion conductance:** Na^+ / K^+ **Activation:** Hyperpolarization and intracellular cAMP binding

Function

- Generates the **I_f current** ("funny current") in the **sinoatrial (SA) node**
- Essential for **spontaneous diastolic depolarization** and **cardiac pacemaker activity**
- In the **CNS**, modulates:
  - Resting membrane potential
  - Synaptic responsiveness
  - Rhythmic and oscillatory neuronal firing
- Sensitive to intracellular **cAMP** (↑ sympathetic tone → ↑ firing rate)

⚠ Pathophysiology

Condition	Description
Familial sinus bradycardia	Loss-of-function mutations → persistently slow heart rate
Sick sinus syndrome	SA node dysfunction causing pauses or arrest
Atrial fibrillation (rare cases)	Linked to altered pacemaker mechanisms
CNS disorders (investigational)	Involvement in epilepsy, depression, autism (under study)

Structure

- Six transmembrane domains (S1–S6)
- P-loop between S5–S6 forms the pore
- Intracellular **cyclic nucleotide-binding domain (CNBD)** at the C-terminus
- Forms **tetrameric structure** for channel function

Clinical Relevance

- **Ivabradine**: Selective I_f current blocker used in:
  - Chronic heart failure
  - Stable angina (reduces HR without negative inotropy)
- Genetic screening for **unexplained bradycardia or syncope**
- Potential target for neuromodulation strategies in CNS diseases