association and linkage studies. Linkage, association, and mutation analyses are the most common methods of evaluating candidate genes in epilepsy. The authors advocate the integration of results from different experimental methods rather than insisting only on replication.

Discovery of susceptibility genes and their association with drug responsiveness and side-effects should permit new diagnostic and therapeutic options in the management of the epilepsies. (Helbig I, Scheffer IE, Mulley JC, Berkovic SF. Navigating the channels and beyond: unravelling the genetics of the epilepsies. **Lancet Neurol** March 2008;7:231-245).

COGNITIVE IMPAIRMENT IN TUBEROUS SCLEROSIS COMPLEX

Seizure histories, EEG recordings and intelligence equivalents and their relation to tuber/brain proportion (TBP) measured by 3 dimensional MRI were evaluated in 61 patients with tuberous sclerosis complex (TSC), in a study at University Medical Center, Utrecht, the Netherlands. Mean age at examination was 17.9 (range 1.6 to 59) years, with 20% of patients age 5 years or less. Diagnosis was confirmed by mutation analysis in 44 (TSC1 mutation in 14 and TSC2 mutation in 30 patients). Seizures occurred in 51 (85%) patients, including infantile spasms in 21 (40%). Age at seizure onset was 1 day to 37 years (mean 2.2 years). EEG epileptiform activity in 46 (79%) patients was unifocal in 16 and multifocal in 30. Tubers detected in all patients numbered from 7 to 58 (mean 28). The mean TBP was 1.3% (range 0.2-5.1%). Intelligence equivalent (IE) ranged from 7-119 (mean 69). IE was below average (<90) in 48 (81%) patients and severely below average (<70) in 33 (56%). Cognition index was a mean of 1.7 (range 1.0-3.7) and was below average in 46 (78%) patients.

Number of tubers was not related to age at seizure onset, infantile spasms, or cognitive function. In contrast, TBP was inversely related to age at seizure onset and cognitive function. Patients with a below average IE had a TBP >1%, and those with above average IE had a TBP <1%. Patients with epilepsy had a lower IE than those without epilepsy. Earlier seizure onset, infantile spasms, and a TSC2 mutation were associated with a lower IE and lower cognition index. (Jansen FE, Vincken KL, Algra A et al. Cognitive impairment in tuberous sclerosis complex is a multifactorial condition. **Neurology** March 2008;70:916-923). (Reprints: Dr FE Jansen, Department of Neurology, C03236, University Medical Centre, PO Box 85500 GA Utrecht, the Netherlands). E-mail: f.e.jansen@umcutrecht.nl

COMMENT. The incidence of seizures and below average intelligence in patients with tuberous sclerosis is 85 and 81%, respectively. Mental retardation (IQ <70) occurs in approximately 50%. Patients with TSC2 mutation are younger at seizure onset, are more cognitively impaired, have more tubers, and have a greater TBP. The proportion of the total brain volume occupied by tubers (TBP) in patients with tuberous sclerosis is a better predictor of cognitive function than tuber number. Age at seizure onset is an independent determinant of cognitive function. The findings point to the importance of aggressive therapy and early seizure control in the management of tuberous sclerosis complex complicated by infantile spasms. Patients with infantile spasms generally have better outlook when treated early. ACTH has a beneficial response in 80% of patients less than one year of age and in 22% when diagnosis and treatment are delayed after one year. (Millichap JG, Bickford RG.

Infantile spasms, hypsarrhythmia, and mental retardation. Response to corticotropin and its relation to age and etiology in 21 patients. **JAMA** 1962;182:523-527).

The phenotypes of tuberous sclerosis patients with TSC1 and TSC2 mutations are compared in an editorial (Nass R, Crino PB. **Neurology** 2008;70:904-905). Cognitive impairments are more frequent in patients with TSC2 mutation, but are not always more severe than in those with a TSC1 mutation. Only the TSC2 group has a bimodal IQ distribution, with a lower peak around 50 and a higher peak around 80. TSC2 (tuberin) gene mutations generally produce more severe neurologic disease than TSC1 mutations. TBP may prove relevant to the autistic as well as general cognitive phenotype of tuberous sclerosis complex.

BEHAVIOR AND LANGUAGE DISORDERS

AUTISM AND HYDROXYGLUTARIC ACIDURIA

A 3-year-old boy with L-2-hydroxyglutaric aciduria (HGA) who demonstrated severe autistic symptoms is reported from Aristotle University of Thessaloniki, Greece; VU University, Amsterdam, the Netherlands; and University Hospital, Heidelberg, Germany. The child was seen at age 4 months because of macrocephaly, noted on in utero ultrasound. He was born with esophageal atresia. Neurologic examination revealed hypotonia, hyperreflexia, and psychomotor retardation. EEG and BAEPs were normal, whereas visual evoked potentials showed prolonged latencies. Brain MRI showed diffuse subcortical encephalopathy with increased signal of subcortical white matter. Metabolic leukodystrophy was suspected. Urinary organic acid analysis showed increased levels of L-2-HGA, and DNA analysis demonstrated 2 missense mutations in the gene L-2-HGDH encoding L-2-HG dehydrogenase. Motor development was moderately impaired, walking at age 19 months, whereas speech development was severely impaired, saying only single words at age 2 years and no phrases at 3 years. Stereotypies including arm flapping and finger wiggling began at age 12 months, repetitive behaviors and movements at age 2, and poor eye contact, aloofness, and absent communication by age 3 years. He reacted with tantrums to any change in his routine. The CARS score was 44/60, indicative of severe autism. Repeat MRI shows progression of white matter changes, and head circumference remains above the 97th percentile (54 cm). (Zafeiriou DI, Ververi A, Salomons GS et al. L-2-hydroxyglutaric aciduria presenting with severe autistic features. **Brain Dev** April 2008;30:305-307). (Respond: DI Zafeiriou. E-mail: jeff@med.auth.gr).

COMMENT. L-2-hydroxyglutaric aciduria is an autosomal recessive neurometabolic disorder characterized by psychomotor delay, ataxia, macrocephaly, and MRI changes of leukoencephalopathy. L2HGDH is the disease-causing gene that encodes L-2-HG dehydrogenase. The authors found no previous reference to autism as a feature of the L-2-HGA phenotype. Nonspecific MRI changes reported in autism include cerebellar vermal hypoplasia. (Courchesne E et al. **Neurology** 1994;44:214-223).