An unusual case of twins

Holger Lerche

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Hertie-Institut
für klinische Hirnforschung

EBERHARD KARLS
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TÜBINGEN

UNIVERSITÄTS
KLINIKUM
TÜBINGEN

Case of twins: Clinical picture

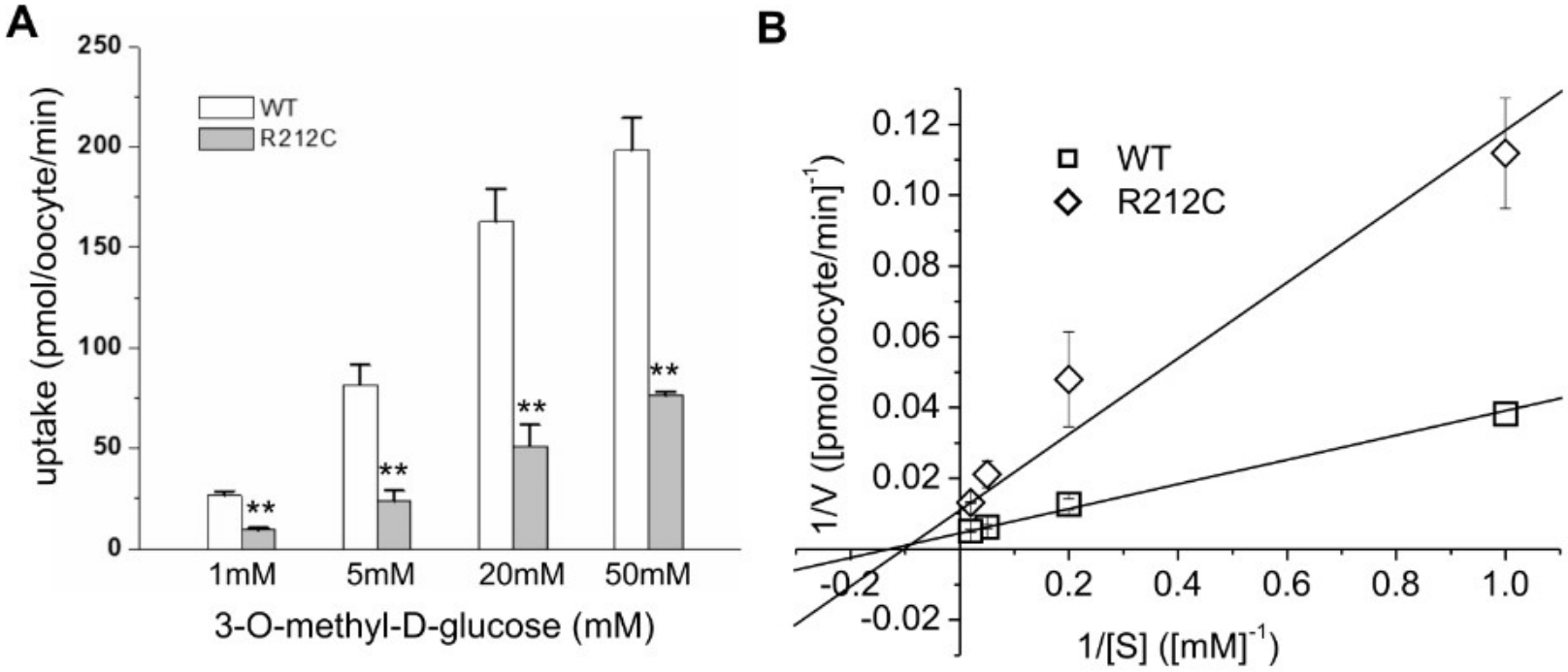
- *Presentation of monozygotic twins:*
  - 41 year-old males
  - Onset as toddlers with abnormal movements:
    painless stiffening of a limb induced by prolonged exercise, followed by choreatic/ballistic movements, spread to other limbs within minutes, lasting minutes to few hours, normal consciousness/awareness, several times weekly
  - Later childhood: progressive permanent gait disturbance
  - Precipitants: prolonged exercise/physical exhaustion, dehydration, caffeine, alcohol, and anticipation of food
  - video

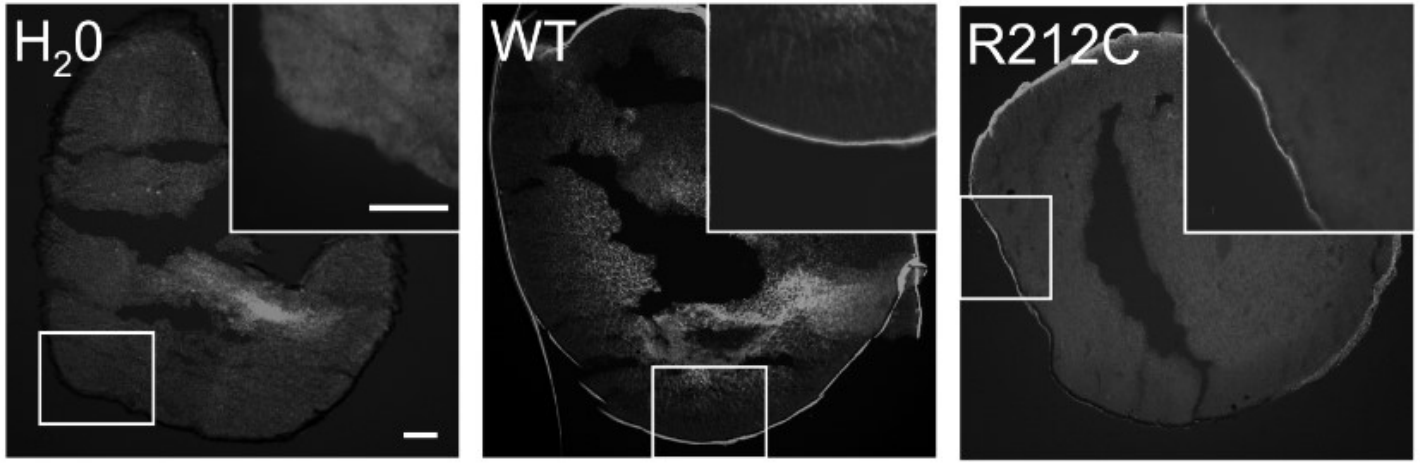
Video shown during presentation

Case of twins: Clinical picture / genetics

- Further clinical signs you want to know? Clinical syndrome?
- Further symptoms: increased tone, sustained clonus, pyramidal pattern weakness I the legs, brisk reflexes, and extensor plantar responses
- Syndrome: Paroxysmal exercise-induced dyskinesia with spastic paraparesis
- Further laboratory tests?
- CSF: reduced CSF/serum glucose ratio
- Treatment?
- Negative trials of phenytoin, valproate, acetazolamide, clonazepam, carbamazepine
- Genetics? Which genes? Patient only? Parents?
- *De novo SLC2A1* / Glut1 mutation, further investigations?

Case of twins: Functional investigations





Paroxysmal choreoathetosis/spasticity (DYT9) is caused by a GLUT1 defect

Y.G. Weber, MD*
C. Kamm, MD*
A. Suls, PhD*
J. Kempfle, MD
K. Kotschet, MD
R. Schüle, MD
T.V. Wuttke, MD
S. Maljevic, PhD
J. Liebrich, MD
T. Gasser, MD
A.C. Ludolph, MD
W. Van Paesschen, MD
L. Schöls, MD
P. De Jonghe, MD, PhD
G. Auburger, MD
H. Lerche, MD

Address correspondence and reprint requests to Prof. Dr. med. Holger Lerche, Abteilung Neurologie mit Schwerpunkt Epileptologie, Hertie Institut für Klinische Hirnforschung,

ABSTRACT

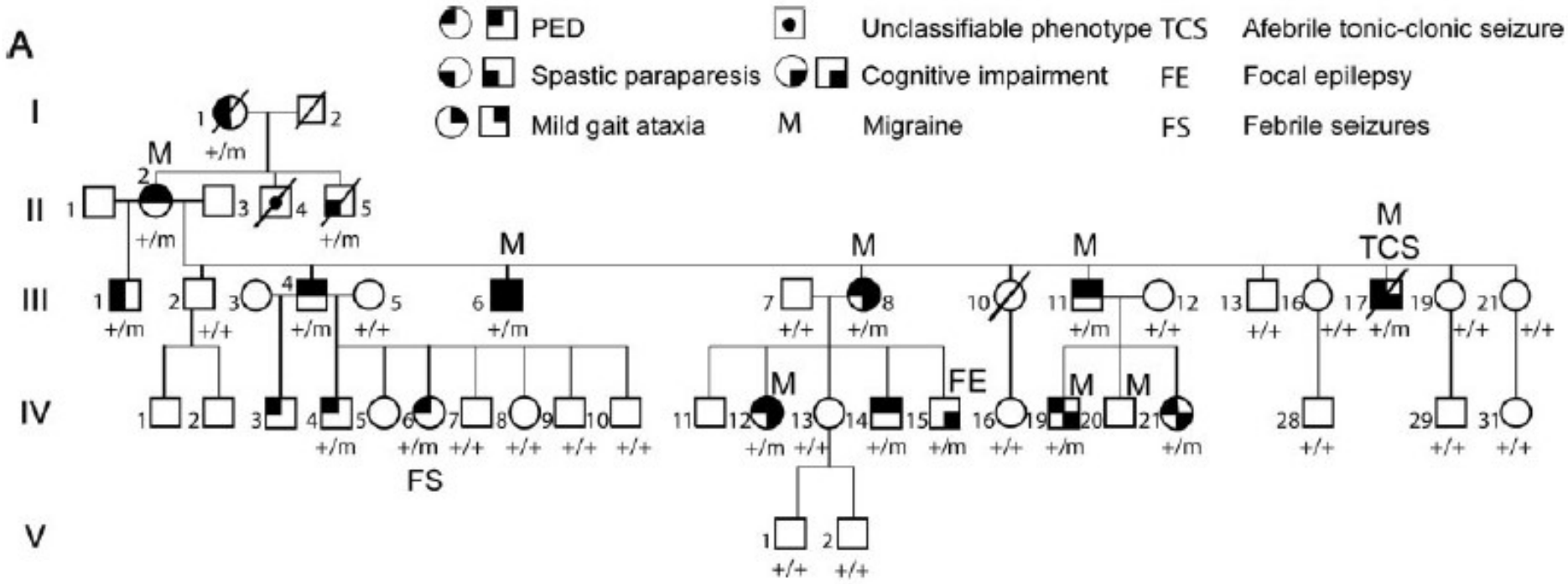
Objective: Mutations in *SLC2A1*, encoding the glucose transporter type 1 (GLUT1), cause a broad spectrum of neurologic disorders including classic GLUT1 deficiency syndrome, paroxysmal exercise-induced dyskinesia (PED, DYT18), and absence epilepsy. A large German/Dutch pedigree has formerly been described as paroxysmal choreoathetosis/spasticity (DYT9) and linked close to but not including the *SLC2A1* locus on chromosome 1p. We tested whether 1) progressive spastic paraparesis, in addition to PED, as described in DYT9, and 2) autosomal dominant forms of hereditary spastic paraparesis (HSP) without PED are caused by *SLC2A1* defects.

Methods: The German/Dutch family and an Australian monozygotic twin pair were clinically (re-)investigated, and 139 index cases with dominant or sporadic HSP in which relevant dominant genes were partially excluded were identified from databanks. *SLC2A1* was sequenced in all cases in this observational study and the functional effects of identified sequence variations were tested in glucose uptake and protein expression assays.

Results: We identified causative mutations in *SLC2A1* in both families, which were absent in 400 control chromosomes, cosegregated with the affection status, and decreased glucose uptake in functional assays. In the 139 index patients with HSP without paroxysmal dyskinesias, we only identified one sequence variation, which, however, neither decreased glucose uptake nor altered protein expression.

Conclusions: This study shows that DYT9 and DYT18 are allelic disorders and enlarges the spectrum of GLUT1 phenotypes, now also including slowly progressive spastic paraparesis combined with PED. *SLC2A1* mutations were excluded as a cause of HSP without PED in our cohort.
Neurology® 2011;77:959-964

First family with PED and spastic paraparesis



GENOMICS 31, 90–94 (1996)
Article No. 0013

A Gene for Autosomal Dominant Paroxysmal Choreoathetosis/ Spasticity (CSE) Maps to the Vicinity of a Potassium Channel Gene Cluster on Chromosome 1p, Probably within 2 cM between D1S443 and D1S197

G. AUBURGER,*,[1] T. RATZLAFF,* A. LUNKES,* H. W. NELLES,* B. LEUBE,* F. BINKOFSKI,* H. KUGEL,† W. HEINDEL,† R. SEITZ,* R. BENECKE,* O. W. WITTE,* AND T. VOIT‡

*Departments of *Neurology and ‡Pediatrics, University Hospital, P.O. Box 101007, 40001 Düsseldorf, Germany; and †Department of Diagnostic Radiology, University of Cologne, Kerpener Strasse 62, 50924 Cologne, Germany

GLUT1 deficiency syndromes

- Classical syndrome: severe, congenital intellectual disability, microcephaly, pharmacoresistant epilepsy, ataxia
- Milder forms of ID/epilepsy/variable other symptoms without microcephaly
- Paroxysmal exercise-induced dyskinesia (rarely with spastic paraparesis) often combined with (mostly generalized) epilepsy
- Early-onset (and rarely classical) absence epilepsy
- Myoclonic-astatic epilepsy (Doose syndrome)
- Therapeutic consequence?
- Ketogenic diet!