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Abstracts

Articles appearing in the December 2017 issue

Germline and somatic mutations in *STXBP1* with diverse neurodevelopmental phenotypes

Objective To expand the clinical phenotype associated with *STXBP1* gene mutations and to understand the effect of *STXBP1* mutations in the pathogenesis of focal cortical dysplasia (FCD).

Methods Patients with *STXBP1* mutations were identified in various ways: as part of a retrospective cohort study of epileptic encephalopathy; through clinical referrals of individuals (10,619) with developmental delay (DD) for chromosomal microarray; and from a collection of 5,205 individuals with autism spectrum disorder (ASD) examined by whole-genome sequencing.

Results Seven patients with heterozygous de novo mutations affecting the coding region of *STXBP1* were newly identified. Three cases had radiologic evidence suggestive of FCD. One male patient with early infantile epileptic encephalopathy, DD, and ASD achieved complete seizure remission following resection of dysplastic brain tissue. Examination of excised brain tissue identified mosaicism for *STXBP1*, providing evidence for a somatic mechanism. Cell-type expression analysis suggested neuron-specific expression. A comprehensive analysis of the published data revealed that 3.1% of severe epilepsy cases carry a pathogenic de novo mutation within *STXBP1*. By contrast, ASD was rarely associated with mutations in this gene in our large cohorts.

Conclusions *STXBP1* mutations are an important cause of epilepsy and are also rarely associated with ASD. In a case with histologically proven FCD, an *STXBP1* somatic mutation was identified, suggesting a role in its etiology. Removing such tissue may be curative for *STXBP1*-related epilepsy.

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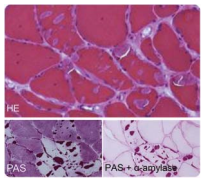
Clinical heterogeneity and phenotype/genotype findings in 5 families with *GYG1* deficiency



Objective To describe the variability of muscle symptoms in patients carrying mutations in the *GYG1* gene, encoding glycogenin-1, an enzyme involved in the biosynthesis of glycogen, and to discuss genotype-phenotype relations.

Methods We describe 9 patients from 5 families in whom muscle biopsies showed vacuoles with an abnormal accumulation of glycogen in muscle fibers, partially α-amylase resistant suggesting polyglucosan bodies. The patients had either progressive early-onset limb-girdle weakness or late-onset distal or scapuloperoneal muscle affection as shown by muscle imaging. No clear definite cardiac disease was found. Histologic and protein analysis investigations were performed on muscle.

Results Genetic analyses by direct or exome sequencing of the *GYG1* gene revealed 6 different *GYG1* mutations. Four of the mutations were novel. They were compound heterozygous in 3 families and homozygous in 2. Protein analysis revealed either the absence of glycogenin-1 or reduced glycogenin-1 expression with impaired glucosylation.

Conclusions Our report extends the genetic and clinical spectrum of glycogenin-1–related myopathies to include scapuloperoneal and distal affection with glycogen accumulation.

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