Genetic variation in a brain-cleansing water channel affects human sleep

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The reason why we sleep remains an unresolved question of the 21st century. Research by Sara Marie Ulv Larsen, Sebastian Camillo Holst and colleagues from the Neurobiology Research Unit at the University Hospital Copenhagen, published this week in the open access journal *PLoS Biology*, now shows that the depth of non-rapid-eye-movement (nonREM) sleep in humans is associated with different genetic versions of a gene that encodes a water channel involved in fluid flow in the brain.

Recent insights suggest that sleep may enable and promote a flow of cerebrospinal fluid into the brain that literally removes metabolic waste. In experimental animals, this process is aided by water channels called AQP4; these form water-permeable pores through the cell membranes of brain cells called astrocytes. The role of these water channels in the human brain and whether they are associated with the regulation of deep nonREM sleep, also called slow wave sleep, had not yet been examined.

A common set of genetic variants that are inherited together are called a haplotype. One such a haplotype (containing eight individual DNA variants) was previously shown to modulate the levels of AQP4. By carefully studying more than 100 healthy individuals, the authors found that the depth of slow wave sleep, which can be measured by analyzing the brain waves recorded during sleep, differs between carriers of this haplotype and a control group. The difference was most pronounced at the beginning of the night, when our need for sleep is highest. Interestingly, the two haplotype groups also coped differently when kept awake for two full days, suggesting that changes in the flow of fluids through AQP4 water channels may modify how we cope with sleep loss.

Because the genetic variants within the AQP4 haplotype were also previously associated with the progression of Alzheimer's disease, the results of this study may suggest that a sleep-driven exchange of fluids through AQP4 water channels could be linked to Alzheimer's progression. To explore the possible association between Alzheimer's disease and AQP4 water channels, further studies are warranted. "A more immediate implication of our results" the authors note, "is by improving our understanding of the importance of sleep". In other words, this is the first study to show that the genetics of AQP4 water channels affect the intensity of deep sleep and how we cope with loss of sleep. These findings add support to the current theory that sleep may be involved in the regulation of "brain clearance" and as such highlights the link between sleep and fluid flow in the human brain.

More information: Sara Marie Ulv Larsen et al, Haplotype of the astrocytic water channel AQP4 is associated with slow wave energy regulation in human NREM sleep, *PLOS Biology* (2020). DOI: 10.1371/journal.pbio.3000623

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