Abstracts

Articles appearing in the December 2018 issue

Duplication and deletion upstream of *LMNB1* in autosomal dominant adult-onset leukodystrophy

Objective To characterize the genetic and clinical features of patients with autosomal dominant adult-onset demyelinating leukodystrophy (ADLD) carrying duplication and deletion upstream of lamin B1 (*LMNB1*).

Methods Ninety-three patients with adult-onset leukoencephalopathy of unknown etiology were genetically analyzed for copy numbers of *LMNB1* and its upstream genes. We examined *LMNB1* expression by reverse transcription qPCR using total RNA extracted from peripheral leukocytes. Clinical and MRI features of the patients with ADLD were retrospectively analyzed.

Results We identified 4 patients from 3 families with *LMNB1* duplication. The duplicated genomic regions were different from those previously reported. The mRNA expression level of *LMNB1* in patients with duplication was significantly increased. The clinical features of our patients with *LMNB1* duplication were similar to those reported previously, except for the high frequency of cognitive impairment in our patients. We found 2 patients from 1 family carrying a 249-kb genomic deletion upstream of *LMNB1*. Patients with the deletion exhibited relatively earlier onset, more prominent cognitive impairment, and fewer autonomic symptoms than patients with duplication. The presence of cerebellar symptoms and lesions may be characteristic in our patients with the deletion compared with the previously reported family with the deletion. MRI of patients with the deletion exhibited a widespread distribution of white matter lesions including the anterior temporal region.

Conclusions We identified 4 Japanese families with ADLD carrying duplication or deletion upstream of *LMNB1*. There are differences in clinical and MRI features between the patients with the duplication and those with the deletion upstream of *LMNB1*.

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Development of a rapid functional assay that predicts GLUT1 disease severity

Objective To examine the genotype to phenotype connection in glucose transporter type 1 (GLUT1) deficiency and whether a simple functional assay can predict disease outcome from genetic sequence alone.

Methods GLUT1 deficiency, due to mutations in *SLC2A1*, causes a wide range of epilepsies. One possible mechanism for this is variable effect of mutations on GLUT1 function. To test this, we measured glucose transport by GLUT1 variants identified in population controls and patients with mild to severe epilepsies. Controls were reference sequence from the NCBI and 4 population missense variants chosen from public reference control databases. Nine variants associated with epilepsies or movement disorders, with normal intellect in all individuals, formed the mild group. The severe group included 5 missense variants associated with classical GLUT1 encephalopathy. GLUT1 variants were expressed in *Xenopus laevis* oocytes, and glucose uptake was measured to determine kinetics (V_{max}) and affinity (K_m).

Results Disease severity inversely correlated with rate of glucose transport between control ($V_{max} = 28 \pm 5$), mild ($V_{max} = 16 \pm 3$), and severe ($V_{max} = 3 \pm 1$) groups, respectively. Affinities of glucose binding in control ($K_m = 55 \pm 18$) and mild ($K_m = 43 \pm 10$) groups were not significantly different, whereas affinity was indeterminate in the severe group because of low transport rates. Simplified analysis of glucose transport at high concentration (100 mM) was equally effective at separating the groups.

Conclusions Disease severity can be partly explained by the extent of GLUT1 dysfunction. This simple *Xenopus* oocyte assay complements genetic and clinical assessments. In prenatal diagnosis, this simple oocyte glucose uptake assay could be useful because standard clinical assessments are not available.

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