**UPDATE: CLOCK GENES AND MIGRAINE**

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Migraine is a common episodic brain disorder with protean manifestations. Migraine often occurs in attacks that may have idiosyncratic but predictable cyclic patterns: circadian, menstrual, circannual, etc.

Data from clinical trials for triptans that were performed largely in temperate latitudes indicate that migraine attacks preferentially occur in a diurnal peak centered at 6 o'clock in the morning. Whereas data from arctic Norway, indicate that migraine has peak incidence at approximately 2 o'clock in the afternoon. Whether the diurnal cues of daylight onset in the morning, the peak of daily social activities, or other factors contribute to the triggering migraine attacks is unclear. However, the thresholds for onset of migraine attacks may also be governed by endogenous circadian rhythms as well. The period duration of such endogenous circadian bio-rhythms (termed tau) is determined by "clock genes" within hypothalamic suprachiasmatic neurons.

We identified two families in which mutations in a clock gene, casein kinase 1δ (CK1δ), co-segregated in individuals with the phenotypes of both migraine (with or without aura) and advanced sleep phase syndrome (ASPS). When tau is shortened, advanced sleep phase syndrome is the consequence. CK1δ phosphorylates the clock protein hPER2 to influence tau. Different point mutations (T44A, H46R) of the conserved catalytic domain of CK1δ were found in each family, both of which reduced enzyme phosphorylation activity *in vitro*. Transgenic mice engineered to overexpress the T44A mutation exhibited phenotypes consistent with both ASPS and migraine. These mice had a significantly shortened tau when placed in environments without diurnal cues. These mice were also (1) more sensitive to pain after treatment with a migraine trigger, nitroglycerin, (2) had reduced thresholds for cortical spreading depression (CSD, the presumptive physiological substrate for migraine aura), (3) had an increased frequency of CSD episodes, (4) had greater arterial dilation with CSD, and (5) had astrocytes that showed increased spontaneous and evoked calcium signaling *in vitro*. Collectively, these genetic, cellular, physiological, and behavioral studies indicate that mutations in CKIδ can contribute to both the pathogenesis of ASPS and of migraine.

Further studies are necessary to elucidate precisely how CK1δ mutations lead to increased migraine susceptibility.