Dystroglycan in brain, eye, and nerve: 
the non-muscle, neuropathology of 
dystroglycanopathies.

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No conflicts of interest to declare.
muscular dystrophy

normal muscle
electron micrograph of skeletal muscle fiber

basement membrane

cell surface membrane

contractile proteins

electron micrograph of skeletal muscle fiber
dystrophin-glycoprotein complex (DGC)

dystrophin-related muscular dystrophies

MDC1A
MDC1C, MDC1D
WWS, MEB, FCMD
LGMD 2I, 2K, 2M, 2N, 2O, 2P
LGMD 2C, 2D, 2E, 2F
DMD/BMD

Merosin
Agrin
Perlecans
Dystroglycan
Sarcoglycan
Sarcolemmal membrane

Dystrophin
Actin
Syntrophin
Dystrobrevin
nNOS
dystrophin-glycoprotein complex (DGC)

dystrophies with brain and eye involvement

dystrophin-related muscular dystrophies
dystroglycanopathies with brain and eye involvement

• Walker-Warburg syndrome - WWS
• muscle-eye-brain disease – MEB
• Fukuyama congenital muscular dystrophy – FCMD
• congenital muscular dystrophy (CMD) or limb-girdle muscular dystrophy (LGMD) with cognitive impairment
WWS with POMT1 mutations
neuroanatomy
brain

cerebrum
gyrus
sulcus
brainstem
cerebellum
brain ventricles

- Anterior (frontal) horn
- Central part
- Inferior (temporal) horn
- Posterior (occipital) horn
- Cerebral aqueduct (of Sylvius)
- 4th ventricle
- L. lateral aperture (foramen of Luschka)
- L. lateral recess
- Median aperture (foramen of Magendie)
- L. interventricular foramen (of Monro)
- 3rd ventricle
- Optic recess
- Interthalamic adhesion
- Infundibular recess
- Pineal recess
- Suprapineal recess
CSF circulation
CSF reabsorption

- Galea aponeurotica
- Arachnoid granulation
- Calvaria
- Superior sagittal sinus
- Pericranium
- Skin

basement membrane
developmental neurobiology

- normal brain development in five slides -
normal neural tube closure

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normal neural tube closure

Embryo at 21 Days (dorsal view)

- Neural plate of forebrain
- Neural groove
- Neural folds
- Fused neural folds
- 1st cervical somite
- Rhomboid sinus
- Neural crest
- basement membrane
normal neural tube closure

basement membrane
normal cerebral cortex development

basement membrane at the surface of the brain

neural tube → ventricle

normal development

radial glia

basement membrane
dystroglycan


drawing by Huy Nguyen
Brain malformations in WWS patients with *POMT1* mutations

- **A**
  - Normal brain at 21 wk gestation

- **B**
  - Patient brain at 19 wk gestation with cerebellar hypoplasia

- **C**
  - CT scan showing enlarged ventricle

- **D**
  - Normal brain histology

- **E**
  - Patient brain histology with glia limitans

- **F**
  - Patient brain histology with subarachnoid space

Beltran-Valero de Bernabe et al., 2002
abnormal cerebral development

Walker-Warburg syndrome cerebrum - 21 week fetus

Fukuyama CMD - cobblestone lissencephaly
abnormal cerebral development in mice without dystroglycan (DG-null)

- midline fusion
- cortical heterotopia

Moore et al., Nature 418:422-425, 2002
basement membrane disruptions

Moore et al., Nature 418:422-425, 2002
Large\textsuperscript{myd} mice

midline fusion

basement membrane

disrupted basement membrane

WT cerebrum

myd cerebrum

WT hippocampus

myd hippocampus

WT cerebellum

myd cerebellum

Michele et al., Nature 418:417-422, 2002
dystroglycan immunofluorescence in DG-null brain

Glial-neuronal heterotopia begin to form at the same time dystroglycan is lost.

Breaches of the basement membrane, disruptions of the positioning of radial glia endfeet, and migration of differentiating neurons into the leptomeningeal heterotopia.

cobblestone lissencephaly


drawing by Huy Nguyen
cerebellar structure and development

from Goldowitz and Hamre, 1998
histogenensis of cerebellar cortex
normal postnatal cerebellar development

dystroglycan

birth (P0) P14
coincident glia limitans disruption and abnormalities of Bergmann glia processes in the absence of dystroglycan

Failure of granule cell migration and bridging across fissures.
cerebellar pathology in dystroglycanopathies

Walker-Warburg syndrome cerebellum

• Basement membrane disruption occurs in both cerebrum and cerebellum.

• Abnormal inside-out migration results in glial neuronal heterotopia filling the cerebral subarachnoid space.

• Abnormal outside-in migration results in cerebellar granule cell heterotopia.
retina
Muller glia
ribbon
synapse
ERG
drawing by Huy Nguyen
neuronal dystroglycan and LTP

drawing by Huy Nguyen
Schwann cell
myelin sheath

modified from Nature Reviews Neuroscience 4:969, 2003
peripheral nerve

- basal lamina (laminin-2)
- α&β dystroglycan
- DRP2
- periaxin
- α6β4 integrin
- caveolin-1
- MAG
- axonal membrane
- periaxonal space
- adaxonal membrane
- abaxonal membrane

compact

axon

myelin

J Periph Nerv Syst 7:2, 2002
Peripheral nerve development

Radial sorting

Myelination

Schwann cell dystroglycan

Drawing by Huy Nguyen
L4 ventral rootlet

Naked axons in myodystrophic mice

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myodystrophic mouse = Large^{myd} mouse
P0-DG null ventral spinal nerve rootlet is similar to Large mutant mice.
peripheral nerve pathology in the absence of dystroglycan
dystroglycan at nodes of Ranvier

drawing by Huy Nguyen
pathology at nodes of Ranvier in the absence of dystroglycan

immunostains by Rita Barresi
Summary

- Dystroglycanopathies are heterogeneous: varying degrees of muscle, brain, eye, and nerve involvement.

- Pathology is largely due to reduced binding of $\alpha$-dystroglycan to basement membranes.

- In brain, eye, and nerve, many of the abnormalities are developmental.

- Additional abnormalities stem from the roles of $\alpha$-dystroglycan at synapses and nodes of Ranvier.
CMD with cognitive impairment - *POMT1* mutations

Wallace et al., Neuromuscular Disorders 24:312–320, 2014
compound heterozygous *POMT1* mutations

- Asp723Glyfs*8* (relatively common mutation)
- Pro653Leu (novel mutation)

- Pro653 is highly conserved.
- Each parent is a carrier of one mutation.
- A third, unrelated patient was identified with the same two mutations. She also has CMD with cognitive impairment and dystroglycanopathy on muscle biopsy.

Wallace *et al.*, *Neuromuscular Disorders* 24:312–320, 2014
homozygous Asp723Glyfs*8 POMT1 mutations

Walker-Warburg syndrome (WWS)

Wallace et al., Neuromuscular Disorders 24:312–320, 2014
Ashkenazi Jewish founder mutation in \textit{FKTN} causes WWS

exon 9 of \textit{FKTN} homozygous 1-base pair insertion (c.1167insA, p.F390Ifs*14)


\textbf{fetal muscle}

\textbf{dystrophin}

\textbf{\(\alpha\)-DG (GT20ADG)}

\textbf{\(\beta\)-DG}

\textbf{\(\alpha\)-DG (IIH6)}

**FKTN** mutations can also cause mild childhood onset LGMD

Puckett et al., Neuromusc Dis 19:352-356, 2009
Severe hydrocephalus is common in nestin-Cre, but rare in GFAP-Cre/DG null mice possibly a result of an obliterated subarachnoid space in nestin-Cre.

dystroglycan
glycobiology
drawing by Huy Nguyen
O-mannosylation of α-dystroglycan

\[ \text{Gal} \rightarrow \beta_{1,4} \rightarrow \text{GlcNAc} \rightarrow \beta_{1,2} \rightarrow \text{Man} \]

\[ \text{ISPD} \rightarrow \text{POMT1/2} \]

\[ \alpha \rightarrow \text{Ser/Thr} \]

\[ \alpha \rightarrow \text{α-dystroglycan} \]

\[ \text{FKTN} \rightarrow \text{FKRP} \rightarrow \text{TMEM5} \rightarrow \text{B3GNT1} \]

\[ \text{POMGNT1} \rightarrow \text{GalNac} \rightarrow \beta_{1,4} \rightarrow \text{GlcNac} \rightarrow \beta_{1,2} \rightarrow \text{Man} \]

\[ \text{POMGNT2} \rightarrow \text{GalNac} \rightarrow \beta_{1,4} \rightarrow \text{GlcNac} \rightarrow \beta_{1,2} \rightarrow \text{Man} \]

\[ \text{B3GALNT2} \rightarrow \text{Gal} \rightarrow \beta_{1,4} \rightarrow \text{GlcNac} \rightarrow \beta_{1,2} \rightarrow \text{Man} \]

\[ \text{ISPD} \rightarrow \text{POMT1/2} \]

\[ \alpha \rightarrow \text{Ser/Thr} \]

\[ \alpha \rightarrow \text{α-dystroglycan} \]

\[ \text{Dol-P-Man} \rightarrow \text{DPM1} \rightarrow \text{DPM2} \rightarrow \text{DPM3} \]

\[ \text{GDP-Man} \rightarrow \text{GMPPB} \]

\[ \text{POMK} \rightarrow \text{xylose glucuronate} \]

\[ \text{Laminin binding glycan domain} \]

\[ \alpha_{1,3} \rightarrow \beta_{1,3} \]

slide modified from original by Toby Willer
neural tube closure defects

meningocele (meningomyelocele)

encephalocele

F. Netter, M.D.