

PAROXYSMAL DISORDERS

GENE IDENTIFICATION IN ALTERNATING HEMIPLEGIA

Researchers at Georg Augustus University Gottingen, Germany studied the genetics of alternating hemiplegia of childhood (AHC) in 24 patients aged 8-35 years, using whole-exome sequencing to identify de novo mutations associated with the disease. ATP1A3 was the disease-associated gene. Three patients showed de novo missense mutations. The remaining 21 patients all showed disease-associated mutations in ATP1A3, including 6 de-novo missense mutations and 1 splice-site mutation. Comparing the genotypes and phenotypes of AHC patients with those of rapid-onset dystonia-parkinsonism, both disorders have ATP1A3 as the disease-associated gene, and overlapping clinical features include dystonic episodes triggered by emotional stress, a rostro-caudal involvement, and signs of brainstem dysfunction. AHC and rapid-onset dystonia-parkinsonism are allelic diseases related to mutations in ATP1A3 and form a phenotypical continuum of a dystonic movement disorder. (Rosewich H, Thiele H, Ohlenbusch A, et al. Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification. **Lancet Neurol** 2012 Sep;11(9):764-73). (Response: Dr H Rosewich, Department of Paediatric Neurology, Georg August University Gottingen, Germany).

COMMENT. In a multi-author report from the Center for Human Genome Variation, Duke University School of Medicine, Durham, NC, exome sequencing of 7 patients with AHC and their unaffected parents identified de novo mutations in ATP1A3 in all 7. In a subsequent sequence analysis of ATP1A3 in 98 other patients with AHC, ATP1A3 mutations were identified in 74% cases. (Heinzen EL, et al. **Nat Genet** 2012 Jul 29;44(9):1030-4).

Evolution of hemiplegic attacks and epileptic seizures in AHC. (Saito Y et al. **Epilepsy Res** 2010 Aug;90(3):248-58). In 9 patients (4-40 years) with AHC, paroxysmal ocular movements and tonic, clonic, or myoclonic movements were the presenting symptoms (birth-8m). Ictal EEG of these episodes and associated hemiplegic episodes showed only generalized slow background activity. Epileptic seizures occurred at 2-16y in 7 patients: generalized tonic, clonic, myoclonic, tonic-clonic, or complex partial seizures. Ictal EEG in 4 patients recorded generalized sharp waves or polyspike-wave activities during clonic/myoclonic seizures. Patients with status epilepticus and psychomotor deterioration showed cerebellar atrophy and hippocampal changes on MRI.

METABOLIC DISORDERS

CEREBRAL FOLATE DEFICIENCY & RECEPTOR MUTATIONS

Researchers at University Medical Centre Gottingen, other centers in Germany, and Helsinki University Central Hospital, Finland screened 72 children with low 5-methyltetrahydrofolate (5-MTHF) concentrations in the CSF who developed neurological abnormalities after infancy. Ten individuals with developmental regression, ataxia,