

A recurrent mutation in Moroccan patients with Dyggve-Melchior-Clausen syndrome: Report of a new case and review

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Dyggve-Melchior-Clausen (DMC) syndrome is a rare autosomal recessive disorder. It is a spondyloepimetaphyseal dysplasia associated with mental retardation. Clinical manifestations include coarse facies, microcephaly, short trunk dwarfism, and mental retardation. Mutations in Dymeclin gene (*DYM*), mapped to chromosome 18q21.1, is responsible for DMC. We report here the observation of a consanguineous Moroccan patient having DMC syndrome. The molecular studies showed a previously reported homozygous mutation at c.1878delA of *DYM* gene. We discuss this recurrent mutation in Moroccan patients with DMC syndrome with a review.

Key words: Dyggve-Melchior-Clausen syndrome, *Dymeclin* gene, recurrent mutation

Introduction

Dyggve-Melchior-Clausen (DMC) syndrome (OMIM 223800) is a rare autosomal recessive spondyloepimetaphyseal dysplasia. Less than 80 cases have been reported. The first cases described with a condition resembling Morquio-Ullrich disease were reported by Dyggve *et al.*^[1] It is characterized by microcephaly, short trunk dwarfism, mental retardation,

and coarse facies. Radiographs show generalized platyspondyly with double-humped end plates, irregularly ossified femoral heads, a hypoplastic odontoid, and a lace-like appearance of iliac crests that are pathognomonic and distinctive of DMC syndrome.^[2] This phenotype is similar to Morquio syndrome (mucopolysaccharidosis [MPS] type IV), but the absence of corneal clouding, the mucopolysacchariduria, and the characteristic radiological findings differentiate this syndrome from MPS IV and DMC. A definite diagnosis is possible by electrophoresis of glycosaminoglycans (GAGs) in the urine and the radiographic findings. Mutations in the *Dymeclin* gene (*DYM*) on chromosome 18q12.1 are responsible for DMC.^[3] Smith-McCort dysplasia (OMIM: 607326), a rare variant of DMC syndrome without MR, was shown to be allelic to DMC syndrome.^[4] The *DYM* gene is composed of 17 exons, encoded for the Dymeclin protein, which is widely expressed in brain, cartilage, and bone.^[5] Dymeclin is a novel peripheral membrane protein that shuttles rapidly between the cytosol and mature Golgi membranes and have an important role in cellular trafficking.^[6] We report here a three-year-old Moroccan boy with typical features of DMC. The molecular studies showed the recurrent homozygous mutation at c.1878delA of *DYM* gene, previously reported in Moroccan patients.

Case Report

The patient is a 3-year-old male, second child of

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healthy Moroccan consanguineous parents. Pregnancy and delivery were normal, and the child was born at term with normal physical measurements at birth. He had short stature and developmental delay. His growth was regular until the age of 18 months. He was hyperactive and has sleep disturbance. At the age of 3 years, his length was 75 cm (<3rd percentile), his weight was 10.5 kg (<3rd percentile), and his head circumference was 45 cm (<3th percentile). The proband's facies was characteristic of DMC, with trigonocephaly, low implanted ears, wide mouth, prominent mandible, and short trunk. He also had sterna bulging, pectus carinatum, bulging of the chest, and short neck. Upper limbs were short and hands were broad. The low limbs were short with extension defects of the knee and genu valgum. He had delayed closure of anterior fontanel. Neurological examination was normal.

MPS was excluded by quantitative estimation and electrophoresis of GAGs. Radiographs showed generalized platyspondyly, the presence of C1-C2 instability, and hypoplasia of the odontoid, with mild notching of the superior and inferior margins of vertebral bodies. There was a slight dorsal scoliosis. The iliac wings were hypoplastic and square with a horizontal acetabular roof. The ilia was small, iliac crests were broad and had irregular margin. The femoral capital epiphyses were small and poorly ossified with multiple small ossification centers [Figure 1]. Long bones were short and stocky, metaphyses were widened, and ribs were flared discretely. The carpal and tarsal bones were misshapened with a discrete cone epiphyses in the phalanges of the hands. Before these characteristic

clinical and radiological features, the diagnosis of DMC syndrome was considered. His oldest sister and parents were clinically normal.

Informed consent was obtained from the proband's parents prior to implementation of the genetic studies reported here. Peripheral blood was collected from the affected child. Molecular genetic testing for suspected DMC syndrome was performed by complete DNA-sequence analysis of the *DYM* gene. This leads to identify the homozygous mutation at c.1878delA (p.K626NfsX94). This mutation in exon 17 of *DYM* gene results in a frameshift alteration and a newly created stop codon at position 719.

Discussion

We describe here a consanguineous Moroccan patient with DMC syndrome due to a recurrent homozygous *DYM* mutation. To the best of our knowledge, the mutational spectrum of *DYM* gene in Moroccan patient was indexed in The Moroccan Human Mutation Database (<http://www.sante.gov.ma/Departements/INH/MoHuMuDa/index.hmt>). The c.1878delA found in our patient is the most common *DYM* mutation and was previously reported in six unrelated DMC Moroccan patients (11 alleles), four reported by El Ghouzzi *et al.* and two by Paupe *et al.*, added to our patient (two alleles) 13/24 alleles, that means 54% of all Moroccan *DYM* mutations reported.^[5,7] Patients carrying this mutation have classical features of DMC. Our patient had microcephaly, short trunk dwarfism, mental retardation, and coarse facies.

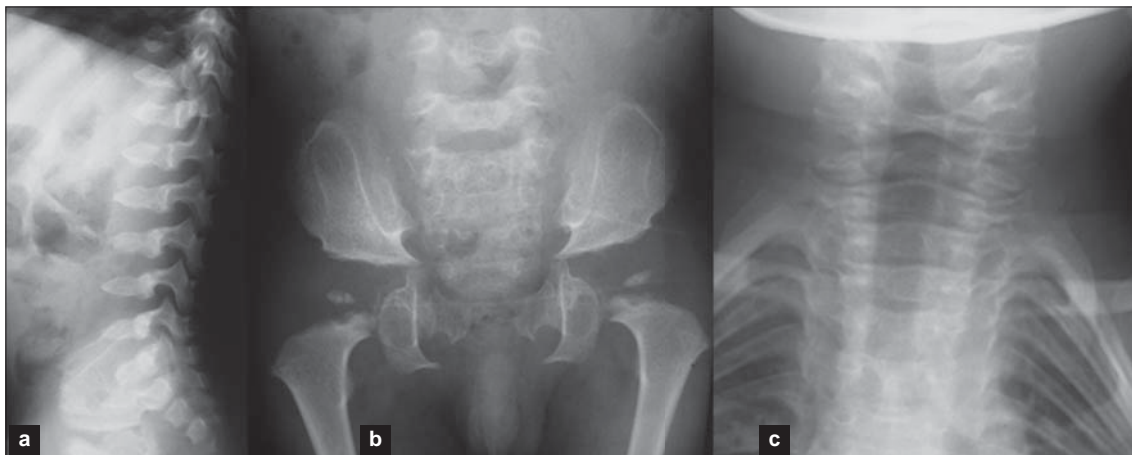


Figure 1: Radiographs of the patient. (a) spine, (b) pelvis and hip joints, (c) cervical of spine

His radiographs showed features described in DMC, platyspondyly with central depression of end plates exhibiting a double-hump shape, C1-C2 instability, and hypoplasia of the odontoid, broad ribs, narrow small pelvis with fine sclerotic bony irregularity giving a lace-like appearance of iliac crests, and irregular acetabular cavities.

Among the six families reported, four were consanguineous. Since DMC with c.1878delA mutation occur with a relatively high frequency, this suggests a founder effect of this mutation in Moroccan population, favored by the high rate of consanguinity (15.25%) in Moroccan population.^[6] Other Moroccan mutations were reported: IVS 10 1125+1G>T, 610C>T, 1447C>T, and 656T>G.^[5,7] Other mutations were reported in DMC patients as substitutions, frameshift mutations, and complex genomic rearrangements which, when expressed, result in exon duplication or repetition.^[9]

We can propose for Moroccan DMC patients to search in first time this recurrent mutation at c.1878delA (54% of all Moroccan *DYM* mutations reported) before screening all the genes. Concerning genetic counseling of the patient, his parents have 25% of risk of recurrence for having another affected child. For the management of the patient, difficult airway due to short neck, macroglossia, and the disturbance of neck flexion was described. DMC syndrome may be more frequent in Morocco than previously reported, especially due to misdiagnosis, or wrongly diagnosed as Morquio syndrome. Awareness of the characteristic features of the syndrome will prevent misdiagnosis. The high consanguinity rate (15.25%) in Morocco favors autosomal recessive disorders. Accurate diagnosis is a prerequisite for proper genetic counseling and management. Molecular studies and the identification of *DYM* gene mutations are important steps to provide an insight into the genetic heterogeneity of the

families and improve the management of patients with DMC syndrome.

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