Morquio-B disease: Clinical and genetic characteristics of a distinct GLB1-related dysostosis multiplex

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Abstract

Background: Morquio-B disease (MBD) is a distinct GLB1-related dysostosis multiplex involving the trabecular parts of long bones and spine, presenting a mild phenocopy of GALNS-related Morquio-A disease.

Methods: We analyzed 63 (n = 62 published) cases with MBD to describe their clinical, biochemical and genetic features.

Results: Forty-one of 51 cases with informative clinical data had pure MBD including progressive growth impairment, kyphoscoliosis, coxa/genua valga, joint laxity, platyspondyly, odontoid hypoplasia. Ten of 51 had MBD plus neuronopathic manifestations including intellectual/developmental/speech delay, spasticity, ataxia dystonia. Corneal clouding, cardiac valve pathology, hepatosplenomegaly, spinal cord compression were infrequent and atlantooccipital dislocation, cardiomyopathy and cherry red spot were never reported. Urinary glycosaminoglycan and oligosaccharide excretion was consistently abnormal. Keratan sulphate-derived oligosaccharides were only detected using LC-MS/MS-based methods. Residual β-galactosidase activities measured against synthetic substrates were 0%-17%.

Among 28 GLB1 variants, W273 L (34/94 alleles) and T500A (11/94 alleles) occurred most frequently. W273L was invariably associated with pure MBD. Pure MBD also was reported in a case homozygous for R201H, and in the majority of cases carrying the T500A variant. Homozygous Y333C and G438E were associated with MBD plus neuronopathic manifestations. T82M, R201H, and H281Y, observed in seven alleles, previously have been found sensitive to experimental chaperones.

Conclusion: Data provide a basis for future systematic collection of clinical, biochemical, morphologic, and genetic data of this ultra-rare condition.

KEYWORDS
dwarfism, literature review, mucopolysaccharidosis, natural history, spondyloepiphyseal dysplasia
1 | BACKGROUND

GLB1-related disorders are caused by a deficiency of β-galactosidase, a lysosomal enzyme facilitating the degradation of complex carbohydrates bound to a variety of structurally unrelated molecules such as gangliosides, proteoglycans, and N- and O-linked glycoproteins. The spectrum of clinical phenotypes is wide: Type 1 (infantile) GM1-gangliosidosis (OMIM 230500) begins before age 1 year with hepatosplenomegaly, progressive loss of neurodevelopmental abilities and vision, cherry red macula spot, seizures, and dystonia/spasticity. Type 2 (late infantile/juvenile) GM1-gangliosidosis is characterized by a later onset of motor and cognitive regression. Type 3 (adult) GM1-gangliosidosis causes extrapyramidal signs, cardiomyopathy, and variable degrees of intellectual disability.1

GLB1-related disorders are also associated with skeletal deformities (eg, kyphoscoliosis and short stature), which, like in other lysosomal storage diseases, nosologically have been classified as dysostosis multiplex.2,3 Morquio-B disease (MBD) (OMIM 253010)4 is a distinct form of GLB1-related disorder presenting with a specific type of dysostosis multiplex which has been known as Morquio syndrome since its first description by Morquio5 and Brailsford.6

Morquio syndrome is characterized by short stature with a disproportionally short trunk, kyphoscoliosis, pigeon chest (pectus carinatum), short neck, large appearing head with midface hypoplasia and mandibular protrusion, large appearing joints (elbows, wrists, knees, ankles), coxa and genu valga and flat feet. Joint laxity, corneal clouding, and cardiac valve disease and tracheal stenosis are additional findings. Characteristic radiological findings include platyspondyly and vertebral beaking, odontoid hypoplasia, spinal canal narrowing, hip dysplasia, dysplasia of the carpal and tarsal bones, as well as shortening and epi-and metaphyseal dysplasia of long bones (eg, shortening of the ulna and sloping of the distal ends of radius and ulna).

Currently two genetic conditions are known to cause Morquio syndrome: GALNS-related Morquio-A disease (OMIM 253000) and GLB1-related Morquio-B disease (MBD). Keratan sulfate is a proteoglycan that accumulates in both Morquio-A and Morquio-B disease.

The GLB1 gene contains 16 exons spanning more than 60 kb. The longest transcript variant (NM_000404.2) is a 2.5 kb mRNA giving rise to a 70 kDa precursor protein which is processed within the lysosomes into the 64-kD mature β-galactosidase enzyme protein.4,7 GLB1 alternatively gives rise to a 2.0 kb mRNA transcript, formed by splicing out exons 3, 4, and 6 which encodes the elastin binding protein, a key-recycling chaperone in the tropoelastin assembly process for elastogenesis in the extracellular matrix.9 The β-galactosidase monomer consists of two β-domains and a TIM barrel domain, which together generate appropriate protein folding and functional integrity.4,7,10 Mutations associated with Type 1/infantile onset GM1-gangliosidosis, for the most part, are located in the core protein region causing β-galactosidase instability, whereas mutations associated with milder phenotypes, such as types 2 and 3 GM1-gangliosidosis, tend to be on the protein surface.7

Patterns and distribution of the accumulating substrates across the various tissues and organs are determined by the impact of the underlying GLB mutation on the molecular pathophysiology of the β-galactosidase protein.4,11 While accumulation of GM1-gangliosides in the brain seems most responsible for neurologic manifestations in GM1-gangliosidosis, excretion of both skeletal and corneal forms of keratan sulfate has been shown in MBD and type 1 (infantile) GM1-gangliosidosis.10

More than 150 pathogenic GLB1 variants are known with the vast majority being associated with GM1 gangliosidosis,1 whereas the number of variants described in association with MBD is rather limited. W273L is the most frequent MBD allele.10-14 Numerous other alleles have been found in both GM1-gangliosidosis and in MBD,11,13,15-17 but the type and degree of overlap between pure skeletal and neuronopathic phenotypes is hard to predict.

We performed a literature review to revisit all cases previously published as GLB1-related MBD, with the aims (a) to describe the clinical phenotype associated with MBD; (b) to compare the clinical data of all genotypes identified in this review against the classical W237L Morquio-B allele. Additionally, we reviewed published data on potentials of small molecules for allele specific rescue of GLB1 deficiency. In

2 | METHODS AND RESULTS

Our literature review enrolled English language PubMed-listed publications and reports of cases diagnosed with MBD from its first description in 197618 to June 2018. Search terms included: “GM1-gangliosidosis,” “Morquio-B,” “Mucopolysaccharidosis,” “Beta-galactosidase deficiency,” “β-galactosidase deficiency,” and “GLB1 deficiency.” In
addition, we added data from three patients presented at the 13th International Symposium on Mucopolysaccharidoses and Related Diseases, Suipe, Bahia, Brazil, August 13-17, 201419 and one thus far unpublished patient with MBD previously diagnosed at our center.

We identified 23 articles/reports containing information about 62 MBD cases. Including our own case (P1), 63 cases (22 male; 18 female; 23 gender not reported) met the inclusion criteria for our analysis: (a) clinical findings consistent with a Morquio phenotype; (b) diagnosis confirmed by demonstration of deficient β-galactosidase activity and/or a homozygous/compound heterozygous GLB1 mutation. We grouped all these cases according to availability of clinical information including skeletal and neuronopathic phenotype, as well as of GLB1 variant data (Table 1).

Fifty-one of 63 reported cases contained clinical data informing about the skeletal phenotype and presence or absence of a neuronopathic phenotype (Table 2). Forty-one of 51 cases had pure MBD presenting with skeletal features consistent with Morquio syndrome only, ten of 51 had neurologic/neurodevelopmental deficits in addition to typical skeletal features.

Most frequently reported skeletal features included short stature, kyphoscoliosis/platyspondyly, coxa valga, and genu valgum, odontoid hypoplasia and joint laxity/hyperextensible joints. In some cases, the skeletal features were described as progressive spondyloepiphyseal dysplasia.18,32 Ulnar deviation of joints. In some cases, the skeletal features were described as valgum, odontoid hypoplasia and joint laxity/hyperextensible stature, kyphoscoliosis/platyspondyly, coxa valga, and genu valgum.

TABLE 1 Summary of 63 cases, including n = 62 reported as GLB1-related Morquio-B disease and one unreported patient (case vignette 1)

| Group | Cases | References |
|-------|-------|------------|
| **Cases with informative clinical data** (skeletal and neuronopathic) | 51 | Arbisser et al 197720; Bagshaw et al 200221; Beck et al 198722; Di Cesare et al 201223; Giugliani et al 198715; Groebe et al 198024; Gucev et al 200825; Hofer et al 200911; Holzgreve et al 198726; Ishii et al 199527; Maroteaux et al 198224; Mayer et al 200916; O'Brien et al 197628; Oshima et al 199129; Pronicka et al 198135; Santamaria et al 200614; Sheth et al 200229; Sohn et al 201230; Trojak et al 198013; van Gemund et al 198332; P1 (unpublished). |
| **Cases with skeletal features only** (pure MBD) | 41/51 | |
| **Cases with skeletal and neurologic/developmental features** (MBD plus) | 10/51 | |
| **Cases without informative clinical data** (data on skeletal or neuronopathic or both phenotypes missing) | 12 | Hinek et al 200033; Oshima et al 199134; Pronicka et al 198135; Santamaria et al 200614 |
| **Cases with unknown genotype** | 16 | Arbisser et al 197720; Beck et al 198722; Di Cesare et al 201223; Groebe et al 198024; Holzgreve et al 198726; Maroteaux et al 198224; O'Brien et al 197628; Pronicka et al 198135; Sheth et al 200229; Trojak et al 198013; van Gemund et al 198332 |
| **Cases with reported genotype** | 47 | Bagshaw et al 200221; Giugliani et al 198715; Gucev et al 200825; Hinek et al 200033; Hofer et al 200911; Ishii et al 199527; Mayer et al 200916; Oshima et al 199134; Paschke et al 200113; Paschke et al 201419; Roze et al 200817; Santamaria et al 200614; Sohn et al 201230; Case vignette 1 (unpublished) |
| **Cases with reported genotype and informative clinical data** | 38 | Bagshaw et al 200221; Giugliani et al 198715; Gucev et al 200825; Hofer et al 200911; Ishii et al 199527; Mayer et al 200916; Paschke et al 200113; Paschke et al 201419; Roze et al 200517; Santamaria et al 200614 (case MB2); Sohn et al 201261 |

Spinal canal narrowing without myelocompression was reported in a 7-year-old male and a 10-year-old female.18,31 and in a 40-year-old woman with myelocompression.23 In a 15-year-old male with pure MBD spinal malalignment had led to spastic paraplegia.

Growth parameters were reported in 21 of 51 patients (Table 3). Short stature was a constant feature in adolescents and adults, whereas most of the younger patients had body heights within 1 SD of mean. The progressive nature of growth impairment is demonstrated by longitudinal growth data available from single patients.

Corneal clouding and cardiac valve pathology were reported in 20 of 51 cases (Table 2). Hepato-splenomegaly, was reported in only two of 51 MBD cases (n = 1 homozygous W273L [case 2: Groebe et al24 and Paschke et al13]; n = 1 homozygous R201H [MB2 Santamaria et al14 = CV 6]).

Abnormal urinary excretion of glycosaminoglycans and of oligosaccharide containing glycoproteins was inconsistently reported. In P1 urinary oligosaccharides showed an abnormal band on thin layer chromatography and glycosaminoglycan excretion was mildly elevated (18 mg/mmol creatinine; reference range < 15) (Cetylpyridinium chloride test). Keratan sulfate was undetectable on urinary glycosaminoglycan electrophoresis, but...
| Allele                      | Reference             | Genotype | N  | Pure MBD | MBD Plus | Corneal Clouding | Cardiac finding | Organo-megaly | U-Keratan sulfate | U-Oligo/GAG | β-Gal activity* |
|-----------------------------|-----------------------|----------|----|----------|----------|-----------------|-----------------|---------------|------------------|-------------|-----------------|
| ND                          | [18,20,22,23,24,26,29,31,66] | -        | 13 | 12       | 1        | 7               | 0               | 0             | 8                | 11          | 0.77 (3.0)      |
| Homozygous Pure MD & MBD   | [13]                  |          |    |          |          |                 |                 |               |                  |             |                 |
| Plus                        | Case#1-12             | W273L    | 12 | 12       | 0        | 3               | 0               | 1             | 2                | 2           | 1.3-10 (3.2)    |
|                            | [14]                  | R201H    | 1  | 1        | 0        | -               | -               | 1             | -                | -           | 2.4             |
|                            | Case#MB2 CV6          | G438E    | 3  | 0        | 3        | 1               | 2               | 0             | 1                | 1           | 2.7-8.7 (5.7)   |
|                            | [17]                  |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | Case#2,3 (CV1)        |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | [21]                  |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | Case#3                |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | [15,16]               | Y333C    | 2  | 0        | 2        | 1               | 1               | -             | 2                | 2           | 3.1-3.4         |
| Compound Heterozygous Pure MBD | [13]                | W273L Spl?# | 3  | 3        | 0        | -               | 0               | 0             | -                | -           | 1.3-1.5 (1.3)   |
|                            | Case#13,14            |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | 11 Case#24            |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | [11]                  | W273L P397A | 1 | 1        | 0        | -               | 0               | 0             | -                | -           | 2.6             |
|                            | Case#22               | W273L D198Y | 1 | 1        | 0        | -               | 0               | 0             | -                | -           | 3.7             |
|                            | Case#23               | W273L N484K | 1 | 1        | 0        | 1               | 1               | 0             | 1                | 1 **         | 5.7             |
|                            | PI                    | W273R H281Y | 1 | 1        | 0        | 1               | 0               | 0             | 1                | 4.7          |                 |
|                            | [25]                  | T500A N484K | 2 | 2        | 0        | 0               | 0               | 0             | 2                | 0           | 1.9-2.1         |
|                            | Case#1                | T500A Q408P | 2 | 2        | 0        | -               | -               | 1             | -                | -           | 1.3-1.3         |
|                            | [21]                  |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | Case#1,2 (family1)    |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | [13]                  | T500A Q408P | 2 | 2        | 0        | -               | -               | 1             | -                | -           | 1.3-1.3         |
|                            | Case#15               |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | [11]                  |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | Case#25               |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | [27]                  | R482C Y43H | 1 | 1        | 0        | 0               | 0               | 0             | 1                | 1           | 9.6             |
|                            | Case#1                | T500A R148C | 1 | 1        | 0        | -               | -               | -             | -                | -           |                 |
| [Paschke Unpublished]      |                      |          |    |          |          |                 |                 |               |                  |             |                 |
|                            | Case#1                | G123R L5HfsX29 | 1 | 1        | 0        | 0               | 1               | 0             | 1                | 1           | 1.5             |
|                           |                      |          |    |          |          |                 |                 |               |                  |             |                 |
|                           | (Continues)           |          |    |          |          |                 |                 |               |                  |             |                 |
keratan sulfate disaccharides were clearly elevated (28.5 μg/mg creatinine; reference range 0.24-2.71) upon UPLC/MS/MS-based determination.36

Ultrastructural examination of a skin biopsy was reported in one single case18 showing interstitial and cytoplasmatic U-shaped lamellar inclusions but absence of lysosomal inclusions found in GM1 gangliosidosis.38 In Holzgreve et al39 description of patients with Morquio syndrome, Adler-Reilly granular abnormalities were found in blood smears of patients with Morquio-A disease but not in the those with MBD.

Quantitative values of β-galactosidase activities were available in 49 of 51 cases with informative clinical data (β-galactosidase was measured but activity was not reported in the case published by Di Cesare et al23; β-galactosidase was not measured in one of three siblings with MBD published by van Gemund et al32). β-galactosidase activities were given in nmol/mg/min or in nmol/mg/min and/or as percent of normal. For reasons of comparability we calculated the percentage of the residual activities based on the respective mean of the normal range for all cases. Activities were measured either in white blood cells or in fibroblasts. Overall, residual β-galactosidase activities ranged between 0% and 17% in pure MBD cases and between 2% and 8.7% in MBD plus cases (Table 2).

In 47 of 63 cases genotypic information was available, harboring 28 different GLB1 variants. The most frequent alleles were W273L (34/94 alleles) and T500A (11/94 alleles). The characteristics of the 28 variants are shown in Table 4. Twenty-five of 28 variants were missense, two were frameshift, and one was splice site. Seven variants found in the reviewed cases had previously been tested for chaperone sensitivity with three of them being reported chaperone sensitive (T82M, R201H, H281Y).

Information about the clinical (skeletal and neurologic) phenotype in conjunction with the underlying GLB1 mutations was available in 38 cases (Table 2). Twenty-nine of 38 had pure MBD (dysostosis multiplex type Morquio syndrome without evidence of neuropathic involvement). Additional neuropathic manifestations (MBD plus) were reported 10 of 51 cases (nine of 38 with known genotype and one of 13 with unknown genotype) (Table 2). Neuronopathic manifestations included: developmental delay/intellectual disability, loss of motor and cognitive skills with onset in late infancy, delayed/impaired speech, ataxia, spasticity, dystonia, myoclonia, choreoatetosis. Brain MRI was reported in only one of the MBD plus cases (Roze et al17 case 2) and was normal. These 38 cases harbored 21 of the 28 GLB1 variants identified in this review.

Four of 21 variants were present in homozygosity: W273L (12 cases/five families); R201H (one case/one family); G438E

| Allele     | Frequency | MBD Plus |
|------------|-----------|----------|
| W273L     | 34/94     |          |
| T500A     | 11/94     |          |

Note: MBD Plus includes developmental delay/intellectual disability and/or neurologic findings such as epilepsy, syringomyelia, dysautonomia. GLB1 refers to the gene encoding β-galactosidase.

Table 2 (Continued)

| Compound | Heterozygous | MBD Plus |
|----------|--------------|----------|
|          |              |          |

*Note: MBD Plus includes developmental delay/intellectual disability and/or neurologic findings such as epilepsy, syringomyelia, dysautonomia. GLB1 refers to the gene encoding β-galactosidase.

**Keratane sulfate containing oligosaccharides were additionally demonstrated upon UPLC/MS/MS-based determination36
TABLE 3  Growth parameters in 21 patients with MBD (n = 16 pure MBD; n = 5 MBD plus)

| (Case number) Reference (Ethnicity) [GLB1 variant] | Age at growth assessment | Body height (percentile %) | Body weight (percentile %) | Calculated BMI (kg/m²) (percentile %) |
|---------------------------------------------------|--------------------------|-----------------------------|---------------------------|---------------------------------------|
| **Pure MBD**                                      |                          |                             |                           |                                       |
| Male                                              |                          |                             |                           |                                       |
| (1) Sheth et al 200229 [East Indian] [ND]         | 3 y                      | 78.8 cm (0.007%, −3.8SD)    | 10 kg (>3%)               | 16.1 (75%)                           |
| (2) van Gemund et al 198332 [Caucasian/Dutch] [ND]| 3 y 8 mo                 | 100.2 cm (60%, +0.2SD)      | 15.6 kg (25%-50%)         | 15.5 (50%)                           |
|                                                   | 5 y 5 mo                 | 109.6 cm (28%, −0.6SD)      |                           |                                       |
|                                                   | 8 y 3 mo                 | 121.6 cm (12%, −1.2SD)      |                           |                                       |
|                                                   | 11 y 3 mo                | 132 cm (0.06%, −3.2SD)      |                           |                                       |
|                                                   | 15 y 4 mo                | 149.7 cm (0.5%, −3.6SD)     |                           |                                       |
| (3) Sohn et al 201230 [Korean] [L5HfsX/G123R]    | 6 y                      | 112.4 cm (22%, −0.8SD)      | 19.9 kg (50%)             | 15.8 (50%)                           |
| (4) Groebe et al 198024 [Caucasian/Greek] [ND]   | 6 y 3 mo                 | 107 cm (1.7%, −2.1SD)       | Not available             | —                                     |
| (5) Trojan et al 198031 [Caucasian] [ND]         | 7 y                      | 119 cm (29%, −0.6)          | 26.6 kg (80%)             | 18.8 (94%)                           |
| (6) Sheth et al 200229 [East Indian] [ND]        | 7 y                      | 94 cm (0%, −5.2SD)          | 14 kg (>3%)               | 15.8 (50%)                           |
| (7) Ishii et al 199527 [Japanese] [Y83H/R482C]   | 11 y 7 mo                | 135.2 cm (5%, −1.6SD)       | 37.8 kg (50%)             | 20.7 (85%)                           |
| (8) Groebe et al 198024 [Caucasian/Austrian] [W273L/W273L]* | 25 y 5 mo | 137 cm (0%, −5.4SD) | 41 kg (<<3%) | 21.8 (50%) |
| (9) (CV 5c) Paschke et al 201419 [South American] [T500A/Gly526GlyfsX5] | 39 y | 162 cm (2.4%, −2SD) | Not available | — |
| (10) P1 [Caucasian/Canadian] [W273L/N484K]       | 5 y 8 mo                 | 112 cm (34%, −0.4SD)        | 23 kg (75%)               | 18.3 (97%)                           |
|                                                   | 10 y 9 mo                | 123 cm (0.4%, −2.7SD)       | 27 kg (10%)               | 17.8 (75%)                           |
|                                                   | 14 y 8 mo                | 134 cm (0.001%, −4.4SD)     | 41 kg (3%)                | 22.8 (85%)                           |
| Female                                           |                          |                             |                           |                                       |
| (11) van Gemund et al 198332 [Caucasian/Dutch] [ND] | 3 y                      | 95.6 cm (69%, +0.5SD)       | 13.5 kg (15%)             | 14.8 (≥50%)                          |
|                                                   | 4 y 6 mo                 | 104.8 cm (50%, ±0SD)        | Not available             | —                                     |
|                                                   | 7 y 6 mo                 | 118.5 cm (18%, −0.91SD)     | Not available             | —                                     |
|                                                   | 11 y 9 mo                | 135.5 cm (2.6%, −1.9SD)     | Not available             | —                                     |
| (12) van Gemund et al 198332 [Caucasian/Dutch] [ND] | 5 y 8 mo                 | 112 cm (46%, −0.1SD)        | 22.5 kg (50%)             | 17.9 (90%)                           |
|                                                   | 7 y 5 mo                 | 118.8 cm (23%, −0.8SD)      | Not available             | —                                     |
|                                                   | 10 y 6 mo                | 127.5 cm (2%, −2.1SD)       | Not available             | —                                     |
|                                                   | 14 y 3 mo                | 134 cm (<0.004%, −3.9SD)    | Not available             | —                                     |
|                                                   | 17 y 4 mo                | 138.5 cm (<0.005%, −3.9SD)  | Not available             | —                                     |
| (13) O’Brien et al 197618 [Caucasian/Italian] [ND] | 12 y                      | 143.5 cm (15%, −1SD)       | 41 kg (50%)               | 19.9 (50%)                           |

(Continues)
Homozygous W273L was invariably associated with pure MBD. Pure MBD was also reported in a unique case homozygous for the R201H allele, in those seven individual compound heterozygous for W273L and W273R, respectively, and in six of the eight cases reported as compound heterozygous for T500A. Patients homozygous for G438E and for Y333C showed neuronopathic features including cerebral neurologic and developmental involvement.

To demonstrate the clinical heterogeneity of MBD plus disease we extracted the following case vignettes from the literature reviewed:

CV 1 (G438E/G438E) (Roze et al., 2005) features an MBD plus phenotype, characterized by early onset developmental delay, intellectual disability, and subsequent progressive dystonia. A 19-year-old woman presented with a history of normal walking at age of 2.5 years and gradual loss of motor performance at age of 7 to 8 years and severe gait disturbances at age 17 years with an ability to walk unsupported for 10 to 20 m only. Neurologically she had generalized dystonia with facial grimacing, dysarthria, swallowing difficulties, drooling, and choreoathetoid movements and myoclonic jerks. She had moderate intellectual impairment.

CV 2 and CV 3 (Y333C/Y333C (case 1, Giugliani et al. 1987) and Mayer et al. 2009) and (T82M/Y270D) (case 16 in Paschke et al. 2014) feature an MBD plus phenotype, characterized by unremarkable early development and progressive spasticity and speech impairment later on. CV 2 was able to walk and had normal speech development at age 18 months. At age 11, he presented with speech ability limited to a few words.

### Table 3 (Continued)

| (Case number) Reference (Ethnicity) [GLB1 variant] | Age at growth assessment | Body height (percentile %) | Body weight (percentile %) | Calculated BMI (kg/m²) (percentile %) |
|---------------------------------------------------|--------------------------|---------------------------|---------------------------|--------------------------------------|
| (14) Arbisser et al 1977 [Caucasian?] [ND]         | 14 y                     | 138.5 cm (0.09%, −3.1SD)  | Not available             |                                      |
| (15) Gucev et al 2008 [Caucasian/Macedonian] [W273R/H281Y] | 24 y                     | 138 cm (0.007%, −3.8SD)   | Not available             |                                      |
| (16) Di Cesare et al 2012 [Caucasian/Italian] [ND] | 43 y                     | 150 cm (3.9%, −1.8SD)     | Not available             |                                      |

**MBD plus**

**Male**

(17) Giugliani et al 1987; Mayer et al 2009 [Arabic] [Y333C/Y333C] 11 y 114 cm (0.002%, −4.1SD) Not available

(18) CV 5b Paschke et al 2014 [South American] [T500A/Gly526GlyfsX5] 30 y 155 cm (12%, −1.2SD) Not available

**Female**

(19) Giugliani et al 1987; Mayer et al 2009 [Arabic] [Y333C/Y333C] 8 y 118 cm (8%, −1.4SD) Not available

(20) Bagshaw et al 2002 [ND] [N484K/T500A] 18 y 147 cm (0.8%, −2.4SD) Not available

(21) Roze et al 2005 [Romanian] [G438E/G438E] 19 y 140 cm (0.03%, −3.4SD) Not available

**Note:** Percentile value obtained from https://tall.life/height-percentile-calculator-age-country/ and CDC Weight for Age Percentiles.

**Abbreviation:** ND, not determined.

*GLB1 mutation published in Paschke et al.*
| Mutant allele | Number of alleles | Clinical phenotype | Exon AA residue location | Base change | Impact on translated GLB1 allele (missense, nonsense, frame shift) | Mechanism of GLB1 deficiency (complete absence, premature degradation, catalytic, unknown) | Amenability to chaperone therapy and degree of β-galactosidase rescue activity (reference) |
|---------------|------------------|--------------------|--------------------------|-------------|---------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| L5H6X29      | 0 1              | 1                  | 0                        | 1           | Signal peptide                                              | Frameshift                                                                      | Truncated protein that lacks most domains                                         |
| T82M         | 0 1              | 0                  | 1                        | 2           | TIMBD          | c.245C>T Missense                                         | Premature degradation                                                        | Sensitive\[^{69}\]                          |
| spl?         | 0 3              | 3                  | 0                        | 3           | —                       | c.246G>T Splice site defect                                 | Inactive two major products lacking exon 2 and exons 2-5                        | Unlikely                                        |
| Y83C/D441    | 0 1              | ui                 | ui                       | 3 TIMBD     | c.248A>G Missense                                         | Affects ligand recognition                                                      | Unlikely                                        |
| Y83H         | 0 1              | 1                  | 0                        | 3 TIMBD     | c.247T>C Missense                                         | Affects ligand recognition                                                      | Unlikely                                        |
| G123R        | 0 1              | 1                  | 0                        | 3 TIMBD     | c.367G>A Missense                                         | Complete absence                                                              | Unlikely                                        |
| R148C        | 0 1              | 1                  | 0                        | 4 TIMBD     | c.442C>T Missense                                         | Complete absence                                                              | Unlikely                                        |
| S149F        | 0 0              | 0                  | 0                        | 4 TIMBD     | c.446C>T Missense                                         | Unknown                                                                        | Insensitive                                    |
| L173P/T500A  | 0 2              | ui                 | ui                       | 5 TIMBD     | c.518 T>C Missense                                         | Complete absence                                                              | Unlikely                                        |
| D198Y        | 0 1              | 1                  | 0                        | 6 TIMBD     | c.592G>T Missense                                         | Located on protein surface and leads to reduced activity                      | Unknown                                        |
| R201H        | 2 2              | 1                  | 2                        | 6 TIMBD     | c.602G>A Missense                                         | Premature degradation                                                         | Sensitive                                        |

(Continues)
| Mutant allele | Number of alleles | MBDb pure (n = number of cases) | MBDb plus (n = number of cases) | Exon AA residue location | Base change | Impact on translated GLB1 allele (missense, nonsense, frame shift) | Mechanism of GLB1 deficiency (complete absence, premature degradation, catalytic, unknown) | Amenable to chaperon therapy and degree of β-galactosidase rescue activity (reference) |
|---------------|-----------------|-------------------------------|---------------------------------|--------------------------|-------------|------------------------------------------------Porno|-------------------------------------------------|--------------------------------------------------------------------------------|
| H281Y         | 0 2 1 1         | 8 TIMBD (catres)              | c.841C>T Missense              | Catalytic               | Sensitive   | *(DLHex-DGJ), 11.1-12.5-fold; 27.3%-33.9% 41            | *(DTIMBD (catres) 8 (n = 18) 1.3-fold; 51% 41 | *(Ph[TFM]2OHex-DGJ) 1.2-fold; 21% 40 |
| W273L         | 24 10 18        | 8 TIMBD (catres)              | c.817TG>CT Missense            | Catalytic               | Insensitive | *(DLHex-DGJ), 1.3-fold; 51% 41            | *(Ph[TFM]2OHex-DGJ) 1.2-fold; 21% 40 | *(TFM)3OHex-DGJ 1.4-fold; 25% 40 |
| W273R         | 0 1 1 0         | 8 TIMBD (catres)              | 817T>C Missense                | Catalytic               | Unlikely    | *(DLHex-DGJ), 1.7-fold; 0.4% 41            | *(Ph[TFM]2OHex-DGJ) 1.2-fold; 21% 40 | *(TFM)3OHex-DGJ 1.4-fold; 25% 40 |
| Y270D         | 0 1 0 1         | 8 TIMBD (catres)              | c.808T>G Missense              | Catalytic               | Insensitive | *(DLHex-DGJ), 1.7-fold; 0.4% 41            | *(Ph[TFM]2OHex-DGJ) 1.2-fold; 21% 40 | *(TFM)3OHex-DGJ 1.4-fold; 25% 40 |
| Y333C         | 4 0 0 2         | 10 TIMBD (catres)             | c.998 A>G Missense             | Catalytic               | Unlikely    | *(DLHex-DGJ), 1.7-fold; 0.4% 41            | *(Ph[TFM]2OHex-DGJ) 1.2-fold; 21% 40 | *(TFM)3OHex-DGJ 1.4-fold; 25% 40 |
| P397A         | 0 1 1 0         | 12 End of TIMβ1 loop          | 1189C>G Missense               | Premature degradation   | Unknown     | *(DLHex-DGJ), 1.7-fold; 0.4% 41            | *(Ph[TFM]2OHex-DGJ) 1.2-fold; 21% 40 | *(TFM)3OHex-DGJ 1.4-fold; 25% 40 |
| Q408P         | 0 2 2 0         | 12 Beta domain 1              | c.1223A>C Missense             | unknown                 | Unknown     | *(DLHex-DGJ), 1.7-fold; 0.4% 41            | *(Ph[TFM]2OHex-DGJ) 1.2-fold; 21% 40 | *(TFM)3OHex-DGJ 1.4-fold; 25% 40 |
| D441N         | 0 1 ui ui       | 13 Beta domain 1              | c.1321G>A Missense             | unknown                 | Unknown     | *(DLHex-DGJ), 1.7-fold; 0.4% 41            | *(Ph[TFM]2OHex-DGJ) 1.2-fold; 21% 40 | *(TFM)3OHex-DGJ 1.4-fold; 25% 40 |
| G438E         | 6 0 3 0         | 13 Beta domain 1              | c.1313G>A Missense             | Reduced activity        | Insensitive | *(DLHex-DGJ), 2.3-fold; 16.4% 41            | *(Ph[TFM]2OHex-DGJ) 1.3-fold; 7.3% 40 | *(TFM)3OHex-DGJ 1.4-fold; 25% 40 |
| Mutant allele | Number of alleles | Clinical phenotype | Exon AA residue location | Base change | Impact on translated GLB1 allele (missense, nonsense, frame shift) | Mechanism of GLB1 deficiency (complete absence, premature degradation, catalytic, unknown) | Amenability to chaperon therapy and degree of β-galactosidase rescue activity (reference) |
|--------------|------------------|------------------|------------------------|-------------|-------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Y444C        | 0 1              | ui               | 13 Beta domain 1       | c.1331A>G   | Missense                                        | Reduced activity                                                                | Unknown                                                                                                                                   |
| N484K        | 0 4              | 4                | 0                     | c.1452C>A   | Missense                                        | unknown                                                                       | Unknown                                                                                                                                   |
| R482C        | 0 1              | 1                | 0                     | c.1444C>T   | Missense                                        | Complete absence                                                               | Unknown                                                                                                                                   |
| R482H        | 0 3              | ui               | 14 Beta domain 1      | c.1445G>A   | Missense                                        | Complete absence                                                               | Unknown                                                                                                                                   |
| G494S        | 0 1              | ui               | 15 Beta domain 1      | c.1480G>A   | Missense                                        | Complete absence                                                               | Unknown                                                                                                                                   |
| T500A        | 0 11             | 5                | 2                     | c.1498A>G   | Missense                                        | Possible catalytic                                                            | Unknown                                                                                                                                   |
| G526GfsX5    | 0 3              | 1                | 2                     | c.1577dupG  | Frame shift                                     | Truncated and inactive gene product lacking a functionally essential domain in exon 16 | Unknown                                                                                                                                   |
| W509C        | 0 1              | ui               | 15 Beta domain 1      | c.1527G>T   | Missense                                        | Unknown                                                                       | Unknown                                                                                                                                   |

**Total # alleles** 36 58

**Total # cases** 18 29

Abbreviations: *, name of chaperone; %, percent of normal activity; catres, adjacent to catalytic residue; fold, −fold increase of baseline activity; HMZ, homozygous; HTZ, heterozygous; TIMBD, TIM barrel domain; ui, uninformative clinical data.
and inability to walk. He had an increased tone of the limbs and brisk tendon reflexes. CV 3 (male) was diagnosed with MBD based on characteristic skeletal abnormalities at the age of 4. While at the age of diagnosis his motor and cognitive development was normal, he gradually lost his ability to speak and he became tetrapastic after the age of 10 years.

CV 4a, 4b, 4c (T500A/c.1577dupG = p.G526GlicX5)19 demonstrate the phenotypic variability of the same genotype. Among three male unrelated patients with the same genotype, two (ages 7 and 39) had skeletal features consistent with MBD without neuronopathic involvement, while one (age 31) had psychomotor delay and speech difficulties at age 3 and thereafter developed borderline intelligence and neurological regression. β-galactosidase activities were not discriminative (4% in both cases with pure MBD and 2% in the MBD plus case).

CV 5 (R201H/S149F) (case 21 in Hofer et al 11) features an unspecific (non-Morquio) type of dysostosis multiplex, associated with mild intellectual disability. This 14-year-old male was described as “atypical” MBD. He presented with mild intellectual disability and dorsolumbar kyphoscoliosis, but characteristic Morquio features (short, disproportionate stature, dysplasia of the odontoid, hip dysplasia, genua valga) were not present when assessed at 19 years. Corneal clouding, cherry red spots, cardiac involvement, and organomegaly were absent.

CV 6 (R201H/R201H) (MBD2 Santamaria et al 14) features the sole described patient with pure MBD who is homozygous for a variant that previously has been described in association with neuronopathic (types 2 and 3) GM1 gangliosidosis. At the age of 16, this male patient exhibited skeletal features characteristic of MBD. He had a history of a normal development, his cognition was within normal range and neurologic signs and symptoms suggestive of a primary neuronopathic course were absent.

3 | DISCUSSION

3.1 | MBD phenotypes

The results of this study have reinforced the general understanding that MBD is a distinct variant of GLB1-related disease with an axial and appendicular dysostosis multiplex as initially described in GALNS-related Morquio-A disease. However, while Morquio-A disease is invariably associated with normal intellectual development and lifelong absence of primary neuropathic manifestations, only just below 80% of the GLB1-related MBD cases presented with a pure skeletal phenotype. The remaining 10 cases showed additional primary neuronopathic manifestations. These findings indicate that GLB1-related MBD occurs in two forms: pure MBD and MBD plus neuronopathic manifestations.

Results also have reinforced the general understanding that the skeletal manifestations are mild in MBD when compared to typical Morquio-A disease and clinically indistinguishable from mild Morquio-A variants. Along with this notion, we previously could show that the height of adult MBD patients is significantly less compromised than of those with typical Morquio-A disease. Notably, three of the five adults (24-39 years old) depicted in Table 3 had only a mildly impaired body height (minus 1.2 SD-minus 2 SD). Conversely, among the six individuals younger than 6 years, only the patient reported by Sheth et al 29 had early onset dwarfism with a body height at minus 3.8 SD at the age of 3 years.

In cases with mild skeletal involvement, such as CV 5 who was described as “atypical Morquio-B” a distinction between MBD and GM1-gangliosidosis with unspecific dysostosis may be challenging. Therefore, for the sake of a precise classification, we recommend that the diagnosis of MBD should be assigned only if there are ≥3 radiological findings characteristic of Morquio syndrome, such as platyspondyly and vertebral beaking involving all segments of the spine, odontoid hypoplasia, epi-and metaphyseal dysplasia of long bones, and hip dysplasia.

Other manifestations, which are typically observed in GALNS-related Morquio-A disease were not reported at all (such as atlantoaxial subluxation, hearing impairment, tracheal stenosis) or were reported only in a minority of cases (such as spinal cord narrowing, myelocopeesion, hepatosplenomegaly, cardiac valve pathology, tooth enamel abnormalities). Cardiomyopathy and retinal cherry red spot, which typically occur in GM1-gangliosidosis, were not reported in any of the MBD cases. Corneal clouding was observed mainly in cases who had mutations in the catalytic domain essential for keratan sulfate substrate processing such as W273L and Y333C.

Impaired elastogenesis has been shown in GM1 gangliosidosis and MBD. Apart from a single study in a skin biopsy of a patient with MBD, biochemical and morphologic studies on extracellular matrix or bone pathology have not been performed for MBD. Future studies similar to those performed for numerous other LSDs and for Morquio-A disease may serve for a better understanding of the clinical differences between Morquio-A disease and MBD (e.g., why surgical operations in MBD patients differ significantly from those with Morquio-A disease both in regards to the types of intervention, and in regards to the age at which these surgeries become necessary.

Neuronopathic manifestations in MBD span from an early onset global developmental delay with delayed achievement of motor milestones, speech delay to intellectual disability, progressive spasticity, and dystonia (CV 1). Onset of neurocognitive deficiencies can be later in life (CV 2), with skeletal findings being the first red flag (CV 3). Clinicians should bear in mind that patients diagnosed with pure MBD in early childhood might develop neuronopathic problems later on.
3.2 | MBD genotypes

W273L was invariably associated with pure MBD. The amino acid residue Trp-273 resides at the entrance of the ligand-binding pocket of β-galactosidase, which acts as a holder of substrates for catalytic reaction. W273L affects the degradation of keratan sulfate more severely than the turn-over of GM1-ganglioside, explaining the predominance of skeletal manifestations.7,10-12,34,54,55

Pure MBD also was reported in single a case homozygous for R201H (CV 6). Arg-201 is located on the lateral face of the TIM barrel domain, which is far from the ligand-binding pocket7,56 thus not specifically affecting the catalytic activity towards keratan sulfate. It has rather been suggested that the R201H mutation results in a mislocalized, unstable precursor protein.11,41 Several cases were found where the R201H allele was associated with type 2 GM1-gangliosidosis,1 while its association with pure MBD12 remains to be confirmed in more cases.

The other GLB1 variants found in homozygosity (G438E and Y333C), were associated with MBD plus (Table 2). G438E causes an abnormal complex formation alone or coupled with keratan sulfate binding21 with a relatively high (6.1%) residual activity.11 Results of enzyme activity assays using different substrates suggest that Y333, similar to W273L, affects the active site of β-galactosidase rather than affecting the enzyme stability16 comparable to D332, the adjacent amino acid residue, which is directly involved in the catalytic reaction.11 Y333H is not invariably associated with MBD, as homozygous cases have been described with Type 2 GM1-gangliosidosis,1 while its association with pure MBD12 remains to be confirmed in more cases.

After W273L, T500A was the second frequent allele occurring in heterozygosity in 11/58 alleles. In the 38 cases with clinical and genetic information, six of eight compound heterozygous cases presented with pure MBD.

3.3 | β-galactosidase activity and biomarkers

We were not able to establish a correlation between residual β-galactosidase activities, genotypes and phenotypes. The main reason for the inability to discriminate molecular characteristics of the various GLB1 mutations is the use of synthetic substrates (eg, 4-MU-β-galactoside) for the determination of β-galactosidase activity, which only allows a rough discrimination between zero residual activities (eg, in infantile GM1-gangliosidosis), and activities up to 2%-10% (eg, in late onset GM1-gangliosidosis and MBD).11 To precisely determine the biochemical characteristics of β-galactosidase mutants, measurements using natural substrates are needed. However, such measurements are laborious and have rarely been performed.54,55 Technical variations in the enzyme assays across the various labs and the type (white blood cells, fibroblasts) and quality of samples used also contribute to the poor correlation of β-galactosidase activity with the genotype.

Likewise, limited information is has been found regarding a correlation between chemical biomarkers and the genotype. Keratan sulfate is the main storage product in MBD, however analytical challenges imposed by the use of traditional methods may explain why in the cases reviewed here keratan sulfate was either not determined or information was mostly restricted to its presence or absence. Quantitative measurements of keratan sulfate using LC-MS/MS-based technologies have only recently become available. As shown in P1, urinary keratan sulfate accumulation could only be shown upon LC-MS/MS-based analysis but not upon traditional glycosaminoglycan electrophoresis. Other studies employing LC-MS/MS-based technology have shown an accumulation of mono- and disulfated keratan sulfate species in blood and urine of single MBD patients57 and a correlation with clinical severity has been shown in Morquio-A patients.45 Further studies are needed to determine age and phenotype related biomarker profiles in MBD patients.

3.4 | Chaperone sensitivity

Several pharmacological chaperones acting on β-galactosidase including galactose, N-octyl-4-epi-beta-valienamine (NOEV), alkylated or fluorinated derivates of desoxynojirimycin (DGJ), and (5aR)-5a-C-Pentyl-4-epi-isofagomine have been tested against numerous GLB1 mutant enzymes.58-62

As a general rule, chaperone responsive mutant proteins harbor intact catalytic sites but fail in achieving full maturaton or appropriate localization in the lysosomes due to protein misfolding or lack of protection by protective protein/cathepsin A.37,40,41,63 Three of the GLB1 alleles identified in this review (T82M, R201H, H281Y) have been shown in the literature to be chaperone responsive. The most pronounced response was observed in the R201H allele using DGJ derivatives as chemical chaperones. Human fibroblasts carrying this variant in homor heterozygosity showed an up to 12.5-fold increase of basal β-galactosidase activity resulting in 30% of normal control activity.40,41 According to theoretical considerations64 and evidence shown in cell cultures,53,65 residual enzyme activities beyond 10% to 15% may be sufficient to avoid substrate accumulation. A comparable magnitude of β-galactosidase enhancement has been reported by59 in 10 out of 15 GLB1-deficient fibroblast lines tested against a 4-epi-isofagomine derivative. Interestingly, six fibroblast lines carried at least one mutation at the amino acid residue Arg-201. Despite significant achievements in preclinical research, with the exception of the aminosugar Miglustat,66 chaperone therapy yet has not been established for patients with GLB1-related conditions.
W273L, the most frequent MBD allele, is not sensitive to chaperon rescue as it encodes for a catalytic mutant within an otherwise stable, normally trafficked and localized protein12,40,67 (Paschke unpublished). Therefore only compound heterozygous individuals harboring a second chaperone-sensitive allele will benefit from this form of therapy. Substantial progress in the development of gene therapies for GLB1-related conditions68 will benefit patients with variants not amenable to chaperone therapies.

4 | CONCLUSION AND OUTLOOK

Overall, this review of published cases with MBD has shown that MBD occurs as a spectrum of distinct skeletal and non-skeletal (neuronopathic) manifestations.

While there is a clear association between pure MBD and the W273L allele, further studies are needed to better determine genotype-phenotype correlations of MBD plus alleles as well as their role in elastogenesis and bone pathology.

Careful clinical phenotyping of this ultra-rare condition is important for elucidation of the natural history of MBD informing the choice of outcomes in future clinical trials. Clinical assessments should include a full skeletal survey with additional attention to the cranio-cervical junction, as well as a full clinical, neurologic, and neurocognitive exams, including a brain MRI. Biochemical phenotyping should include the determination of β-galactosidase activity in white blood cells or fibroblasts, as well as quantitative (LC-MS/MS based) determination of urinary glycosaminoglycans and keratan sulfate-derived oligosaccharides. We have started collecting data via an international patient registry8 and are currently initiating repositories for longitudinal data and biological sample collection.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

I.S.A. performed the literature review, extracted and analyzed data, and wrote the manuscript. N.Y. coordinated Morquio-B related research, participated in manuscript writing and editing. E.P. contributed and critically reviewed data and biochemical/genetic data. S.S.-I. initiated this research project, and supervised progress of work and data analysis, analyzed data, contributed to manuscript writing, and edited the final version of the manuscript.

ETHICS APPROVAL

Not applicable.

PATIENT CONSENT

Obtained from patient 1 (P1).

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