Abstracts

Articles appearing in the October 2018 issue

Increased *KCNJ18* promoter activity as a mechanism in atypical normokalemic periodic paralysis

Objective To identify the genetic basis of a patient with symptoms of normokalemic sporadic periodic paralysis (PP) and to study the effect of *KCNJ18* mutations.

Methods A candidate gene approach was used to identify causative gene mutations, using Sanger sequencing. *KCNJ18* promoter activity was analyzed in transfected HEK293 cells with a luciferase assay, and functional analysis of Kir2.6 channels was performed with the 2-electrode voltage-clamp technique.

Results Although we did not identify harmful mutations in *SCN4A*, *CACNA1S*, *KCNJ2*, or *KCNE3*, we detected a monoallelic fourfold variant in *KCNJ18* (R39Q/R40H/A56E/I249V), together with a variant in the respective promoter of this channel (c.-542T/A). The exonic variants in Kir2.6 did not alter the channel function; however, luciferase assays revealed a 10-fold higher promoter activity of the c.-542A promoter construct, which is likely to cause a gain-of-function by increased expression of Kir2.6. We found that reducing extracellular K⁺ levels causes a paradoxical reduction in outward currents, similar to that described for other inward rectifying K⁺ channels. Thus, reducing the extracellular K⁺ levels might be a therapeutic strategy to antagonize the transcriptionally increased *KCNJ18* currents. Consistently, treatment of the patient with K⁺-reducing drugs dramatically improved the health situation and prevented PP attacks.

Conclusions We show that a promoter defect in the *KCNJ18* gene is likely to cause periodic paralysis, as the observed transcriptional upregulation will be linked to increased Kir2.6 function. This concept is further supported by our observation that most of the PP attacks in our patient disappeared on medical treatment with K⁺-reducing drugs.

[NPub.org/NG/9123a](https://pubmed.ncbi.nlm.nih.gov/30123123/)

Protein network analysis reveals selectively vulnerable regions and biological processes in FTD

Objective The neuroanatomical profile of behavioral variant frontotemporal dementia (bvFTD) suggests a common biological etiology of disease despite disparate pathologic causes; we investigated the genetic underpinnings of this selective regional vulnerability to identify new risk factors for bvFTD.

Methods We used recently developed analytical techniques designed to address the limitations of genome-wide association studies to generate a protein interaction network of 63 bvFTD risk genes. We characterized this network using gene expression data from healthy and diseased human brain tissue, evaluating regional network expression patterns across the lifespan as well as the cell types and biological processes most affected in bvFTD.

Results We found that bvFTD network genes show enriched expression across the human lifespan in vulnerable neuronal populations, are implicated in cell signaling, cell cycle, immune function, and development, and are differentially expressed in pathologically confirmed frontotemporal lobar degeneration cases. Five of the genes highlighted by our differential expression analyses—*BALAP2*, *ERBB3*, *POU2F2*, *SMARCA2*, and *CDC37*—appear to be novel bvFTD risk loci.

Conclusions Our findings suggest that the cumulative burden of common genetic variation in an interacting protein network expressed in specific brain regions across the lifespan may influence susceptibility to bvFTD.

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