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- **RESEARCH ARTICLE**

MIGRAINE

Casein Kinase Iδ Mutations in Familial Migraine and Advanced Sleep Phase

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Abstract

Migraine is a common disabling disorder with a significant genetic component, characterized by severe headache and often accompanied by nausea, vomiting, and light sensitivity. We identified two families, each with a distinct missense mutation in the gene encoding casein kinase Iδ (CKIδ), in which the mutation cosegregated with both the presence of migraine and advanced sleep phase. The resulting alterations (T44A and H46R) occurred in the conserved catalytic domain of CKIδ, where they caused reduced enzyme activity. Mice engineered to carry the CKIδ-T44A allele were more sensitive to pain after treatment with the migraine trigger nitroglycerin. CKIδ-T44A mice also exhibited a reduced threshold for cortical spreading depression (believed to be the physiological analog of migraine aura) and greater arterial dilation during cortical spreading depression. Astrocytes from CKIδ-T44A mice showed increased spontaneous and evoked calcium signaling. These genetic, cellular, physiological, and behavioral analyses suggest that decreases in CKIδ activity can contribute to the pathogenesis of migraine.

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