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CASE REPORT

Case report of a novel homozygous variant in a Saudi patient with alpha mannosidosis

Rehab Al Jawad[1,2*], Omhani Malibari[1,3]

ABSTRACT

Background: Alpha-mannosidosis [Online Mendelian Inheritance in Man (OMIM): 248500] is an autosomal recessive disorder due to a deficiency of the lysosomal enzyme alpha-mannosidase. It is an ultra-orphan disease. In this paper, we report a case of alpha-mannosidosis in a Saudi boy of consanguineous parents, who was referred to our hospital to be worked up for possible mucopolysaccharidosis.

Case Presentation: The patient was presented with dysmorphic features, global developmental delay, hearing defect, and recurrent respiratory tract infections. On examination, he had short stature, a short neck, cataracts, hearing impairment, chest deformity, hepatomegaly, umbilical hernia, right inguinal hernia, and two Mongolian spots in the back. He had normal peripheral blood smear: urinary oligosaccharide and dry blood spot for mucopolysaccharide enzyme assay founded to be negative. Definitive diagnosis was performed by directly sequencing the *MAN2B1* gene of the peripheral blood leukocytes. It showed a homozygous variant c.1065delC; p.Ala356fs*7 (NM_001173498.1) as likely pathogenic.

Conclusion: We report a novel variant mutation in *MAN2B1* gene mutation. Also, to the best of authors' knowledge, this is the first reported case of alpha-mannosidosis in a Saudi patient.

Keywords: MAN2B1, lysosomal enzyme, alpha-mannosidosis, lysosomal storage disease, human gene mutation database.

Introduction

Alpha-mannosidosis [Online Mendelian Inheritance in Man (OMIM): 248500] is an autosomal recessive lysosomal storage disease resulting from the deficiency of the enzyme alpha-mannosidase. It is a rare disease with an estimated prevalence of 1:500.000 (1). It is a multisystemic disorder in which usually affected children appear healthy at birth. Still, later the dysmorphic features appear, and they develop progressive mental retardation, skeletal changes, hearing loss, hepatomegaly and recurrent infections. Some children are born with ankle equinus or develop hydrocephalus in the first year of life.

However, the main feature is immune deficiency manifested by recurrent infections especially in the first decade of life. The affected gene is Mannosidase Alpha Class 2B Member 1 (MAN2B1) (OMIM: 609458), and it is located on chromosome 19p13.2 (1).

A total of 130 disease-associated sequence variants in the MAN2B1 have been identified in 191 patients from 41 countries. Most of the variants were family-specific. However, c.2248C> T (p.Arg750Trp) was detected in 66 patients from 22 countries (2).

Case Report

A 2 year-old Saudi boy was referred to our hospital for investigation of dysmorphic features. This boy was born as a second child of first-degree consanguineous parents with no similar condition in the family (Figure 1). His perinatal history was unremarkable. The patient had recurrent respiratory tract infections and a history of adenoidectomy at the age of 1 year due to obstructive sleep apnea. He had a developmental delay. He started to sit with support at 8 months, crawling at the 1st year, stand with support at 18 months and without support at 30 months. He then became able to walk upstairs with assistance, but he cannot jump until now. He started to coos at the age of 3 months, and he was able to say one word at 12 months, two words at 18 months, and now he

Correspondence to: Rehab Al Jawad
*Department of Pediatrics, Madina Maternity and Children Hospital, Al-Madinah Al-Munawara, Saudi Arabia.
Email: rehab.aljawad@gmail.com
Full list of author information is available at the end of the article.
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says about 10 wards. He cannot hold the pencil properly until now. He cannot copy shapes. He recognizes his family members and places he usually visits. He is toilet trained, and he plays actively with his siblings. He can dress and also can wear his shoes with assistance. On physical examination, his height was 93 cm (5th percentile), his weight was 14 kg (25th percentile), and his head circumference was 50.5 cm (50th percentile). He had coarse facial appearance, frontal bossing, faint eyebrows, hypertelorism, strabismus, depressed nasal bridge, large back ears, protruded upper jaw, gum hypertrophy, high-arched plate, large and protruded tongue and wide mouth (Figures 2 and 3). He had chest excavatum (Figure 3B), umbilical hernia, right inguinal hernia, and multiple Mongolian spots.

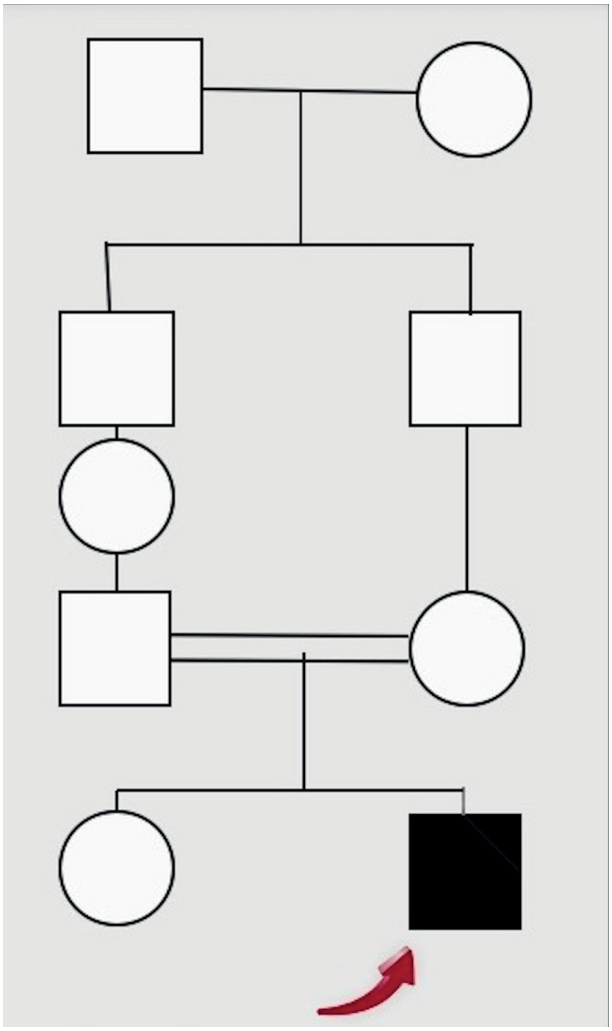

Figure 1. *Pedigree.*

He had two large spots that were observed at the time of birth in the back, their sizes were 4 × 10 cm and 6 × 10 cm, and their colors were green. They subsided gradually until they disappear at the age of 6 years (Figure 3C). He also had mild hepatomegaly and no splenomegaly. Neurological examination revealed hypotonia with slightly impaired power. His sensory examination was normal, but his cerebellar testing showed an unsteady waddling gait. He had genu valgum (knock-knees) and flat foot. Ophthalmologic examination showed cataracts, and audiology examination showed decreased hearing acuity. His hair was excessive in the back, thighs, and upper hands. His peripheral blood smear was normal. Urinary oligosaccharide and dry blood spot for mucopolysaccharide enzyme assay were negative. Peripheral blood sample for sequencing the *MAN2B1* gene showed homozygous variant c.1065delC; p.Ala356fs*7 (NM_001173498.1) that is likely pathogenic. Skeletal X-ray findings showed mild dysostosis multiplex with thickened calvaria, mild bilateral broadening of the ribs, mild scoliosis, and shallow and irregular acetabulum (Figure 4). Initial chest X-ray showed mild cardiomegaly. At the age of 3.5 years, the echo showed hypertrophic cardiomyopathy in mild biventricular hypertrophy. Two years later, he started to have mild aortic insufficiency and trivial pericardial effusion. His brain magnetic resonance imaging was normal. The patient now is 8-year old who is having a moderate intellectual disability. He is partially independent; he needed assistance in the activity of daily living. He is on regular follow up for speech therapy and physiotherapy. Our patient is not a candidate for enzyme replacement therapy or bone marrow transplantation as he was diagnosed after the appearance of complications.

Discussion

The lysosomal storage disorder alpha-mannosidosis is caused by a deficiency of the lysosomal enzyme alpha-mannosidase. The worldwide incidence ranged from 0.07 to 1.51 per 100,000 live births. Globally, 191 cases were reported in the alpha mannosidosis mutation database. The highest number of cases was published in Germany,

Figure 2. *Dysmorphism; A: 3 months; B: 6 months; C: 10 months; and D: 18 months.*

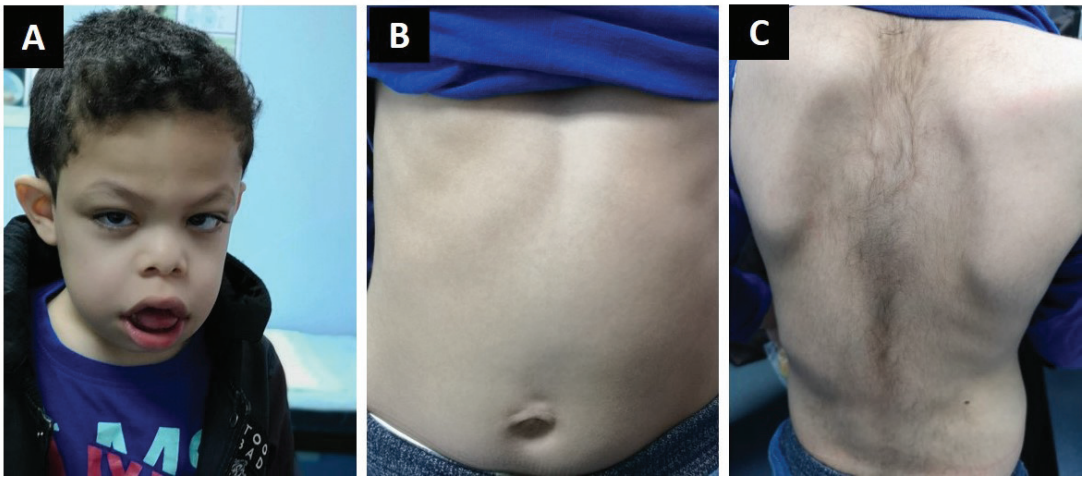

Figure 3. *A: dysmorphism; B: chest excavatum; and C: scoliosis.*

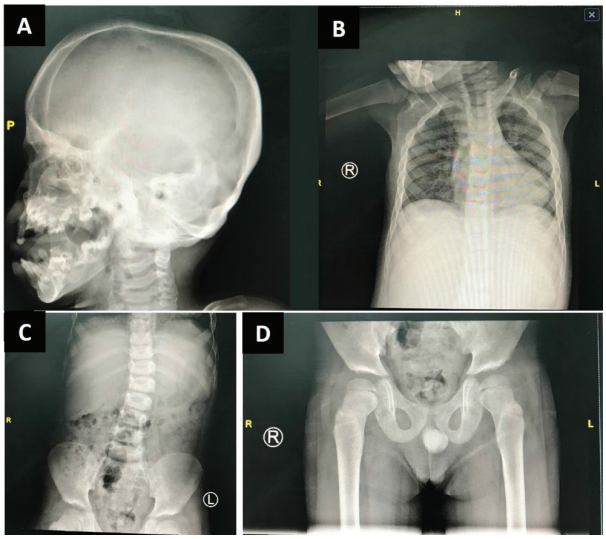

Figure 4. *Skeletal X-ray showing mild dysostosis multiplex with A) thickened calvaria, B) bilateral mild broadening of the ribs, C) mild scoliosis, and D) shallow and irregular acetabulum.*

followed by the United States (27 and 22, respectively) (2). Alpha-mannosidosis is classified into type1, mild and late-onset, and type 2, which is severe and onset early at infancy. Lately, a third clinical subtype has been suggested: they added a moderate form between the previous two types. However, the three clinical phenotypes of alpha-mannosidosis are not distinguishable; they form a series of different severity (1). Alpha-mannosidosis presentation characterized by a range of clinical phenotypes. The significant manifestations are facial dysmorphism, mental retardation, hearing and speech impairment, skeletal changes, immunodeficiency, and recurrent infections of the gastrointestinal respiratory tract, leading to early death (1, 3).

Our case is similar to previously reported cases. A previous case of a Turkish boy diagnosed with alpha-mannosidosis had facial dysmorphism, hearing impairment, dysostosis multiplex, umbilical hernia, widespread Mongolian spots, and recurrent bronchopneumonia. In contrast to our patient, the patient had splenomegaly and pectus carinatum, who didn't have them. The Turkish case founded to have vacuolated lymphocytes on the peripheral blood smear, abnormal urinary oligosaccharide. In addition to detection of low level of alpha-mannosidase activity in serum and cultured skin fibroblasts (4). In our patient's peripheral blood smear and urinary oligosaccharide were normal, dry blood spot for mucopolysaccharide enzyme assay was negative and diagnosed with alpha-mannosidosis by DNA sequencing.

The affected gene in alpha mannosidosis is *MAN2B1*. The gene span is 21.5 kb and includes 24 exons (1). It provides the instructions for making the enzyme alpha-mannosidase. This lysosomal enzyme helps break down complexes of sugar molecules called oligosaccharides that containing mannose. They found no correlation between the mutation types in the *MAN2B1* gene and the disease's clinical phenotype (5). Disease-causing mutations are scattered throughout the gene. The missense mutations were the most common recorded mutation, but other mutations are also detected, such as nonsense, splice site, and small deletion mutations. Some mutations change one amino acid, and others result in an abnormally truncated enzyme or cause the enzyme to be assembled incorrectly. These mutations interfere with the ability of the alpha-mannosidase enzyme to perform its role, causing accumulation of oligosaccharides in the lysosomes and cellular death.

In 191 patients with alpha-mannosidosis, 130 disease-associated sequence variants have been identified in the *MAN2B1* gene. The most common alpha-mannosidosis causing variants are c.2248C>T (p.Arg750Trp) in exon 18, c.1830+1G>C (p.Val549_Gluc610del) in intron 14, and c.2426T>C (p.Leu809Pro) in exon 20 (2). In our patient, the *MAN2B1* gene was sequenced from the peripheral blood leukocytes and showed a homozygous variant c.1065delC; p.Ala356fs*7- (NM_001173498.1) that is likely pathogenic. The classification of this variant as likely pathogenic is based on the American College of Medical Genetics (ACMG) and Genomics scoring criteria for the interpretation of sequence variants (6). Sequencing technology has evolved rapidly with the advent of high-throughput next-generation sequencing. By adopting and leveraging next-generation sequencing, clinical

laboratories are now performing an ever-increasing catalogue of genetic testing spanning genotyping, single genes, gene panels, exomes, genomes, transcriptomes, and epigenetic assays for genetic disorders. By virtue of increased complexity, this shift in genetic testing has been accompanied by new challenges in sequence interpretation. In this context the ACMG convened a workgroup in 2013 comprising representatives from the ACMG, the Association for Molecular Pathology (AMP). This variant was not identified previously. Homogenous variants could be expected with the high degree of consanguinity in Saudi Arabia. Riise Stensland et al. (96 disease-associated sequence variants were identified in 130 unrelated alpha-mannosidosis patients from 30 countries). Eighty-three novel variants were detected, extending the mutation spectrum from 42 to 125. In total, 256 of the 260 mutant alleles (98.5%), mentioned a non-published case in Saudi Arabia with an identified heterozygous variant c.1929-2A>G in intron 15 due to splice mutation (7).

Conclusion

In conclusion, we are reporting a novel homozygous variant in a Saudi patient. The patient had the same symptoms and signs of previously reported cases of alpha-mannosidosis but had normal peripheral blood smear with a negative urinary oligosaccharide.

Author contribution
RAJ conducted the literature review, and prepared the manuscript, OM critically reviewed the manuscript.

List of abbreviations

ACMG	American College of Medical Genetics
MAN2B1	Mannosidase Alpha Class 2B Member 1
OMIM	Online Mendelian Inheritance in Man

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Declaration of conflicting interests
The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication
Written informed consent was obtained from the parents.

Author details
Rehab Al Jawad[1,2], Omhani Malibari[1,3]
1. Department of Pediatrics, Madina Maternity and Children Hospital, Al-Madina Al-Munawara, Saudi Arabia
2. Master of Advanced Studies in Clinical Research, University of California, San Diego, La Jolla, CA
3. Pediatric Metabolic Department, Madina Maternity and Children Hospital, Al-Madina Al-Munawara, Saudi Arabia

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