Molecular Genetics and Metabolism 94 (2008) 391–396

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

# $GM_1$ gangliosidosis: Review of clinical, molecular, and therapeutic aspects

Nicola Brunetti-Pierri [a], Fernando Scaglia [a,b,*]

[a] Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA
[b] Texas Children's Hospital, Houston, TX 77030, USA

ARTICLE INFO

*Article history:*
Received 16 February 2008
Received in revised form 12 April 2008
Accepted 12 April 2008
Available online 3 June 2008

*Keywords:*
$GM_1$ gangliosidosis
*GLB1*
Lysosomal storage disorders
β-galactosidase

ABSTRACT

$GM_1$ gangliosidosis is a lysosomal storage disorder due to deficiency of the β-galactosidase enzyme. This deficiency results in accumulation of $GM_1$ gangliosides and related glycoconjugates in the lysosomes leading to lysosomal swelling, cellular damage, and organ dysfunction. The disease is lethal in the infantile and juvenile forms. To date, up to 102 mutations distributed along the β-galactosidase gene (*GLB1*) have been reported. This review gives an overview of the clinical and molecular findings in patients with $GM_1$ gangliosidosis. Furthermore, it describes therapeutic approaches which are currently under investigation in animal models of the disease.



$GM_1$ gangliosidosis (MIM# 230500) is a lysosomal storage disorder due to deficiency of the β-galactosidase enzyme (E.C. 3.2.1.23) which hydrolyzes the terminal β-galactosyl residues from $GM_1$ ganglioside, glycoproteins, and glycosaminoglycans [1] (Fig. 1). The incidence of $GM_1$ gangliosidosis has been estimated to be 1 in 100,000–200,0000 live births [2]. Although the disorder is panethnic, an increased prevalence has been found in Brazil (1:17,000) [3,4], in the Roma population (1:10,000) [2,5], in the Maltese Islands (1:3700) [6], and in a Cypriot population [7].

$GM_1$ gangliosidosis can be classified into three types based on the clinical phenotype: (1) type 1 or infantile form with onset between birth and 6 months, rapidly progressive with hypotonia, severe central nervous system (CNS) degeneration and death by 1–2 years of age; (2) type 2 late infantile or juvenile with onset between 7 months and 3 years, lag in motor and cognitive development, and slower progression; and (3) type 3 adult or chronic variant with late onset (3–30 years), a progressive extrapyramidal disorder due to local deposition of glycosphingolipid in the caudate nucleus [8]. Adult patients have been mostly reported in the Japanese population. The severity of each type is inversely related to the residual activity of the mutant β-galactosidase enzyme [9]. β-galactosidase deficiency is also responsible for Morquio disease type B (MIM# 253010) characterized by marked skeletal abnormalities, corneal clouding, cardiac involvement, increased urinary excretion of keratan sulfate but no clinical signs of storage in neural tissues. However, the demarcation between $GM_1$ gangliosidosis and Morquio B can be often obscured as in patients displaying mental regression and the skeletal abnormalities of Morquio B.

The deficiency of β-galactosidase enzymatic activity, but in combination with neuraminidase deficiency, is also present in a different disorder, galactosialidosis (MIM# 256540) [10,11] due to a defect in the protective protein/cathepsin A (PPCA) [12] stabilizing the β-galactosidase/neuraminidase complex [13]. The clinical presentation of galactosialidosis partially overlaps with $GM_1$ gangliosidosis. However, the predominant clinical manifestations of galactosialidosis are attributed to the severe neuraminidase deficiency rather than the partial deficiency of the β-galactosidase enzyme.

## Disease pathogenesis

The clinical manifestations of $GM_1$ gangliosidosis result from the massive storage of $GM_1$ ganglioside and related glycoconjugates in different tissues and particularly in the CNS (Figs. 1–3). However, the molecular mechanisms leading to the disease pathogenesis are still incompletely understood. Neuronal cell death and demyelination accompanied by astrogliosis and microgliosis are usually observed in areas of severe neuronal vacuolation. Neuronal apoptosis, endoplasmic reticulum (ER) stress response [14,15], abnormal axoplasmic transport resulting in myelin deficiency [16], and disturbed neuronal–oligodendroglial interactions [17,18] have been proposed as possible pathomechanisms involved in $GM_1$ gangliosidosis. Furthermore, inflammatory responses are considered to contribute to the pathogenesis and/or disease progression [19]. More recently, an activation of autophagy leading to mitochondrial dysfunction in β-galactosidase deficient mouse brains has been implicated in the disease pathogenesis [20].

* Corresponding author. Address: Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA. Fax: +1 832 825 4294.
*E-mail address:* fscaglia@bcm.edu (F. Scaglia).

1096-7192/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.ymgme.2008.04.012

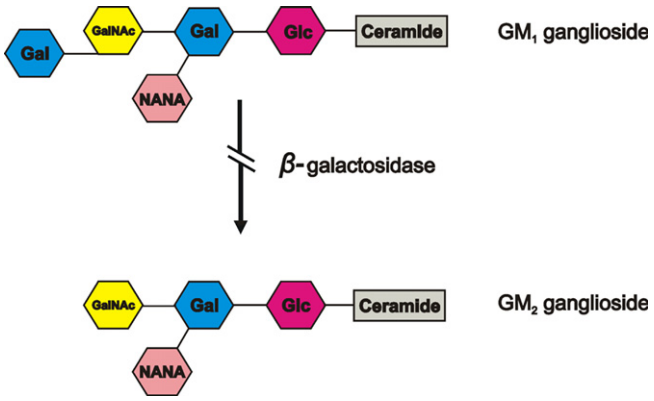


**Fig. 1.** Biochemical defect in $GM_1$ gangliosidosis. β-galactosidase enzyme hydrolyzes the terminal β-galactosyl residues from $GM_1$ ganglioside. Lack of β-galactosidase leads to massive accumulation of $GM_1$ ganglioside. *Abbreviations:* Glc, glucose; Gal, galactose; GalNAc, *N*-acetylgalactosamine; NANA, *N*-acetyl neuraminic acid.

## Clinical features

The clinical suspicion of $GM_1$ gangliosidosis is usually based on the presence of signs of storage such as coarse facial features, gingival hypertrophy, corneal clouding, cherry-red macula, hepatosplenomegaly, vacuolated lymphocytes, and skeletal dysostosis in addition to a history of psychomotor regression. In the absence of these findings the diagnosis is more elusive. To determine the prevalence of the "cardinal features" in $GM_1$ gangliosidosis, we have searched the Medline database and analyzed the published cases of infantile, juvenile, and adult or chronic variant $GM_1$ gangliosidosis. The search was performed with the key words "$GM_1$ gangliosidosis" and "beta-galactosidase deficiency". The reference lists of the reports thus retrieved were also scrutinized. We analyzed published cases with sufficient clinical data, and with a diagnosis of $GM_1$ gangliosidosis confirmed by either biochemical assay of β-galactosidase and neuraminidase and/or by *GLB1* molecular analysis. A total of 209 patients met our selection criteria; 130 were infantile, 23 juvenile, and 56 adult $GM_1$ gangliosidosis. Data were analyzed for clinical features and molecular findings. The main clinical features are listed in Table 1. As expected, we found that signs and symptoms of the CNS involvement were invariably present in all cases. In the infantile form, although present with high prevalence, the classic features seen in storage disorders such as coarse facial features (87%), cherry-red macula (59%), hepatosplenomegaly (85%), skeletal dysostosis (82%) were not constantly present, at least at the time of the diagnosis. Macular cherry-red spot, hepatosplenomegaly, and skeletal involvement had higher prevalence in the infantile form compared to the juvenile form (Table 1). Cardiomyopathy has been reported in patients with all three forms and it is overall present in about one third of the cases. About 6% of the infantile cases presented at birth with hydrops fetalis and there have been very few case reports of extensive Mongolian spot [21–24] or angiokeratoma [25].

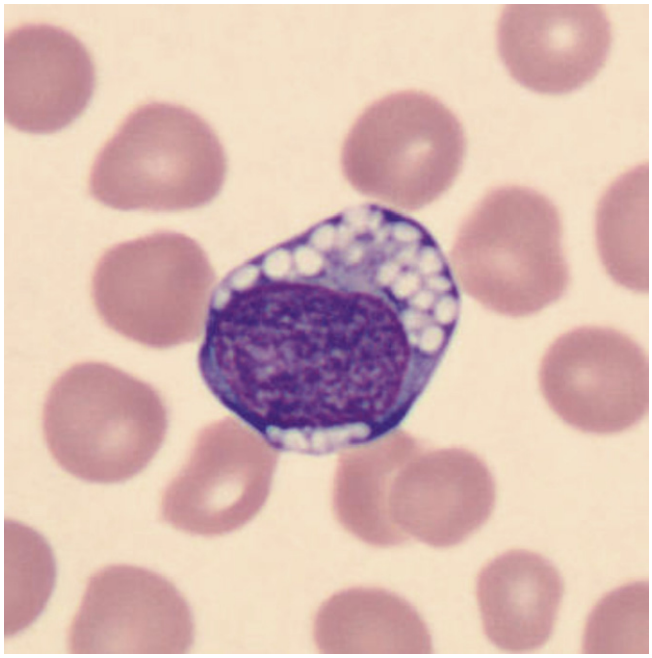

**Fig. 2.** Photomicrograph of May-Grunwald-Giemsa stained blood film showing one lymphocyte with many large bold vacuoles.

## Biochemical defect

β-galactosidase is synthesized as an 85-kDa precursor that is post-translationally glycosylated to an 88 kDa form and processed into the mature 64 kDa lysosomal enzyme [13]. The enzyme in lysosomes is complexed with two other hydrolases: PPCA and neuraminidase. In white blood cells and fibroblasts, β-galactosidase enzyme activity is deficient in both $GM_1$ gangliosidosis and galactosialidosis. Nevertheless, galactosialidosis can be distinguished biochemically from $GM_1$ gangliosidosis because it presents with normal β-galactosidase activity in serum or plasma while enzyme activity is deficient in $GM_1$ gangliosidosis [26]. However, a definitive diagnosis is based on measurement of neuraminidase activity. Due to its instability, neuraminidase is not measured in leukocytes [27] and its activity has to be determined in fibroblasts. Alternatively, the diagnosis of $GM_1$ gangliosidosis can be confirmed by β-galactosidase gene (*GLB1*) molecular testing.

Residual β-galactosidase activity in fibroblasts from patients, measured using the artificial 4-methylumbelliferyl β-galactopyranoside substrate, varies from 0.07–1.3% of control values in infantile patients to 0.3–4.8% in the juvenile form and up to 9% in adults. Residual β-galactosidase activities in Morquio B disease fibroblasts range between 1.3 and 7% of the normal [28].

## *GLB1* mutations in $GM_1$ gangliosidosis

*GLB1* maps to the short arm of chromosome 3 and contains 16 exons. It gives rise to two alternatively spliced mRNAs: a transcript of 2.5 kb encoding the lysosomal enzyme and a transcript of 2.0 kb, encoding the elastin binding protein (EBP), a major component of the nonintegrin cell surface elastin receptor complex localized on the cell surface [29,30]. In the 2 kb transcript, exons 3, 4, and 6 are missing, and exon 5 has a different reading frame giving rise to a unique stretch of 32 amino acids that allows EBP to bind tropoelastin [31,32]. Although EBP may have some role in the development of $GM_1$ gangliosidosis and Morquio B, its potential role is still under discussion [33,34] and the relationship between *GLB1* mutations, $GM_1$ gangliosidosis and Morquio B disease is still unclear.

A total of 102 mutations have been reported in *GLB1* [2,5,7,26,32–62]. The reported mutations are summarized in Fig. 4. There is extensive molecular heterogeneity in $GM_1$ gangliosidosis, hindering a clear genotype/phenotype correlation. Of the 102 reported mutations, 78 are missense/nonsense mutations, 10 are splicing mutations, 7 are insertions, and 7 are deletions. Some mutations such as R59H have higher prevalence especially among Brazilians, Iberian, and Roma patients [2,5]. Missense/nonsense mutations are primarily located in exon 2, 6, and 15 (Fig. 1)

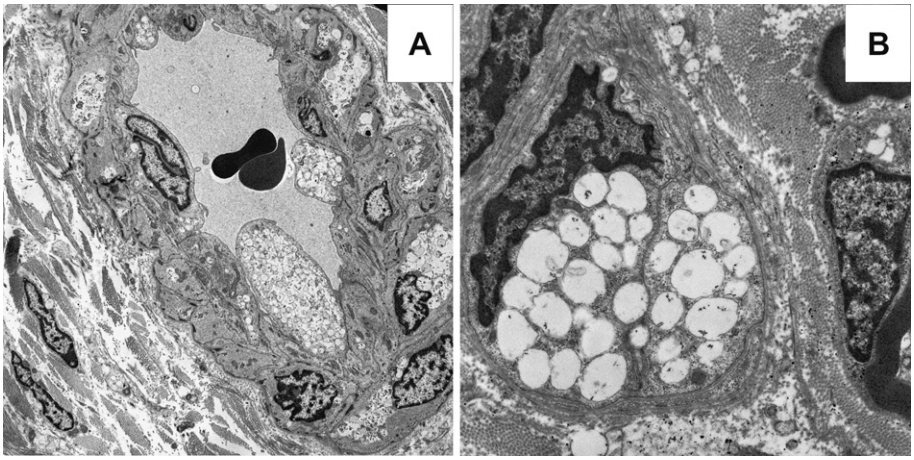


**Fig. 3.** Electron Microscopy in $GM_1$ gangliosidosis. (A) Vacuolar appearance of endothelial cells, pericytes, and smooth muscle cells of a capillary (B) Schwann cell with extensive vacuolization.

**Table 1**
Clinical features in patients with infantile, juvenile, and adult $GM_1$ gangliosidosis (review of the literature)*.

| | *Infantile (n = 130)* | | *Juvenile (n = 23)* | | *Adult (n = 56)* | |
|---|---|---|---|---|---|---|
| *Pregnancy* | | | | | | |
| Hydrops | 8/130 | 6% | – | – | – | – |
| IUGR | 2/130 | 1% | – | – | – | – |
| *General* | | | | | | |
| Dysmorphic features | 90/103 | 87% | 10/15 | 66% | 2/7 | 28% |
| Localized edema | 3/130 | 2% | – | – | – | – |
| *Neurological* | | | | | | |
| Hypotonia | 107/111 | 96% | 11/22 | 50% | – | – |
| Hypertonia | 3/111 | 3% | 1/22 | 4% | – | – |
| Developmental delay/Mental retardation | 115/115 | 100% | 22'/23 | 96% | – | – |
| Seizures | 10/115 | 9% | 4/22 | 18% | 1/36 | 3% |
| Extrapyramidal signs | – | – | – | – | 23/36 | 64% |
| Dystonia | – | – | – | – | 8/36 | 22% |
| Gait disturbances | – | – | – | – | 16/36 | 44% |
| Speech difficulties | – | – | – | – | 12/36 | 33% |
| *Other system involvement* | | | | | | |
| Cherry-red spot | 50/84 | 59% | 3/17 | 18% | 1/27 | 4% |
| Cardiomyopathy | 18/53 | 34% | 3/8 | 38% | 3/8 | 38% |
| Hepatosplenomegaly | 104/122 | 85% | 6/20 | 30% | 1/26 | 4% |
| Skeletal abnormalities | 62/76 | 82% | 11/16 | 69% | 36/38 | 95% |

IUGR: intrauterine growth retardation.
* Cases of GM1 gangliosidosis from the medical literature were reviewed. With the exception of the features of hydrops, 1UGR, and localized edema, the denominator indicates the number of cases in which the feature was commented upon.

suggesting that the regions encoded by these exons may have important catalytic and/or regulatory functions.

## Therapeutic approaches

At present, only symptomatic and supportive therapy is available for patients with $GM_1$ gangliosidosis. Different strategies have been explored to treat this disease and they include bone marrow transplantation (BMT), gene therapy approaches, and substrate reduction therapy. The availability of small and large animal models has facilitated the exploration of experimental therapies. In animals, naturally occurring $GM_1$ gangliosidosis has been recorded in cats, dogs, sheep, and calves [8]. In addition, a mouse model lacking a functional β-galactosidase gene has been generated by homologous recombination and embryonic stem cell technology [63,64], and a mouse model lacking an original β-galactosidase gene that expresses the R201C mutation has been also developed as an appropriate model of human disease [65].

Allogenic BMT has been attempted in a child with infantile $GM_1$ gangliosidosis. However, despite complete normalization of white blood cell β-galactosidase levels the patient continued to deteriorate neurologically [66]. Imino sugars inhibiting ganglioside biosynthesis have been investigated in rodents and have resulted in reduction of gangliosides accumulation in the CNS suggesting that substrate deprivation therapy may be a potentially effective early intervention therapy for $GM_1$ gangliosidosis [67,68].

Gene therapy is a promising approach for the treatment of neurodegenerative diseases that are caused by a single-gene defect. Correction of the enzyme deficiency and reduction in glycosphingolipid accumulation have been shown in β-$gal^{-/-}$ mice following intravenous injection of an adenoviral vector or intracerebroventricular injection of an adeno-associated virus (AAV) expressing the mouse β-galactosidase [69,70]. However, these approaches are still far from reaching clinical application. Instead, a recently developed strategy using chemical chaperones appears to be more rapidly available for clinical translation. In this approach, a chemical chaperone (*N*-octyl-4-epi-β-valienamine, NOEV) is used to stabilize the mutant β-galactosidase protein for restoration of enzyme activity [65]. Oral treatment with NOEV in mice carrying the mutant gene resulted in marked increase of the enzyme activity,

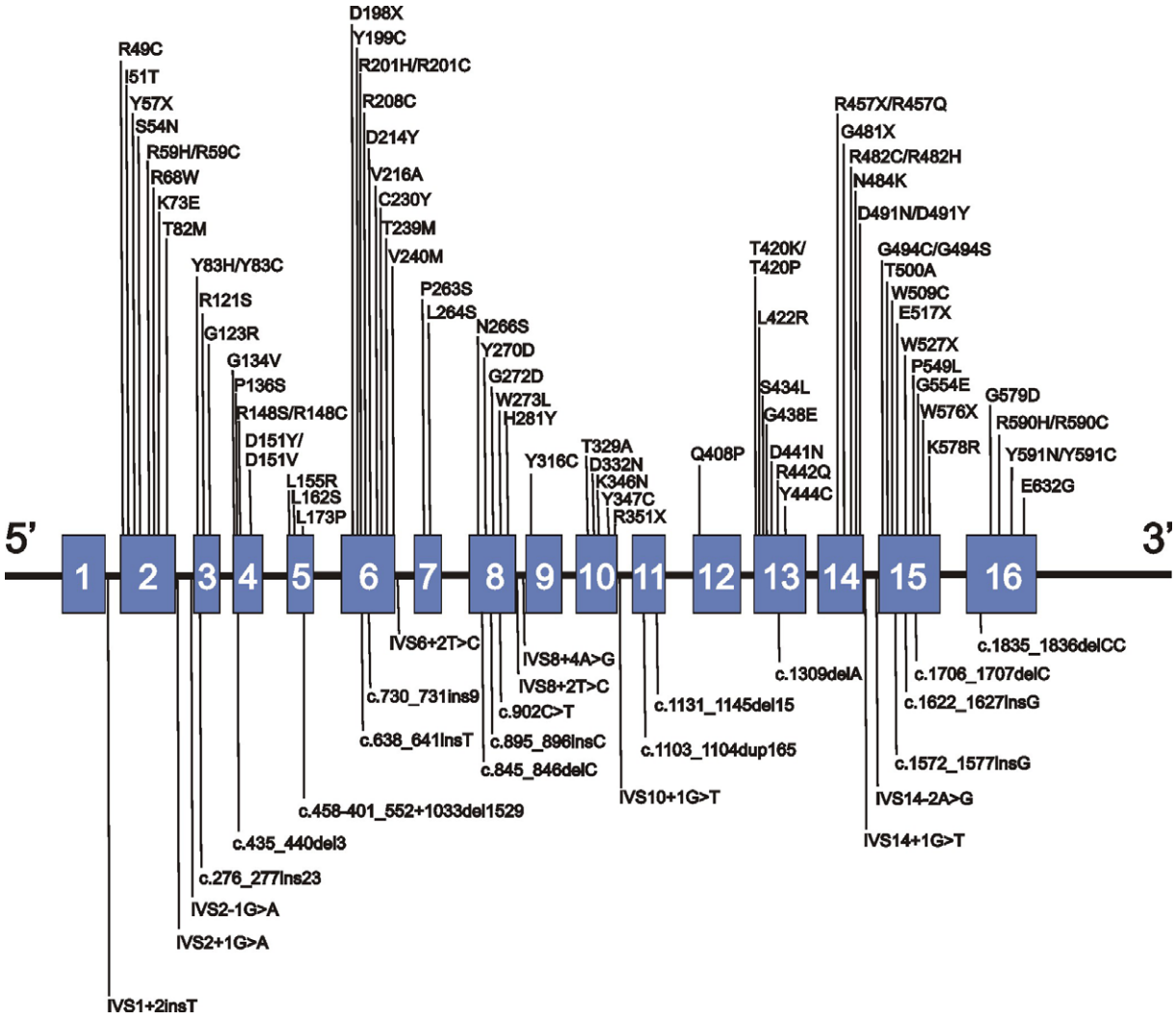


**Fig. 4.** Summary of the genetic mutations reported in the *GLB1* gene. A total of 102 mutations have been reported [2,5,7,26,32–57,59–62]. Some mutations resulting in higher residual enzymatic activity (p.Y83C, p.Y83H, p.R201H, p.W273L, p.T420K, p.N484K, p.T500A) have been associated with Morquio B phenotype [5,51,56,58,74].

reduction in CNS $GM_1$ ganglioside content, and prevention of neurological deterioration [65,71]. However, this molecular therapy will be effective only in patients with some level of β-galactosidase expression. Nevertheless, it could represent the first step towards an effective treatment of the disease. In the perspective of future available therapies, having biomarkers to evaluate the efficacy of new treatment strategies is important. Thus far, CSF biomarkers ($GM_1$ ganglioside concentration, AST, LDH, neuron-specific enolase and myelin basic protein) and brain Proton Magnetic Spectroscopy indexes (*N*-acetylaspartate, myoinositol) have been proposed to monitor investigational approaches for $GM_1$ gangliosidosis [72,73].

## References

[1] S. Okada, J.S. O'Brien, Generalized gangliosidosis: beta-galactosidase deficiency, Science 160 (1968) 1002–1004.
[2] I. Sinigerska, D. Chandler, V. Vaghjiani, I. Hassanova, R. Gooding, A. Morrone, I. Kremensky, L. Kalaydjieva, Founder mutation causing infantile GM1-gangliosidosis in the Gypsy population, Mol. Genet. Metab. 88 (2006) 93–95.
[3] J.C. Coelho, M. Wajner, M.G. Burin, C.R. Vargas, R. Giugliani, Selective screening of 10,000 high-risk Brazilian patients for the detection of inborn errors of metabolism, Eur. J. Pediatr. 156 (1997) 650–654.
[4] M.H. Severini, C.D. Silva, A. Sopelsa, J.C. Coelho, R. Giugliani, High frequency of type 1 GM1 gangliosidosis in southern Brazil, Clin. Genet. 56 (1999) 168–169.
[5] R. Santamaria, A. Chabas, M.J. Coll, C.S. Miranda, L. Vilageliu, D. Grinberg, Twenty-one novel mutations in the GLB1 gene identified in a large group of GM1-gangliosidosis and Morquio B patients: possible common origin for the prevalent p.R59H mutation among gypsies, Hum. Mutat. 27 (2006) 1060.
[6] H.M. Lenicker, P. Vassallo Agius, E.P. Young, S.P. Attard Montalto, Infantile generalized GM1 gangliosidosis: high incidence in the Maltese Islands, J. Inherit. Metab. Dis. 20 (1997) 723–724.
[7] T. Georgiou, G. Stylianidou, V. Anastasiadou, A. Caciotti, Y. Campos, E. Zammarchi, A. Morrone, A. D'Azzo, A. Drousiotou, The Arg482His mutation in the beta-galactosidase gene is responsible for a high frequency of GM1 gangliosidosis carriers in a Cypriot village, Genet. Test. 9 (2005) 126–132.
[8] Y. Suzuki, E. Nanba, β-Galactosidase deficiency (β-galactosidosis) $GM_1$-gangliosidosis and Morquio B disease, The Metabolic and Molecular Basis of Inherited Disease, McGraw-Hill, New York, 2001.
[9] Y. Suzuki, N. Nakamura, K. Fukuoka, GM1-gangliosidosis: accumulation of ganglioside GM1 in cultured skin fibroblasts and correlation with clinical types, Hum. Genet. 43 (1978) 127–131.
[10] D.A. Wenger, T.J. Tarby, C. Wharton, Macular cherry-red spots and myoclonus with dementia: coexistent neuraminidase and beta-galactosidase deficiencies, Biochem. Biophys. Res. Commun. 82 (1978) 589–595.
[11] G. Andria, G. Pontarelli, W.S. Sly, W.E. Dodson, in: G. Tettamanti, P. Durand, S.D. DiDonato (eds.), Infantile neuraminidase and β-galactosidase deficiencies (galactosialidosis) with mild clinical courses (Sialidases and Sialidoses), Edi Ermes, Milan, Italy, 1981, pp. 379.
[12] N.J. Galjart, N. Gillemans, A. Harris, G.T. van der Horst, F.W. Verheijen, H. Galjaard, A. d'Azzo, Expression of cDNA encoding the human "protective protein" associated with lysosomal beta-galactosidase and neuraminidase: homology to yeast proteases, Cell 54 (1988) 755–764.
[13] A. D'Azzo, A. Hoogeveen, A.J. Reuser, D. Robinson, H. Galjaard, Molecular defect in combined beta-galactosidase and neuraminidase deficiency in man, Proc. Natl. Acad. Sci. USA 79 (1982) 4535–4539.
[14] A. Tessitore, M. del P Martin, R. Sano, Y. Ma, L. Mann, A. Ingrassia, E.D. Laywell, D.A. Steindler, L.M. Hendershot, A. d'Azzo, GM1-ganglioside-mediated

activation of the unfolded protein response causes neuronal death in a neurodegenerative gangliosidosis, Mol. Cell. 15 (2004) 753–766.
[15] A. d'Azzo, A. Tessitore, R. Sano, Gangliosides as apoptotic signals in ER stress response, Cell. Death Differ. 13 (2006) 404–414.
[16] J.P. van der Voorn, W. Kamphorst, M.S. van der Knaap, J.M. Powers, The leukoencephalopathy of infantile GM1 gangliosidosis: oligodendrocytic loss and axonal dysfunction, Acta Neuropathol. (Berl.) 107 (2004) 539–545.
[17] R.D. Folkerth, Abnormalities of developing white matter in lysosomal storage diseases, J. Neuropathol. Exp. Neurol. 58 (1999) 887–902.
[18] E.M. Kaye, J. Alroy, S.S. Raghavan, G.A. Schwarting, L.S. Adelman, V. Runge, D. Gelblum, J.G. Thalhammer, G. Zuniga, Dysmyelinogenesis in animal model of GM1 gangliosidosis, Pediatr. Neurol. 8 (1992) 255–261.
[19] M. Jeyakumar, R. Thomas, E. Elliot-Smith, D.A. Smith, A.C. van der Spoel, A. d'Azzo, V.H. Perry, T.D. Butters, R.A. Dwek, F.M. Platt, Central nervous system inflammation is a hallmark of pathogenesis in mouse models of GM1 and GM2 gangliosidosis, Brain 126 (2003) 974–987.
[20] A. Takamura, K. Higaki, K. Kajimaki, S. Otsuka, H. Ninomiya, J. Matsuda, K. Ohno, Y. Suzuki, E. Nanba, Enhanced autophagy and mitochondrial aberrations in murine G(M1)-gangliosidosis, Biochem. Biophys. Res. Commun. 367 (2008) 616–622.
[21] M. Hanson, J.R. Lupski, J. Hicks, D. Metry, Association of dermal melanocytosis with lysosomal storage disease: clinical features and hypotheses regarding pathogenesis, Arch. Dermatol. 139 (2003) 916–920.
[22] M. Silengo, G. Battistoni, M. Spada, Is there a relationship between extensive mongolian spots and inborn errors of metabolism?, Am J. Med. Genet. 87 (1999) 276–277.
[23] T.T. Tang, N.B. Esterly, M.S. Lubinsky, H.W. Oechler, J.M. Harb, R.A. Franciosi, GM1-gangliosidosis type 1 involving the cutaneous vascular endothelial cells in a black infant with multiple ectopic Mongolian spots, Acta Derm. Venereol. 73 (1993) 412–415.
[24] L.D. Bloch, F.Y. Matsumoto, W. Belda Jr., R. Giugliani, L.F. Menezes, C.A. Kim, M.C. Machado, Dermal melanocytosis associated with GM1-gangliosidosis type 1, Acta Derm. Venereol. 86 (2006) 156–158.
[25] N.G. Beratis, A. Varvarigou-Frimas, S. Beratis, S.L. Sklower, Angiokeratoma corporis diffusum in GM1 gangliosidosis, type 1, Clin. Genet. 36 (1989) 59–64.
[26] N. Ishii, A. Oshima, H. Sakuraba, Y. Fukuyama, Y. Suzuki, Normal serum beta-galactosidase in juvenile GM1 gangliosidosis, Pediatr. Neurol. 10 (1994) 317–319.
[27] J.W. Callahan, Molecular basis of GM1 gangliosidosis and Morquio disease, type B. Structure-function studies of lysosomal beta-galactosidase and the non-lysosomal beta-galactosidase-like protein, Biochim. Biophys. Acta 1455 (1999) 85–103.
[28] T. Okumiya, H. Sakuraba, R. Kase, T. Sugiura, Imbalanced substrate specificity of mutant beta-galactosidase in patients with Morquio B disease, Mol. Genet. Metab. 78 (2003) 51–58.
[29] A. Oshima, A. Tsuji, Y. Nagao, H. Sakuraba, Y. Suzuki, Cloning, sequencing, and expression of cDNA for human beta-galactosidase, Biochem. Biophys. Res. Commun. 157 (1988) 238–244.
[30] H. Morreau, N.J. Galjart, N. Gillemans, R. Willemsen, G.T. van der Horst, A. d'Azzo, Alternative splicing of beta-galactosidase mRNA generates the classic lysosomal enzyme and a beta-galactosidase-related protein, J. Biol. Chem. 264 (1989) 20655–20663.
[31] S. Privitera, C.A. Prody, J.W. Callahan, A. Hinek, The 67-kDa enzymatically inactive alternatively spliced variant of beta-galactosidase is identical to the elastin/laminin-binding protein, J. Biol. Chem. 273 (1998) 6319–6326.
[32] A. Hinek, S. Zhang, A.C. Smith, J.W. Callahan, Impaired elastic-fiber assembly by fibroblasts from patients with either Morquio B disease or infantile GM1-gangliosidosis is linked to deficiency in the 67-kD spliced variant of beta-galactosidase, Am. J. Hum. Genet. 67 (2000) 23–36.
[33] A. Caciotti, M.A. Donati, A. Boneh, A. d'Azzo, A. Federico, R. Parini, D. Antuzzi, T. Bardelli, D. Nosi, V. Kimonis, E. Zammarchi, A. Morrone, Role of beta-galactosidase and elastin binding protein in lysosomal and nonlysosomal complexes of patients with GM1-gangliosidosis, Hum. Mutat. 25 (2005) 285–292.
[34] A. Morrone, T. Bardelli, M.A. Donati, M. Giorgi, M. Di Rocco, R. Gatti, R. Parini, R. Ricci, G. Taddeucci, A. D'Azzo, E. Zammarchi, Beta-galactosidase gene mutations affecting the lysosomal enzyme and the elastin-binding protein in GM1-gangliosidosis patients with cardiac involvement, Hum. Mutat. 15 (2000) 354–366.
[35] S. Chakraborty, M.A. Rafi, D.A. Wenger, Mutations in the lysosomal beta-galactosidase gene that cause the adult form of GM1 gangliosidosis, Am. J. Hum. Genet. 54 (1994) 1004–1113.
[36] A. Caciotti, T. Bardelli, J. Cunningham, A. D'Azzo, E. Zammarchi, A. Morrone, Modulating action of the new polymorphism L436F detected in the GLB1 gene of a type-II GM1 gangliosidosis patient, Hum. Genet. 113 (2003) 44–50.
[37] A. Caciotti, M.A. Donati, T. Bardelli, A. d'Azzo, G. Massai, L. Luciani, E. Zammarchi, A. Morrone, Primary and secondary elastin-binding protein defect leads to impaired elastogenesis in fibroblasts from GM1-gangliosidosis patients, Am. J. Pathol. 167 (2005) 1689–1698.
[38] A.J. Kooper, P.M. Janssens, A.N. de Groot, M.L. Liebrand-van Sambeek, C.J. van den Berg, G.B. Tan-Sindhunata, P.P. van den Berg, E.K. Bijlsma, A.P. Smits, R.A. Wevers, Lysosomal storage diseases in non-immune hydrops fetalis pregnancies, Clin. Chim. Acta 371 (2006) 176–182.
[39] K. Yoshida, A. Oshima, M. Shimmoto, Y. Fukuhara, H. Sakuraba, N. Yanagisawa, Y. Suzuki, Human beta-galactosidase gene mutations in GM1-gangliosidosis: a common mutation among Japanese adult/chronic cases, Am. J. Hum. Genet. 49 (1991) 435–442.
[40] N.C. Chiu, W.H. Qian, A.L. Shanske, S.S. Brooks, R.M. Boustany, A common mutation site in the beta-galactosidase gene originates in Puerto Rico, Pediatr. Neurol. 14 (1996) 53–56.
[41] J. Nishimoto, E. Nanba, K. Inui, S. Okada, K. Suzuki, GM1-gangliosidosis (genetic beta-galactosidase deficiency): identification of four mutations in different clinical phenotypes among Japanese patients, Am. J. Hum. Genet. 49 (1991) 566–574.
[42] R.M. Boustany, W.H. Qian, K. Suzuki, Mutations in acid beta-galactosidase cause GM1-gangliosidosis in American patients, Am. J. Hum. Genet. 53 (1993) 881–888.
[43] C.M. Silva, M.H. Severini, A. Sopelsa, J.C. Coelho, A. Zaha, A. d'Azzo, R. Giugliani, Six novel beta-galactosidase gene mutations in Brazilian patients with GM1-gangliosidosis, Hum. Mutat. 13 (1999) 401–409.
[44] A. Gururaj, L. Sztriha, J. Hertecant, J.G. Johansen, T. Georgiou, Y. Campos, A. Drousiotou, A. d'Azzo, Magnetic resonance imaging findings and novel mutations in GM1 gangliosidosis, J. Child. Neurol. 20 (2005) 57–60.
[45] A. Caciotti, M.A. Donati, E. Procopio, M. Filocamo, W. Kleijer, W. Wuyts, B. Blaumeiser, A. d'Azzo, L. Simi, C. Orlando, F. McKenzie, A. Fiumara, E. Zammarchi, A. Morrone, GM1 gangliosidosis: molecular analysis of nine patients and development of an RT-PCR assay for GLB1 gene expression profiling, Hum. Mutat. 28 (2007) 204.
[46] R. Santamaria, M. Blanco, A. Chabas, D. Grinberg, L. Vilageliu, Identification of 14 novel GLB1 mutations, including five deletions, in 19 patients with GM1 gangliosidosis from South America, Clin. Genet. 71 (2007) 273–279.
[47] E.M. Kaye, C. Shalish, J. Livermore, H.A. Taylor, R.E. Stevenson, X.O. Breakefield, Beta-galactosidase gene mutations in patients with slowly progressive GM1 gangliosidosis, J. Child Neurol. 12 (1997) 242–247.
[48] S. Zhang, R. Bagshaw, W. Hilson, Y. Oho, A. Hinek, J.T. Clarke, J.W. Callahan, Characterization of beta-galactosidase mutations Asp332 > Asn and Arg148 > Ser, and a polymorphism, Ser532 > Gly, in a case of GM1 gangliosidosis, Biochem. J. 348 Pt. 3 (2000) 621–632.
[49] T. Georgiou, A. Drousiotou, Y. Campos, A. Caciotti, L. Sztriha, A. Gururaj, P. Ozand, E. Zammarchi, A. Morrone, A. D'Azzo, Four novel mutations in patients from the Middle East with the infantile form of GM1-gangliosidosis, Hum. Mutat. 24 (2004) 352.
[50] A. Oshima, K. Yoshida, M. Shimmoto, Y. Fukuhara, H. Sakuraba, Y. Suzuki, Human beta-galactosidase gene mutations in morquio B disease, Am. J. Hum. Genet. 49 (1991) 1091–1093.
[51] E. Paschke, I. Milos, H. Kreimer-Erlacher, G. Hoefler, M. Beck, M. Hoeltzenbein, W. Kleijer, T. Levade, H. Michelakakis, B. Radeva, Mutation analyses in 17 patients with deficiency in acid beta-galactosidase: three novel point mutations and high correlation of mutation W273L with Morquio disease type B, Hum. Genet. 109 (2001) 159–166.
[52] N. Ishii, T. Oohira, A. Oshima, H. Sakuraba, F. Endo, I. Matsuda, K. Sukegawa, T. Orii, Y. Suzuki, Clinical and molecular analysis of a Japanese boy with Morquio B disease, Clin. Genet. 48 (1995) 103–108.
[53] N. Brunetti-Pierri, A. Mian, R. Luetchke, B.H. Graham, Intrauterine growth retardation and placental vacuolization as presenting features in a case of GM1 gangliosidosis, J. Inherit. Metab. Dis. 30 (2007) 823.
[54] A. Oshima, K. Yoshida, A. Ishizaki, M. Shimmoto, Y. Fukuhara, H. Sakuraba, Y. Suzuki, GM1-gangliosidosis: tandem duplication within exon 3 of beta-galactosidase gene in an infantile patient, Clin. Genet. 41 (1992) 235–238.
[55] A. Morrone, H. Morreau, X.Y. Zhou, E. Zammarchi, W.J. Kleijer, H. Galjaard, A. d'Azzo, Insertion of a T next to the donor splice site of intron 1 causes aberrantly spliced mRNA in a case of infantile GM1-gangliosidosis, Hum. Mutat. 3 (1994) 112–120.
[56] M. Hirayama, Y. Kitagawa, S. Yamamoto, A. Tokuda, T. Mutoh, T. Hamano, T. Aita, M. Kuriyama, GM1 gangliosidosis type 3 with severe jaw-closing impairment, J. Neurol. Sci. 152 (1997) 99–101.
[57] E. Roze, E. Paschke, N. Lopez, T. Eck, K. Yoshida, A. Maurel-Ollivier, D. Doummar, C. Caillaud, D. Galanaud, T. Billette de Villemeur, M. Vidailhet, A. Roubergue, Dystonia and parkinsonism in GM1 type 3 gangliosidosis, Mov. Disord. 20 (2005) 1366–1369.
[58] R.D. Bagshaw, S. Zhang, A. Hinek, M.A. Skomorowski, D. Whelan, J.T. Clarke, J.W. Callahan, Novel mutations (Asn 484 Lys, Thr 500 Ala, Gly 438 Glu) in Morquio B disease, Biochim. Biophys. Acta 1588 (2002) 247–253.
[59] K. Yoshida, S. Ikeda, K. Kawaguchi, N. Yanagisawa, Adult GM1 gangliosidosis: immunohistochemical and ultrastructural findings in an autopsy case, Neurology 44 (1994) 2376–2382.
[60] K. Yoshida, A. Oshima, H. Sakuraba, T. Nakano, N. Yanagisawa, K. Inui, S. Okada, E. Uyama, R. Namba, K. Iwasaki, S. Kondo, K. Takamiya, Y. Suzuki, GM1 gangliosidosis in adults: clinical and molecular analysis of 16 Japanese patients, Ann. Neurol. 31 (1992) 328–332.
[61] K. Suzuki, H. Sakuraba, O. Akiro, β-galactosidase deficiency (β-galactosidosis): GM1-gangliosidosis and Morquio B disease, The Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill, New York, 1995, pp. 2785–2823.
[62] W.L. Hilson, Y. Okamura-Oho, S. Zhang, J.T. Clarke, D. Mahuran, J.W. Callahan, Novel missense mutations in β-galactosidase that results in GM1-gangliosidosis, Am. J. Hum. Genet. 55 (S3) (1994) 1302.
[63] J. Matsuda, O. Suzuki, A. Oshima, A. Ogura, Y. Noguchi, Y. Yamamoto, T. Asano, K. Takimoto, K. Sukegawa, Y. Suzuki, M. Naiki, Beta-galactosidase-deficient mouse as an animal model for GM1-gangliosidosis, Glycoconj. J. 14 (1997) 729–736.

[64] C.N. Hahn, M. del Pilar Martin, M. Schroder, M.T. Vanier, Y. Hara, K. Suzuki, K. Suzuki, A. d'Azzo, Generalized CNS disease and massive GM1-ganglioside accumulation in mice defective in lysosomal acid beta-galactosidase, Hum. Mol. Genet. 6 (1997) 205–211.
[65] J. Matsuda, O. Suzuki, A. Oshima, Y. Yamamoto, A. Noguchi, K. Takimoto, M. Itoh, Y. Matsuzaki, Y. Yasuda, S. Ogawa, Y. Sakata, E. Nanba, K. Higaki, Y. Ogawa, L. Tominaga, K. Ohno, H. Iwasaki, H. Watanabe, R.O. Brady, Y. Suzuki, Chemical chaperone therapy for brain pathology in G(M1)-gangliosidosis, Proc. Natl. Acad. Sci. USA 100 (2003) 15912–15917.
[66] J.P. Shield, J. Stone, C.G. Steward, Bone marrow transplantation correcting beta-galactosidase activity does not influence neurological outcome in juvenile GM1-gangliosidosis, J. Inherit. Metab. Dis. 28 (2005) 797–798.
[67] J.L. Kasperzyk, A. d'Azzo, F.M. Platt, J. Alroy, T.N. Seyfried, Substrate reduction reduces gangliosides in postnatal cerebrum-brainstem and cerebellum in GM1 gangliosidosis mice, J. Lipid Res. 46 (2005) 744–751.
[68] J.L. Kasperzyk, M.M. El-Abbadi, E.C. Hauser, A. D'Azzo, F.M. Platt, T.N. Seyfried, *N*-butyldeoxygalactonojirimycin reduces neonatal brain ganglioside content in a mouse model of GM1 gangliosidosis, J. Neurochem. 89 (2004) 645–653.
[69] N. Takaura, T. Yagi, M. Maeda, E. Nanba, A. Oshima, Y. Suzuki, T. Yamano, A. Tanaka, Attenuation of ganglioside GM1 accumulation in the brain of GM1 gangliosidosis mice by neonatal intravenous gene transfer, Gene. Ther. 10 (2003) 1487–1493.
[70] M.L. Broekman, R.C. Baek, L.A. Comer, J.L. Fernandez, T.N. Seyfried, M. Sena-Esteves, Complete correction of enzymatic deficiency and neurochemistry in the GM1-gangliosidosis mouse brain by neonatal adeno-associated virus-mediated gene delivery, Mol. Ther. 15 (2007) 30–37.
[71] Y. Suzuki, S. Ichinomiya, M. Kurosawa, M. Ohkubo, H. Watanabe, H. Iwasaki, J. Matsuda, Y. Noguchi, K. Takimoto, M. Itoh, M. Tabe, M. Iida, T. Kubo, S. Ogawa, E. Nanba, K. Higaki, K. Ohno, R.O. Brady, Chemical chaperone therapy: clinical effect in murine G(M1)-gangliosidosis, Annals Neurol. 62 (2007) 671–675.
[72] H. Satoh, O. Yamato, T. Asano, M. Yamasaki, Y. Maede, Increased concentration of GM1-ganglioside in cerebrospinal fluid in dogs with GM1- and GM2-gangliosidoses and its clinical application for diagnosis, J. Vet. Diagn. Invest. 16 (2004) 223–226.
[73] N. Brunetti-Pierri, M.B. Bhattacharjee, Z.J. Wang, C. Zili, D.A. Wenger, L. Potocki, J. Hunter, F. Scaglia, Brain proton magnetic resonance spectroscopy and neuromuscular pathology in a patient with GM1 gangliosidosis, J. Child Neurol. 23 (2008) 73–78.
[74] R. Santamaria, A. Chabas, J.W. Callahan, D. Grinberg, L. Vilageliu, Expression and characterization of 14 GLB1 mutant alleles found in GM1-gangliosidosis and Morquio B patients, J. Lipid Res. 48 (2007) 2275–2282.