

## on the other side

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We all need sleep. Yet sleep spells ‘off our guards’ and, from a purely biological point of view, it is not a wise move. In the land of Nod, an organism is vulnerable and an easy prey for predator. So there must be something essential in taking a nap for Mother Nature to have thought it up. Indeed, when asleep, organisms are shut off from their surroundings for a period – a period they use to build up the energy they spend their time depleting when awake. It is all a question of vital energy balance. For such a system to work, however, we need something that not only measures our body’s level of energy but also has a role in our sleeping behaviour. There happen to be many known systems that do one or the other but it is the first time that scientists have found a protein that reacts to levels of ATP and is directly involved in the length of time we sleep.



Reprise, by Eric Zener

Courtesy of the artist

We live in a day and age when we are told to live our life to the full. Meaning, for many, the less you sleep, the better off you are and the more you can get out of life. But is little sleep good for us? The medical profession tells us that 7 hours a night is about the optimal amount of time for a human to shut down and refuel. Yet we all know that some people can do with far less while others need substantially more. So what does it come down to? There are some sleeping behaviours that seem to run in families, which would suggest a genetic component. Sleep, however, is something particularly difficult to measure. It is made up of three ingredients: quality, duration and timing. Each of these ingredients is dependent on the season, latitude and geographical location, but also on a person’s environment, their social occupation, their

biological rhythm, gender, age, psychiatric disposition and so on.

With this in mind, a few scientists took it upon themselves to find out whether a person’s tendency to sleep long hours or not has a genetic basis. To do this, they examined a cohort of over 4’000 individuals, from seven different European populations whose close ancestors were also of European extraction. For the study, none of the individuals had performed any shift-work in the past three months. None of them took any form of medication which could influence their sleeping behaviour in any way and alarm clocks were not allowed on days off work. The scientists then performed genome wide association studies and came up with one gene – known as ABCC9 – a certain variant of which was found in people who were happy to sleep fewer hours than their peers. For confirmation, they turned to *Drosophila* and knocked out its homologue: and the fruit flies slept less! This was proof that not only the gene has a direct role in sleeping behaviour but that it must also be quite important since it has been around for a pretty long time.

In mammals, ABCC9 is found in many tissues, amongst which the heart, skeletal muscle, the brain and the pancreas. ABCC9 is not a stranger to the medical profession. It has been known for some time now to have a role in smooth muscle tonality and is involved in diabetes, heart disease and certain psychiatric disorders. It so happens that these afflictions are also accompanied by sleep irregularities. Which makes ABCC9 and the discovery of its probable involvement in sleeping

behaviour a very attractive gene indeed. This would suggest that certain metabolic pathways – such as glucose uptake or vascular tone regulation in smooth muscle, for instance – are linked to the phenomenon of sleep.

But what is ABCC9? ABCC9, also known as Sulfonylurea receptor 2 (SUR2), is one of the subunits that is part of an octameric potassium channel complex fuelled by ATP ( $K_{ATP}$  channel).  $K_{ATP}$  channels are transmembrane, and are found in cell or mitochondrial membranes. They are made up of two different parts: the pore and the part which regulates the whole system. ABCC9 is the subunit which has the regulatory role. There are four regulatory subunits in a  $K_{ATP}$  channel and four pore subunits. ABCC9 sports no less than 17 transmembrane domains and is able to bind to ATP. In fact, ABCC9 acts as an ATP sensor. If the surrounding ATP is depleted, there is none to bind to the ABCC9, which obviously affects the  $K_{ATP}$  channel and the passage of potassium. As an example, depending on intracellular ATP, ABCC9 is able to influence the action potential duration and vasodilation in vascular smooth muscle, as well as glucose metabolism in voluntary striated muscle. This could explain the roles of ABCC9 in heart disease and diabetes. As for sleep...?

$K_{ATP}$  channels are found in the brain. In particular, in orexin neurons. This is particularly interesting because orexin neurons are part of our arousal system, i.e. the part that keeps us awake or not. When ATP levels begin to fall, the  $K_{ATP}$  channels mediate hyperpolarization of the orexin neurons, thus promoting sleep and giving our bodies time to top up on energy. If the system doesn't work, despite having used up the surrounding ATP, we can't fall asleep. One very intriguing illness linked to the orexin neurons is narcolepsy – a sleep disorder which causes those afflicted with it to fall asleep at any time of the day.

There is constant talk about creative insomnia and the fact that genius does not require much sleep. So does this mean that people who do are naturally disadvantaged? The phenomenon of sleep has kept all sorts of learned people busy in the past millennia. It does flirt with the mystical. One moment you're there, the next you're not. Nowadays, scientists can have a shot at the molecular side of things to grasp a greater understanding of the passage from consciousness to unconsciousness, and vice versa. Certainly, finding a candidate that senses metabolic status and is at the crossroads of sleep and the onset of certain diseases should be fertile ground for the development of all sorts of drugs – against sleep disorders, diabetes and heart disease to name a few.

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*N.B. Also read Protein Spotlight issues 8, 15 & 101*

## Cross-references to UniProt

ATP-binding cassette sub-family C member 9, *Homo sapiens* (Human): O60706

ATP-binding cassette sub-family C member 9, *Drosophila melanogaster* (Fruit fly): Q9VL32

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