

Natural Evolution of Morquio A Syndrome Caused by Two Heterozygous Mutations of the *GALNS* Gene

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A 21-month-old boy (Figure 1a; Figure 1b) presented to the surgery department with foot and spine deformity. He was born after a full-term pregnancy with no complications. His parents were healthy and nonconsanguineous. Birth anthropometric parameters were within the normal standard range. His birth weight was 3310 g (46th percentile), birth height was 50 cm (52nd percentile), and head circumference was 34 cm (36th percentile). Apgar scores at 1 and 5 min were 10 and 10, respectively. His foot deformity was treated with plaster splints but worsened during the next few months. Throughout his infancy, he suffered from recurrent bronchoconstriction and pneumonia. Further disease progression led to deleterious skeletal and joint manifestations with disproportionate short stature, short neck, pectus carinatum deformity of the chest, short trunk, spinal scoliosis, genu valgus deformity of the knee, and abnormal gait. At 5 years (Figure 1c), he had a body height of 86 cm (less than the 3rd percentile). Due to the worsening of his skeletal manifestations, a rare lysosomal storage disease was suspected. A diagnosis of Morquio A syndrome was established, with enzyme galactosamine-6-sulfate sulfatase activity <0.1 μmol/l/h (reference range ≥ 2.0 μmol/l/h) caused by two heterozygous mutations in the protein-coding *GALNS* (Galactosamine (N-Acetyl)-6-Sulfatase) gene. The first mutation was located in exon 5, NM_001323544.1:c.364G>A (p.Gly122Ser), and the second in exon 9, NM_001323544.1:c.878C>T (p.Ser293Leu). The *GALNS* gene was analyzed by PCR and sequencing of the entire coding region and the highly conserved exon-intron splice junctions. The reference sequences of the *GALNS* gene were NM_001323544.1 and NM_000512.4.

The detected mutations are classified as Class 1 (pathogenic) according to the American College of Medical Genetics recommendations. At 2 years of follow-up, no linear growth

was observed, and skeletal and joint manifestations worsened (Figure 1d). Morquio A syndrome (Mucopolysaccharidosis type 4A) is a rare autosomal recessive inborn error of metabolism caused by mutations at the locus 16q24.3, usually due to a homozygous mutation or heterozygous compound in the *GALNS* gene¹. Specifically, mutations result in galactosamine-6-sulfate sulfatase deficiencies, leading to intralysosomal accumulation of glycosaminoglycans, such as keratan sulfate (KS) and chondroitin-6-sulfate, and causing abnormal skeletal development and additional symptoms. The incidence of Morquio A syndrome was estimated to be 1:201.000 and varied among different populations². Treatment of Morquio A syndrome is possible with an enzyme-replacement therapy³; however, this treatment was not available where the patient was residing. Natural evolution leads to a deleterious effect on growth and development. Considering the irreversible damage in patients who suffer from Morquio A syndrome, newborn screening of Morquio A syndrome could be beneficial. However, long-term follow-up is essential to fully understand the clinical symptoms when patients are detected by newborn screening⁴. Prenatal diagnosis is possible through molecular analysis in trophoblasts or amniocytes.

Both mutations have previously been reported as disease-causing mutations, but not in the form of these two heterozygous mutations. To the best of our knowledge, this combination of *GALNS* mutations has been revealed for the first time. This report expands the clinical variability of Morquio A syndrome and may have implications for genotype–phenotype correlation in Morquio A syndrome⁵.

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FIG. 1. (a, b) A 21-month-old boy presented with mild manifestations of Morquio syndrome. (c) A 5-year-old boy presented with moderate manifestations of Morquio syndrome. (d) A 7-year-old boy presented with serious manifestations of Morquio syndrome

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