Episodic ataxia with intermittent headache, ataxia, and diplopia

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Purpose: Episodic ataxia (EA) is characterized by intermittent periods of headache, ataxia and visual problems of variable expression. We characterize the phenotypic spectrum and the genetic basis, using next generation sequencing (NGS), of familial EA presenting with episodic diplopia, ataxia and environmental triggers. Methods: Three affected brothers, with onset within the third decade, their affected mother, the unaffected father and 4 offspring were recruited. All affected subjects and their offspring underwent full ophthalmology and neurological assessment including eye movement recordings and MRI. Using NGS we screened for candidate of known association with EA. Affected subjects were prescribed a trial of acetazolamide and 4-aminopyridine. Results: The primary presentation of all 3 brothers was headache, vertical diplopia of variable severity and duration, which reversed throughout the day. The mother reported diplopia at the same age, although resolved during pregnancy. All affected subjects and offspring had abnormal vertical saccades, smooth pursuit and fixation. Two subjects had endpoint nystagmus. MRI scans were normal. The eldest brother had dysarthria and ataxia prior to starting treatment. NGS excluded previously reported EA genes including *KCNA1, CACNA1A, CACNB4 and SLC1A3* genes suggesting a potential novel gene within this family. Acetazolamide did not improve symptoms. 4-aminopyridine reduced the frequency of symptoms, including the headache, in the most affected subjects. Conclusions: We report a dominantly inherited, aminopyridine responsive EA likely harboring a novel gene, possibly a channelopathy. The selection for possible causative gene mutations has been thus narrowed.