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## **Diseases of the nervous system associated with calcium channelopathies**

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## Diseases of the Nervous System Associated with Calcium Channelopathies

B. Todorov

### Propositions

1. The auxiliary subunits  $\alpha_2\delta$ -2,  $\beta_4$ , and  $\gamma_2$  of  $\text{Ca}_v2.1$  channels are dispensable for neurotransmitter release at the NMJ synapse.  
(*This thesis*)
2. *Cacna1a* conditional knockout mice will be instrumental in dissecting the cell-specific role of  $\text{Ca}_v2.1$  channels in motor behaviour.  
(*This thesis*)
3. Dysfunction of Purkinje cells, rather than cerebellar granule cell neurons, is the cause of the abnormal cerebellar morphology and ataxia seen in  $\text{Ca}_v2.1$   $\alpha 1$  knockout mice.  
(*This thesis*)
4. Increased, not decreased, irregularity in Purkinje cell simple spiking results in motor deficits and cerebellar ataxia.  
(*This thesis*)
5. The fact that the FHM1 S218L gain-of-function mutation causes cerebellar ataxia compromises the hypothesis that only loss-of-function mutations in *CACNA1A* cause this phenotype.  
(*Hans M. et al., J Neurosci 1999; 19:1610-1619; Guida S. et al., Am J Hum Genet 2001; 68:759-764*)
6. Drugs such as aminopyridines and EBIO that restore normal Purkinje cell function in experimental animal models, deserve to be tested in prospective clinical trials of patients with cerebellar ataxia  
(*Strupp M. et al., Neurology 2004; 62:1623-1625; Walter JT. Et al., Nat Neurosci 2006; 9:389-397*)
7. Modulation of calcium channel function by G-proteins and auxiliary subunit interaction is perhaps more relevant to explain disease pathology than direct biophysical consequences of *CACNA1A* mutations on these channels.  
(*Weiss N. et al., Pflugers Arch 2008; 457:315-326; Mullner C. et al., J Biol Chem 2004; 279:51844-51850*)
8. “Neurological disorders are among the greatest threats to public health.”  
(*Neurological Disorders: Public Health Challenges. World Health Organisation, 2006*)
9. “Translational research means different things to different people, but it seems important to almost everyone.”  
(*Woolf SH, JAMA 2008; 299:211-213*)
10. “The real act of discovery consists not in finding new lands, but in seeing with new eyes.”  
(*Mascel Proust*)