

“Gluing” phenotypes together

The case of GLUT1

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The identification of an increasing number of diseases caused by specific gene mutations is gradually bridging the gap between clinical and genetic diagnosis, paving the way to precise nosology, pathophysiologic characterization of diseases, and availability of potential treatments. In this way, discoveries have linked distinct clinical disorders to mutations in the same gene; and conversely, individual diseases were associated with several genetic determinants. This phenomenon, characterized by medical geneticists as “lumping and splitting,”¹ provides an increased level of complexity when dealing with neurologic disorders with a genetic basis, hampering the diagnosis and delaying management of patients.

GLUT1-associated disorders represent an excellent example of such complexity. The *GLUT1/SLC2A1* gene encodes the glucose transporter type 1, the main glucose transporter across the blood–brain barrier. Impaired function of this transporter results in low CSF glucose concentrations in the presence of normoglycemia, the diagnostic hallmark of all GLUT1-related disorders.² The first identified mutations in *GLUT1* were heterozygous, and were linked causally to an epileptic encephalopathy with early onset (GLUT1 deficiency syndrome), characterized by intractable epilepsy in the first 2 years of life, global developmental delay, acquired microcephaly, and variably associated with spasticity, ataxia, and other movement disorders.³ Beside this classic presentation, the clinical spectrum associated with *GLUT1* mutations progressively expanded to include a “late onset classic” form, with seizures appearing later in life; milder, “nonclassic” forms, with developmental delay and chronic or paroxysmal movement disorders, but without epilepsy; early onset absence epilepsy; and paroxysmal exercise-induced dyskinesia (PED), with or without epilepsy.⁴ The episodic nature of GLUT1-associated manifestations is presumably related to a reduced transport of glucose to the brain, causing an unstable metabolic state more likely to be perturbed in presence of environ-

mental stressors such as fasting, anxiety, or prolonged exercise. The same phenotypes, however, also occur in conditions other than GLUT1 deficiency, indicating that the CNS may have a relatively limited repertoire of responses to such disturbances, and that additional genetic determinants are likely in play.

In this issue of *Neurology*®, Weber and collaborators⁵ further expand the range of GLUT1-related conditions to include a form of PED associated with slowly progressive spastic paraparesis. This condition had been previously described in a large German pedigree and linked to a chromosome 1p locus (termed DYT9) considered to be close by, but not encompassing, the *GLUT1* gene. Clinical and genetic reassessment of this family now allowed expansion of the DYT9 locus to include *GLUT1*; and in fact a heterozygous pathogenic missense mutation fully segregated with the disease. As a further proof, the authors identified another causative mutation in a pair of monozygotic twins presenting with a similar phenotype of PED and spasticity.⁶

Such phenotypic heterogeneity associated with *GLUT1* gene defects remains largely unexplained. To some extent, there is a correlation between the type of *GLUT1* mutation and clinical features, such as the severity of mental retardation and the presence of complex movement disorders, with missense mutations being associated with more benign phenotypes.⁴ However, these genotype–phenotype correlates only partly explain the striking clinical variability observed in different families and among relatives who carry the same *GLUT1* mutation. For instance, out of the 17 definitely affected individuals in the original DYT9 German pedigree, 4 persons had PED with spastic paraparesis, 11 presented with PED alone, 1 had spastic paraparesis without PED, and the last only showed focal epilepsy and cognitive impairment.⁵ Similarly, in the largest family reported so far, 10 of 22 *GLUT1* mutation carriers had both PED and epilepsy, 6 had only PED, and 3 had only epilepsy, while 3 persons were asymptomatic, demonstrating reduced penetrance.⁷ These observations

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clearly point to the presence of additional genetic, epigenetic, or environmental factors acting as phenotype modifiers: their identification represents the next challenge of genetic research.

The newly reported association between a paroxysmal movement disorder such as PED and a slowly progressive neurologic condition such as spastic paraparesis is intriguing. Weber and collaborators sought to verify whether GLUT1 deficiency could also account for a subset of patients with pure or complicated hereditary spastic paraparesis, but failed to identify pathogenic mutations in a large cohort of 139 index cases.⁵ Thus, the most consistent clinical “red flag” associated with the spectrum of GLUT1 phenotypes seems to be the presence of episodic disorders with variable clinical expression (epilepsy, migraine, or paroxysmal dyskinesia), either in isolation or combined with a stable neurologic deficit, such as developmental delay, cognitive impairment, acquired microcephaly, or spasticity. In the presence of such features, it becomes important to raise the clinical suspicion of GLUT1-pathies, since a timely diagnosis and the subsequent specific dietary treatment may substantially ameliorate or even completely resolve the episodic symptoms, with consequent dramatic improvement in the patient’s quality of life.⁸

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DISCLOSURE

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