



Case Report

Congenital disorder of deglycosylation 2. Report of a novel *MAN2C1* pathogenic variant and additional phenotypic implications

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ABSTRACT

The *MAN2C1* gene encodes an enzyme with alpha-mannosidase 2C1 activity, which is responsible for the degradation of defective glycoproteins in the cytoplasm. The purpose of this report is to present a novel *MAN2C1* pathogenic variant in a patient with a congenital disorder of deglycosylation 2. We describe a case with 15q24.1q24.3 microdeletion syndrome which also presented a deleterious variant in the *MAN2C1* gene located at the opposite allele. We discussed the phenotypic consequences when *MAN2C1* gene transcript is missing.

1. Introduction

The *MAN2C1* gene, located at 15q24.2, causes congenital disorder of deglycosylation 2 (CDD2). The phenotypic consequences of CDD2 are facial dysmorphisms, global developmental delay, cerebral dysgenesis such as hydrocephaly, callosal anomalies, hypothalamic hamartoma, interhemispheric cysts, and cerebellar hypoplasia [1]. Microdeletions in the 15q24.1q24.3 region are clinically characterized by global developmental delay, hypotonia, facial dysmorphisms, malformations in the urogenital system, ears, eyes, heart, brain, diaphragm, and skeletal structures [2,3]. In addition, immune system disorders, autism, and myeloproliferative disease [4] are also reported. The clinical spectrum of microdeletions depends on the genes involved in each specific affected individual. Thus, the missing information about the phenotypic-genotypic correlation of 15q24 deletion syndrome is broad. The aim of this report is to present a novel *MAN2C1* gene pathogenic variant in a patient with CDD2 phenotype. Furthermore, we line up the clinical manifestations of CDD2 as part of the 15q24.1q24.3 microdeletion syndrome.

1.1. Case presentation

The proband is the product of the fourth pregnancy, a male patient who was presented for genetic consultation at 3 days old with multiple congenital anomalies. Family history revealed non-consanguineous and healthy parents, a 39-year-old mother, and a 40-year-old father who had four pregnancies. The first pregnancy was a healthy female; the second was a molar pregnancy; and the third was a macrosomic female baby who presented with a birth weight of 4800 g. The rest of the family history is unremarkable. Hydrocephalus was identified in our index case prenatally at 19 weeks of gestation during a routine ultrasound. The delivery occurred at 34 weeks of gestation via C-section due to premature rupture of membranes. He was admitted immediately to the NICU because of prematurity and respiratory distress. In the physical examination, he presented with a birth weight of 2977 g (90th centile), a length of 49 cm (>97th centile), and a head circumference of 37 cm (>97th centile). He also exhibited macrosomia, asymmetrical facial features, a high forehead, epicanthus inversus, a depressed nasal bridge, a wide nasal base, long eyelashes, a left low-set ear with posterior rotation, a right ear normally implanted, and broad thumbs (Fig. 1).

Further MRI evaluation revealed an increased amplitude of the

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supratentorial ventricular system, with an Evans index of 0.47. Stenosis of the Sylvian aqueduct was found, which caused an upward arching of the corpus callosum and displacement of the adjacent parenchyma. Ventriculoperitoneal shunt (VP) was performed, and after surgery, comparative MRI showed an increased amplitude of the cisterna of the velum interpositum and quadrigeminal cistern, hippocampus malrotated to the right, agenesis of the corpus callosum, and frontal hypoplasia (Fig. 1). To complete the diagnostic approach, ophthalmology detected retinal immaturity and optic nerve hypoplasia, and cytogenetic analysis at the 400-band level reported a 46,XY karyotype. Thus, exome sequencing was done where a subsequent result 46,XY,del(15q24.1q24.3).seq[GRCh37/hg19](74,425,095–78,101,598)*1 was detected. Besides, the pathogenic variant c.76_80delTTTAC (p.Phe26Argfs*3) in the *MAN2C1* gene was reported. Informed Consent was obtained from parents for publication purposes.

The last follow-up consultation was conducted at 7 months of age, after which further evaluations were declined, and contact with the family was eventually lost. Up to that point, medical evaluations showed neurodevelopment consistent with his age.

2. Discussion

Tjio and Levan [5] used human embryonic lung fibroblasts to identify the exact number of chromosomes in humans. They both revolutionized not only the field of cytogenetics but also the understanding of the complexity of the genotype-phenotype relationship. After many years, biotechnology has enabled us to take a different approach, termed by Slavotinek [6] as “reverse dysmorphology”, where a copy number variation (CNV) is first identified and then the phenotype of the corresponding chromosomal region is delimited. In this regard, it is essential to note that microdeletions are also classified as contiguous gene syndromes (CGS). Therefore, each patient demands that we personalize the clinical evaluation and management. In this report, we document a case with a central genetic disorder characterized by a microdeletion of 15q24.1-q24.3. Interestingly, the proband also presented a genetic variation in the *MAN2C1* gene located in the same region but on the opposite chromosome. That double genetic alteration allowed the phenotypic overlap between a well-known microdeletion syndrome and a monogenic disorder.

Sharp et al. [3] reported that developmental delay, growth retardation, microcephaly, high anterior hairline, broad medial eyebrows, hypertelorism, downslanted palpebral fissures, broad nasal base, long and smooth philtrum, full lower lip, digital abnormalities, hypospadias, and loose connective tissue are the main traits of the 15q24 microdeletion syndrome. As expected, many other features have been added by recent reports, such as autism [7], myeloproliferative disease [4], behavioral anomalies [8], congenital diaphragmatic hernia [9], cysts in the corpus callosum [10], and common variable immunodeficiency [11]. We have detected a missing fragment in the present proband at

15q24 (74425095–78,101,598), with a length of approximately 3.68 Mb. This region contains 22 genes, of which seven are associated with autosomal dominant conditions; the *MAN2C1* gene is one of the 15 listed as recessive.

On the other hand, protein glycosylation is a post-translational process in which a glycoside (oligosaccharide) from the rough sarcoplasmic reticulum is attached to the synthesized protein, creating a glycoprotein. This change allows the peptide to generate cell signaling properties, protection against proteases, proper folding, and increases its solubility [12]. The *MAN2C1* gene, which encodes an enzyme with alpha-mannosidase 2C1 activity, is responsible for the degradation of glycoproteins in the cytoplasm [13]. Mutations in this gene result in a decrease in catalytic activity, which promotes the persistence of misfolded or nonfunctional proteins within the cell, thereby interfering with their normal function [1]. It was reported the variant c.76_80delTTTAC (p.Phe26Argfs*3) in the *MAN2C1* gene located at the non-deleted allele of the proband. Consequently, our patient presented at the same time, the clinical diagnosis of congenital disorder of deglycosylation type 2 (CDD2). The mentioned variant identified in this patient is a five-nucleotide deletion in exon 1 of the *MAN2C1* gene. This deletion, being located at the beginning of the coding sequence, generates a change in the reading frame starting at codon 26 and results in the substitution of this for an arginine, followed by the appearance of a premature termination codon (p.Argfs3) at position 3. The *MAN2C1* (cytosolic alpha-mannosidase) protein (Fig. 2-A) plays a crucial role in the process of glycoprotein deglycosylation, specifically in the removal of mannose residues from complex oligosaccharides in the cytosol. This enzyme participates in the degradation pathway of glycoproteins that have not been correctly folded in the endoplasmic reticulum [14]. Loss of the five nucleotides in the c.76_80delTTTAC variant produces a significantly truncated protein of only 28 amino acids compared to the full-length *MAN2C1* protein consisting of 978 amino acids (Fig. 2-B). Severe truncation of the *MAN2C1* protein, as revealed by in silico analysis, predicts the complete disruption or total loss of its catalytic function, as the remaining portion of the protein is insufficient to form a functional domain or maintain the three-dimensional structure necessary for enzymatic activity. Based on the criteria of the American College of Medical Genetics and Genomics (ACMG), this variant meets some of the requirements to be considered disease-causing [15].

There is limited information about CDD2. Akula et al. [16], for example, reported an individual with polymicrogyria associated with compound heterozygous pathogenic variants in the *MAN2C1* gene. Gialluisi et al. [17] found an association of heterozygous variants in the *MAN2C1* gene with late-onset Parkinson's disease. The most detailed report about the phenotypic impact of biallelic pathogenic variants in the *MAN2C1* gene was done by Maia et al. [1]. In Table 1, we gathered most of the phenotypes reported in the medical literature (MIM#154580; [1,3]). After the clinical comparison, we determined that the phenotype of our proband is more compatible with CDD2.

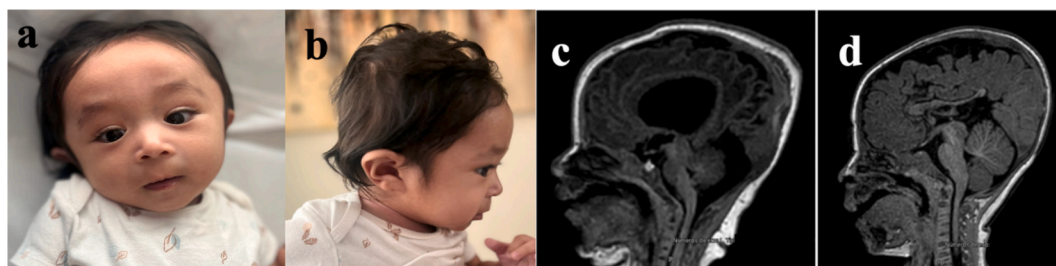


Fig. 1. Craniofacial traits in the index case and cranial magnetic resonance imaging (MRI). (a) Subtle asymmetric face, left side shorter, high and prominent forehead, epicanthic inversus, eyelashes trichomegaly, depressed nasal bridge, long and flat philtrum. (b) Brachycephaly, earlobe coloboma, and prominent antihelix. (c) Pre-surgery findings: Supratentorial dilatation of the ventricular system, stenosis of the aqueduct of Sylvius, and dilatation of the superior cerebellar cistern and cisterna magna with compression of the cerebellum. (d) Post-operative findings after VP shunt placement: Frontal hypoplasia, corpus callosum dysgenesis with splenium hypoplasia, and quadrigeminal cistern dilatation.

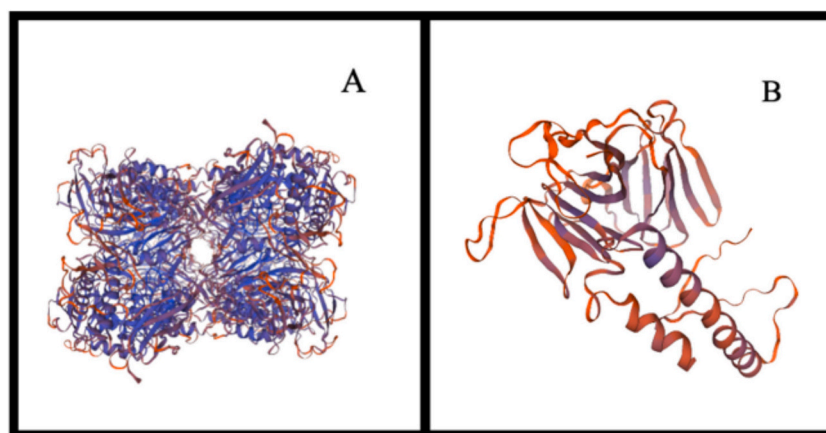


Fig. 2. Protein prediction of both the wild type and the mutated proteins. (A) Tridimensional protein structure of *MAN2C1* alpha-mannosidase. Obtained from: <https://swissmodel.expasy.org/>. (B) Tridimensional structure of the product of the frameshift variant identified in the patient, causing an early-truncating *MAN2C1* protein. Obtained from an in silico prediction model at: <https://swissmodel.expasy.org/>.

Table 1

Clinical and imaging comparison between 15q24.1q24.3 microdeletion syndrome and CDD2.

Phenotype	15q24.1q24.3 microdeletion syndrome	CDD2	Proband
Growth retardation	+	–	–
Overgrowth	–	–	+
Macrocephaly	–	+	+
High forehead/high anterior hairline	+	+	+
Broad medial eyebrows/hypertelorism	+	–	–
Downslanted palpebral fissures	+	–	–
Broad nasal base	+	–	+
Long and smooth philtrum	+	–	+
Full lower lip	+	–	–
Micro/retrognathia	–	+	+
Facial asymmetry	–	+	+
Microtia	–	+	+
Hearing loss	–	+	+
Retinal coloboma	–	+	+
Tongue hamartoma/slightly enlarged tongue	–	+	–
Cleft palate/high-arched palate	–	+	+
Joint abnormalities	+	+	–
Broad thumbs	–	+	+
Congenital strabismus	–	+	+
Renal-genitals abnormalities	+	+	–
Intellectual disability	+	+	NA
Motor impairment	+	+	+
Polymicrogyria	–	+	+
Ventriculomegalia	–	+	+
Hypothalamic hamartoma	–	+	–
Vermis hypoplasia	–	+	+
Heterotopia	–	+	–
Brainstem hypoplasia	–	+	+
Autism spectrum disorder	+	+	+
Behavioral problem	+	+	NA
Developmental delay	+	+	+

NA – Not Available.

The clinical presentation of the reported individual shows overlapping features of both *MAN2C1*-CDDG and the associated microdeletion syndrome; however, manifestations typically attributed to *MAN2C1* deficiency were more prominent. This phenotypic distribution may reflect variable expressivity and differential gene dosage effects. While the microdeletion encompasses multiple genes, not all are necessarily dosage-sensitive or contribute equally to the phenotype. In contrast, the identified *MAN2C1* variant is predicted to have a direct and substantial impact on protein function, potentially representing the

primary driver of the clinical manifestations.

Furthermore, incomplete penetrance and the influence of genetic modifiers may explain the absence of certain expected features from either condition. Such variability has been widely reported in rare congenital disorders of glycosylation and chromosomal microdeletions, emphasizing the complexity of genotype–phenotype relationships in these patients.

In summary, we propose that the variant c.76_80delTTTAC (p. Phe26Argfs*3) in the gene *MAN2C1* can be considered a disease-causing variant. Furthermore, we reported a new individual with a phenotype constellation compatible not only with a microdeletion syndrome but also, more specifically with CDD2. Also, we reinforced the need to add clinical information about the catabolism of free oligosaccharides disorders as much as possible.

2.1. Limitations

A limitation of this study is the absence of functional validation at the protein level. Due to loss of patient follow-up, no additional biological samples were available to assess *MAN2C1* protein expression or stability by Western blot or related assays. As a result, the pathogenicity of the identified variant is inferred from in silico predictions, variant rarity, and phenotypic correlation rather than direct functional evidence. Future studies including functional characterization will be important to confirm the molecular mechanisms underlying *MAN2C1* deficiency. Similar limitations have been reported in rare disease studies where sample availability is constrained, underscoring the challenges of functional validation in ultra-rare disorders.

Another limitation we identified was our inability to conduct long-term clinical follow-up with the patient and their family, which limited monitoring of his neurodevelopment and prevented us from identifying other neurological complications, such as seizures or behavioral problems, in a timely manner.

Authors contribution

ANLA: Conceptualization, review and editing, patient care, methodology; **RMVU:** Conceptualization, formal analysis, validation, writing original draft, review and editing; **HRMF:** Writing original draft, review and editing; **MDE:** Project administration; Funding acquisition; **CPMR:** Conceptualization, review and editing, patient care, methodology; **ALMA:** patient care; **OPE:** Writing original draft; **AGRL:** Conceptualization, Supervision, validation, writing original draft, review and editing.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

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