available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Short Communication

Absence of the basilar pons in mice lacking a functional *Large* glycosyltransferase gene suggests a defect in pontine neuron migration

E. David Litwack[a,*], *Yongsuk Lee*[b], *Jacob M. Mallott*[a]

[a]*Department of Anatomy and Neurobiology, University of Maryland School of Medicine, 20 Penn Street, HSF2-S251, Baltimore, MD 21201, USA*
[b]*The Jackson Laboratory, 600 Main Street, Bar Harbor, ME 04609, USA*

ARTICLE INFO

Article history:
Accepted 3 August 2006
Available online 7 September 2006

Keywords:
Muscular dystrophy
Glycosyltransferase
Basilar pons
Migration
Dystroglycan
Dystrophin
Precerebellar nucleus

ABSTRACT

Several forms of congenital muscular dystrophy result from mutations in glycosyltransferases that modify α-dystroglycan. As pontine hypoplasia has been reported in some clinical cases of congenital muscular dystrophy, we have begun to examine whether these glycosyltransferases are required for the normal development of the basilar pons, one of several precerebellar nuclei of the hindbrain. In *veils* (*Large*^{vls}) mice, which carry a loss-of-function mutation in the *Large* glycosyltransferase gene, the basilar pons is absent. Instead, ectopic clusters of pontine neurons are found lateral to their normal site, suggesting that these neurons are unable to migrate to their appropriate site. Two other precerebellar nuclei, the lateral reticular nucleus and the inferior olive, are present in *Large*^{vls} mice. In addition, the basilar pons forms normally in dystrophin-deficient mice. These results demonstrate that the *Large* glycosyltransferase but not dystrophin is required for normal basilar pontine development.

Many forms of congenital muscular dystrophy, such as Walker–Warburg syndrome and Fukuyama congenital muscular dystrophy, result from mutations in glycosyltransferases that normally modify α-dystroglycan. Collectively known as dystroglycanopathies, one hallmark of these disorders is the appearance of brain malformations such as type II lissencephaly ("cobblestone cortex") and cerebellar hypoplasia (Grewal and Hewitt, 2003; Muntoni, 2004). At the histological level, breaches in the glia limitans, a disordered basal lamina, and glioneuronal heterotopia have been observed (Saito et al., 1999). This disrupted organization is also found in brains from *myodystrophy* (*Large*^{myd}) mice, which carry a mutation in the *Large* glycosyltransferase gene (Holzfeind et al., 2002; Michele et al., 2002). Mice deficient in another glycosyltransferase, POMGnT1, exhibit similar but not identical defects (Liu et al., 2006). The cortical and cerebellar malformations observed in dystroglycanopathies are consistent with defects in neuronal migration along radial glia, suggesting functions for specific glycosyltransferases and glycosylated α-dystroglycan in regulating radial migration.

Like other precerebellar nuclei of the hindbrain, the basilar pons (BP) is derived from the rhombic lip (Rodriguez and Dymecki, 2000). Once generated, BP neurons undergo a circumferential ventrally directed migration just beneath the pial surface of the brain, through a pathway known as the anterior extramural stream. Observations of pontine hypoplasia and basilar pontine heterotopias in clinical cases of congenital muscular dystrophy suggest that the underlying

* *Corresponding author*. Fax: +1 410 706 2512.
E-mail address: elitw001@umaryland.edu (E.D. Litwack).

0006-8993/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2006.08.008

affected genes may regulate pontine neuron migration during development (Saito et al., 2003; van der Knaap et al., 1997). However, as pontine neurons undergo tangential migration, not in association with a radial glial scaffold, the mechanism of such regulation is unknown. To begin to address the potential functions of glycosyltransferases related to congenital muscular dystrophy and of glycosylated α-dystroglycan in regulating pontine development, we examined the BP in *veils* (*Large*^{vls}) mice (Lee et al., 2005), which, like *Large*^{myd} mice, possess a loss-of-function mutation in the *Large* gene.

Pontine morphology was examined in serial thionin-stained sections of *Large*^{vls} mice and wild-type littermates. Sagittal sections of wild-type brains reveal the normal position of the BP (Fig. 1A). In similar sections of *Large*^{vls} brains, however, no significant nucleus is observed, although a small amount of thionin-stained material and some white matter is still present (Fig. 1B). Furthermore, the reticulotegmental nucleus (RTN), another precerebellar nucleus whose neurons migrate through the anterior extramural stream, is absent (Figs. 1A, B). In more lateral sections, where normally no BP would be observed (Fig.

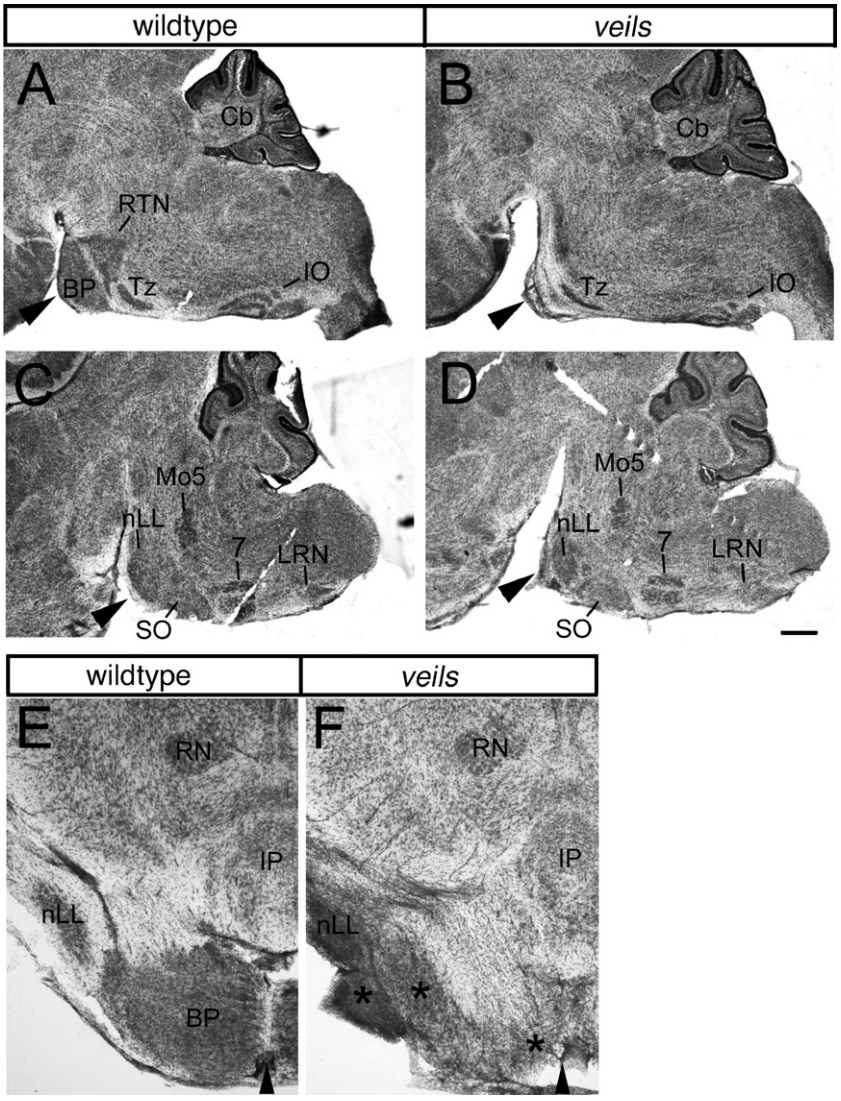

Fig. 1 – Absence of the BP in *Large*^{vls} mice. Sagittal thionin-stained sections of P4 (A) wild-type and (B) *Large*^{vls} hindbrain demonstrate an absence of the *Large*^{vls} BP and RTN. Arrowheads indicate the normal position of the BP. The IO and Tz are present at this sagittal level in both animals. Sagittal sections of (C) wild-type and (D) *Large*^{vls} brain, lateral to those in panels A and B, show that while the BP is not normally observed at this level (arrowhead in panel C), an ectopic cell mass is found in *Large*^{vls} mice (arrowhead in panel D). Several other hindbrain nuclei (7, LRN, Mo5, nLL, and SO) are present at this sagittal level in both animals. Coronal sections of P4 (E) wild-type and (F) *Large*^{vls} hindbrain demonstrate ectopic clusters of cells (asterisks in panel F) extending lateral to the normal site of the BP. At this coronal level, the IP, nLL, and RN are present in both animals. Arrowheads in panels E and F indicate the midline. In panels A–D, rostral is to the left; in panels E and F, lateral is to the left. Abbreviations: 7, facial nucleus; BP, basilar pons; Cb, cerebellum; IO, inferior olive; IP, interpeduncular nucleus; LRN, lateral reticular nucleus; Mo5, motor trigeminal nucleus; nLL, nucleus of the lateral lemniscus; RN, red nucleus; RTN, reticulotegmental nucleus; SO, superior olive; Tz, nucleus of the trapezoid body. Scale bars: D = 0.5 mm (for A–D), 0.25 mm (for E, F).