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 ± 5), mild (V_{max} = 16 ± 3), and severe (V_{max} = 3 ± 1) groups, respectively. Affinities of glucose binding in control (K_{m} = 55 ± 18) and mild (K_{m} = 43 ± 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.