The expanding phenotype of Glut1-deficiency syndrome

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Pediatrics and Pediatric Neurology
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FACILITATED TRANSFER OF GLUCOSE FROM BLOOD INTO BRAIN TISSUE

By C. CRONE

From the Institute of Medical Physiology A, University of Copenhagen, Denmark

(Received 19 February 1965)
facilitative glucose transporter and Na$^+$/glucose co-transporter family members

<table>
<thead>
<tr>
<th>Protein</th>
<th>Major isoform (aa)$^1$</th>
<th>$K_m$ (mM)</th>
<th>Major sites of expression</th>
<th>Proposed function</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT1</td>
<td>492</td>
<td>3-7</td>
<td>Ubiquitous distribution in tissues and culture cells</td>
<td>Basal glucose uptake; transport across blood tissue barriers</td>
</tr>
<tr>
<td>GLUT2</td>
<td>524</td>
<td>17</td>
<td>Liver, islets, kidney, small intestine</td>
<td>High-capacity low-affinity transport</td>
</tr>
<tr>
<td>GLUT3</td>
<td>496</td>
<td>1.4</td>
<td>Brain and nerves cells</td>
<td>Neuronal transport</td>
</tr>
<tr>
<td>GLUT4</td>
<td>509</td>
<td>6.6</td>
<td>Muscle, fat, heart</td>
<td>Insulin-regulated transport in muscle and fat</td>
</tr>
<tr>
<td>GLUT5</td>
<td>501</td>
<td>?$^3$</td>
<td>Intestine, kidney, testis</td>
<td>Transport of fructose</td>
</tr>
<tr>
<td>GLUT6</td>
<td>507</td>
<td></td>
<td>Spleen, leukocytes, brain</td>
<td>Transport of fructose</td>
</tr>
<tr>
<td>GLUT7</td>
<td>524</td>
<td>0.3</td>
<td>Small intestine, colon, testis</td>
<td>Transport of fructose</td>
</tr>
<tr>
<td>GLUT8</td>
<td>477</td>
<td>2</td>
<td>Testis, blastocyst, brain, muscle, adipocytes</td>
<td>Fuel supply of mature spermatozoa; Insulin-responsive transport in blastocyst</td>
</tr>
<tr>
<td>GLUT9</td>
<td>511/540</td>
<td>?</td>
<td>Liver, kidney</td>
<td></td>
</tr>
<tr>
<td>GLUT10</td>
<td>541</td>
<td>0.3</td>
<td>Liver, pancreas</td>
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<tr>
<td>GLUT11</td>
<td>496</td>
<td>?</td>
<td>Heart, muscle</td>
<td>Muscle-specific; fructose transporter</td>
</tr>
<tr>
<td>GLUT12</td>
<td>617</td>
<td>?</td>
<td>Heart, prostate, mammary gland</td>
<td></td>
</tr>
<tr>
<td>HMIT</td>
<td>618/629</td>
<td>?</td>
<td>Brain</td>
<td></td>
</tr>
</tbody>
</table>

**Na$^+$/glucose cotransporters (SGLT)**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Major isoform (aa)</th>
<th>$K_m$ (mM)</th>
<th>Major sites of expression</th>
<th>Proposed function</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT1</td>
<td>664</td>
<td>0.2</td>
<td>Kidney, intestine</td>
<td>Glucose reabsorption in intestine and kidney</td>
</tr>
<tr>
<td>SGLT2</td>
<td>672</td>
<td>10</td>
<td>Kidney</td>
<td>Low affinity and high selectivity for glucose</td>
</tr>
<tr>
<td>SGLT3</td>
<td>660</td>
<td>2</td>
<td>Small intestine, skeletal muscle</td>
<td>Glucose activated Na$^+$ channel</td>
</tr>
</tbody>
</table>

Zhao & Keating 2007 Curr Genomics
Head circumference in infants who were premature averages 0.5 cm - 1.5 cm less than in full term infants after reaching 2500 gm to 12 years of age.
BRIEF REPORTS

DEFECTIVE GLUCOSE TRANSPORT ACROSS THE BLOOD–BRAIN BARRIER AS A CAUSE OF PERSISTENT HYPOGLYCORRHACHIA, SEIZURES, AND DEVELOPMENTAL DELAY

Darryl C. De Vivo, M.D.,
Rosario R. Trifiletti, M.D., Ph.D.,
Ronald I. Jacobson, M.D.,
Gabriel M. Ronen, M.D.,
Ramin A. Behmand, B.S.,
and Sami I. Harik, M.D.

responded dramatically to treatment with a ketogenic diet. We believe that these two children have a primary defect of glucose transport into the brain.

CASE REPORTS

Patient 1

The gestation of a male infant was complicated by mild oligohydramnios and a viral illness in the mother during the fifth month of pregnancy. At birth the infant weighed 3235 g, and his Apgar scores were 6 and 7 at one and five minutes, respectively. He had transient neonatal respiratory distress, suckled poorly, and had mild hypotonia. He was treated with oxygen for one day and was apparently well when he went home at the age of five days. His first seizure occurred at the age of 2.5 months. The seizures were described as myoclonic jerks of one limb lasting up to eight minutes and associ-

GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier

Glen Seidner¹, Marcela Garcia Alvarez⁵, Jih-I Yeh², Kevin R. O’Driscoll⁵, Jörg Klepper⁵, Tammy S. Stump⁴, Dong Wang⁵, Nancy B. Spinner⁴, Morris J. Birnbaum¹,³ & Darryl C. De Vivo⁵
Glut1-DS phenotype

- **classic**
  - epilepsy
    - onset 1. - 4. month of life
    - myoclonic jerks of the head, nodding
    - irregular eye movements
    - atypical absences
    - atonic seizures
    - later: generalised tonic clonic seizures
  - motor and mental retardation
  - movement disorder
    - ataxia, dystonia, spasticity
  - deceleration of head growth
    - secondary microcephaly in 50%
Glut1-DS phenotype

• classic
  – seizures
  – developmental delay
  – acquired microcephaly
  – low CSF glucose (hypoglycorrachia)
  – lowered CSF/blood glucose ratio (<0.4 [0.65])
  – low-to-normal CSF lactate
  – reduced glucose uptake in erythrocytes
  – *de novo* mutations of *SLC2A1/GLUT1*:
    hemizygosity, nonsense, frameshift, splice-site
Glut1-DS phenotype

- classic
familial epilepsy

- two brothers, mother
- developmental delay, mild / severe
- seizures
- ataxia, dystonia
- fluctuating performance, worse after fasting, improved after a meal
EEG before breakfast and after breakfast.
familial epilepsy

- two brothers, mother
- hypoglycorrhachia
- reduced glucose uptake in red blood cells
- heterozygous missense mutation R126H
- carbohydrate responsive Glut1-DS

Ann Neurol 2001;50:476
Glut1-DS phenotype

• classic
• carbohydrate-responsive
movement disorder without epilepsy

- 9-yo boy, ataxia, retardation, mild dystonia
- no seizures
- EEG, MRI normal
- hypoglycorrhachia
- heterozygous missense mutation N34I

GLUT-1 deficiency without epilepsy—an exceptional case

W. C. G. Overweg-Plandsoen, J. E. M. Groener, D. Wang, W. Onkenhout, O. F. Brouwer, H. D. Bakker and D. C. De Vivo

J Inherit Metab Dis 2003;26:559
prominent movement disorder

• 10-yo normocephalic boy
• prominent ataxia, dystonia, choreoathetosis, retardation
• spells in infancy: blinking, abn. eye movements
• EEG, MRI normal
• hypoglycorrhachia
• heterozygous insertion mutation
• improvement after ketogenic diet
monozygotic twin girls with ataxia

free walking at 19 months
monozygotic twin girls with ataxia

subcortical WM changes
monozygotic twin girls with ataxia

- mild developmental delay
- deceleration of head growth
- no seizures
- hypoglycorrhachia
  - glucose 26 resp. 27 mg/dl [45 – 70 mg/dl]
  - CSF/blood-glucose ratio 0.37 resp. 0.39 [ > 0.6]
  - lactate 0.6 resp. 0.9 mmol/l [1.1 – 1.8 mmol/l]
- heterozygous missense mutation R153L, de novo
  (DC DeVivo, D Wang, NYC)
- ketogenic diet: ataxia improved
Glut1-DS phenotype

- classic
- carbohydrate-responsive
- ataxia, dystonia without seizures
familial disorder

- hemolytic anemia
- paroxysmal exertion-induced dyskinesia
- seizures
- mild mental retardation

Weber et al. 2008 J Clin Invest
two half-brothers

- congenital hemolytic anemia
- single RBC transfusion
- hemolysis well compensated in later life
- seizures, sudden loss of muscle tone, nodding, predominantly in the morning
- mild ataxia, dystonia
- pat.1: parox. exertion-induced dyskinesia
- learning difficulties, normocephalic
patient 1, EEG

before breakfast

after breakfast
father

• paroxysmal dyskinesia after physical exercise, onset at 6 years
• hemolytic anemia, well compensated

-> video
echinocytes

intracellular concentrations of Na, K in erythrocytes: xerocytosis

pedigree

<table>
<thead>
<tr>
<th></th>
<th>glucose [mg/dL]</th>
<th>CSF-blood-glucose-ratio [0.62-0.68]</th>
<th>lactate [mmol/L] [1.2-2.1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>brother 1</td>
<td>38</td>
<td>0.47</td>
<td>0.8</td>
</tr>
<tr>
<td>brother 2</td>
<td>39</td>
<td>0.55</td>
<td>0.8</td>
</tr>
<tr>
<td>father</td>
<td>38</td>
<td>0.39</td>
<td>0.75</td>
</tr>
</tbody>
</table>
SLC2A1 mutation: 12-BP-deletion  c.1022_1033del, exon 6

loss of 4 amino acids QQLS in 7. transmembrane segment

cation leak: intracellular concentrations of Na, K in oocytes

cation leak

- QQSL-deletion results in increased Ca\(^{2+}\)-permeability
- Increased \([\text{Ca}^{2+}]_i\) triggers suicidal erythrocyte death
- Hemolysis increased in Ca\(^{2+}\)-containing NaCl solution

familial Glut1-DS with PED

- ketogenic diet
- marked improvement of PED, seizures in two half-brothers, father
- boys` cognitive performance improved
- father did not adhere to KD
- no impact on hemolysis
GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak

Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in SLC2A1, encoding the glucose transporter GLUT1.
Glut1-DS phenotype

- classic
- carbohydrate-responsive
- ataxia, dystonia without seizures
- paroxysmal exertion-induced dyskinesias
  - hemolytic anemia due to cation leak
Early-onset absence epilepsy

- 34 patients with early-onset absence epilepsy
- onset < 4 years, generalized sw > 2.5 Hz
- 4 patients (12%) with SLC2A1 mutations
- cognitive functions normal / mildly impaired
- CSF glucose ? Head growth ?
- No clinical difference between patients with and without SLC2A1 mutations

Suls et al. 2009 Ann Neurol
Glut1-DS phenotype

- classic
- carbohydrate-responsive
- ataxia, dystonia without seizures
- paroxysmal exertion-induced dyskinesia
- early-onset absence epilepsy
familial idiopathic generalized epilepsies with absences

15 patients from 2 families with \textit{SLC2A1} mutations
12 pat. with epilepsies: „IGE“, absences, myoclonic-astatic, focal epilepsies
onset 3 – 34 years
phenotype indistinguishable from IGE
subtle PED in 7 patients

Mullen et al. 2010 Neurology
Glut1-DS phenotype

- classic
- carbohydrate-responsive
- ataxia, dystonia without seizures
- paroxysmal exertion-induced dyskinesia
- early-onset absence epilepsy
- familial "idiopathic" generalized epilepsy, variable age of onset
### Glut1-DS phenotype-genotype correlation

<table>
<thead>
<tr>
<th>Residual Glut1 function</th>
<th>100%</th>
<th>75%</th>
<th>50%</th>
<th>25%</th>
<th>0</th>
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</thead>
<tbody>
<tr>
<td><strong>Phenotype</strong></td>
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<tr>
<td>normal</td>
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<tr>
<td>mild</td>
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<tr>
<td>classic</td>
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<td>severe</td>
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<td>embryonic lethal</td>
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<tr>
<td><strong>Genotype</strong></td>
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<tr>
<td>no mutation</td>
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<td>missense</td>
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<td>hemizygosity</td>
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<td>insertion</td>
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<td>deletion</td>
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<td>splice site</td>
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<td>compound heterozygosity</td>
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<tr>
<td>homozygous pathogenic mutation</td>
<td></td>
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</tbody>
</table>

De Vivo et al. 2002 J Child Neurol
# Glut1-DS phenotype-genotype correlation

57 patients with *SLC2A1* mutations

<table>
<thead>
<tr>
<th>Missense</th>
<th>Nonsense frame shift</th>
<th>Splice site translation initiation</th>
<th>Multiple exon deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild mental retardation</td>
<td>Movement disorders</td>
<td>Movement disorders</td>
<td>Early-onset classical phenotype</td>
</tr>
<tr>
<td></td>
<td>CSF:blood glucose ratio lower</td>
<td>CSF:blood glucose ratio lower</td>
<td></td>
</tr>
</tbody>
</table>

Leen et al. 2010 Brain
Tacka dig för din uppmärksamhet!