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NEURODEGENERATION

Switch to the potassium channel

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Misfolded and aggregated proteins generally take the centre stage of aetiological research into many neurodegenerative disorders, including Huntington's disease, Parkinson's disease, spinocerebellar ataxia (SCA) and Alzheimer's disease. However, the results of a new study suggest that potassium channel dysfunction could also be involved. Reporting in *Nature Genetics,* Pulst and colleagues show that, in two families with SCA, mutations in the voltage-gated potassium channel gene *KCNC3* are to blame. Is it time for a switch in our thinking about neurodegeneration?

SCA can manifest a wide spectrum of motor disorders, such as ataxia, dysarthria and oculomotor abnormalities, and also other neurological symptoms such as cognitive decline, epilepsy and psychiatric disorders. So far, 12 SCA-associated genes have been identified. Although the functions of the majority of these genes are unknown, the causative mutations are mostly in the form of expanded polyglutamine stretches (suggesting protein misfolding and aggregation pathways in disease progression).

Pulst's group had previously characterized a Filipino family with late-onset SCA and, through linkage analysis, showed that the candidate genomic locus was within a 4 cM region on chromosome 19q13. Encouragingly, this 4 cM was within a region previously identified in a French family with early-onset SCA and mental retardation. Using additional genetic markers, the team was able to narrow their search to a region of just 800 kb, which contained ~40 genes — one was *KCNC3*. The expression of KCNC3 in Purkinje cells of the cerebellum (involved in motor coordination) made it a prime suspect. And the researchers' suspicions were confirmed when they carried out sequencing analyses and found that the gene was mutated in both families.

In the Filipino family, the mutation gave rise to a single amino acid substitution affecting the main voltage-sensing domain of KCNC3. In the French family, the mutation caused a different amino acid substitution, this time affecting the protein's cytoplasmic domain, which controls pore opening. To investigate the effect on function, the team overexpressed the two mutant variants in *Xenopus* oocytes and compared channel activity with that of the wild-type protein. Using a voltage clamp analysis, they found that the Filipino mutation resulted in the total loss of channel activity (no detectable current), whereas the French mutation altered the voltage sensitivity of KCNC3 such that pores were open longer (prolonged current). As potassium channels also regulate intracellular calcium concentrations, the authors suggest that longer duration of electrical activity spikes might increase calcium influx and lead to neuronal death. They argue that this latter phenotype is potentially worse than total loss of channel activity, which might explain the different severities and onset ages observed between the Filipino and French families.

There are several reports that link alterations in potassium channel expression with Hungtinton's disease, Parkinson's disease and Alzheimer's disease. The finding that mutations in the potassium channel gene *KCNC3* are responsible for SCA in two families suggests that, in addition to investigating protein misfolding and aggregation in the aetiology of neurodegenerative diseases, researchers might also benefit from considering the role of potassium channels.

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ORIGINAL RESEARCH PAPER Waters, M. F. *et al.* Mutations in voltage-gated potassium channel KCNC3 cause degenerative and developmental central nervous system phenotypes. *Nature Genet.* 26 February 2006 (doi:10.1038/ng1758)

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