

## **Heat sensation of temperature sensitive TRPV1 channel supported by the transmembrane core domain**

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Several transient receptor potential vanilloid (TRPV) channels serve as molecular temperature sensors. However, the structural basis for their high-sensitivity heat activation is strongly debated. Inspired by the recent finding of intrinsic high temperature sensitivity in homologous voltage-gated potassium channels (Kv), here we investigated this issue using two complementary strategies, unstructured peptide-insertion screening (UPS) and chimera screening. We showed that the transmembrane (TM) S1-S6 region of TRPV1 is sufficient to support heat activation, while both N and C termini contribute to this process. Furthermore, within the TM region, the pore domain plays a central role in determining the heat activation process; swapping the pore-forming region of TRPV1 with TRPV2 and TRPV3 could transfer distinct heat activation properties among these channels.