



Research paper

A novel homozygous LMNA mutation (p.Met540Ile) causes mandibuloacral dysplasia type A



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ABSTRACT

Mandibuloacral dysplasia with type A lipodystrophy (MADA) is a rare genetic disorder inherited in an autosomal recessive fashion characterized by hypoplasia of the mandible and clavicles, acroosteolysis and lipodystrophy due to mutations in the LMNA or ZMPSTE24 genes. In the current study, we have investigated a consanguineous family clinically diagnosed with mandibuloacral dysplasia type A having an affected child for the LMNA gene alteration(s). Mother is now 15 weeks pregnant, seeking advice on the health of her fetus.

Peripheral blood was obtained from all family members after informed consent was achieved.

Genomic DNA was isolated. The sequence of the LMNA gene, including all exons and intron boundaries was analyzed by PCR and Sanger sequencing. Chorionic villus was collected from the placenta to reveal the condition of the fetus.

Molecular analysis ascertained a homozygous mutation c.1620G>A (p.M540I) in the proband and heterozygous alteration in the family. Genomic DNA isolated from the CVS was amplified using specific primers for identified deleterious mutation and analyzed by Sanger sequencing. Two pathogenic mutations c.1620G>A and c.1698C>T were identified in the fetus.

Genetic counseling as well as justified rapid and sensitive genetic testing can provide reassurance for the families to prevent the high burden of genetic disorders.

We have also applied several online tools including PolyPhen2, MUpro, SIFT, PoPMuSiC, Project HOPE and Mutation Taster to predict the impact of p.Met540Ile substitution as a hotspot region within LMNA. All tools showed reduction in the stability of the protein structure. We conclude that p.M540I mutation may cause disease in the homozygous state.

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1. Introduction

Mandibuloacral dysplasia (MAD; OMIM 248370) is a unique genetically and phenotypically heterogeneous disease with an autosomal recessive mode of inheritance identified by skeletal deformities, growth retardation, craniofacial abnormalities, under developed mandible and clavicles (causing small chin and sloped shoulder appearance), round bulbous finger tips (acro-osteolysis), skin pigmentation, joint

complications, prominent veins, metabolic disorders such as diabetes and lipodystrophy which is the most common characteristic of MAD. Some affected individuals may also display features of premature aging (Progeria) such as dental anomalies, thinning of skin, alopecia, nail dysplasia, pinched nose and bulging eyes (Al-Haggar et al., 2012). Based on the distribution pattern of fat throughout the body, mandibuloacral dysplasia is divided into two types of MADA and MADB. Type A is partial lipodystrophy with degeneration of fat tissue from the torso and limbs and type B is generalized lipodystrophy with loss of fat from the face, torso and limbs (Simha et al., 2003). Mutations in the two genes LMNA and ZMPSTE24 cause type A and type B respectively. LMNA encode lamin A and C the fibrous matrix of the inner surface of the nuclear envelope through alternative splicing (Novelli et al., 2002) and ZMPSTE24 encodes a zinc metalloproteinase involved in the post-translational processing of prelamin A to mature lamin A to become the component of nuclear lamina (Agarwal et al., 2003). In comparison to MAD patients with LMNA mutations, individuals with

Abbreviations: MADA, mandibuloacral dysplasia type A; MADB, mandibuloacral dysplasia type B; LMNA, lamin A; ZMPSTE24, Zinc Metalloproteinase STE24; PND, Prenatal Diagnosis.

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ZMPSTE24 mutations are premature at birth and express early onset symptoms with more severe clinical phenotypes, but since the main clinical features are common in the impaired genes; differential diagnosis can be crucial (Ahmad et al., 2010).

Here we report the first novel homozygous missense mutation (p.M540I) in the *LMNA* gene of a boy born to a consanguineous family from Iran presenting early onset MAD associated with progeria and lipodystrophy. The mother was 15 weeks pregnant at the time of genetic test reports.

2. Clinical description

The subject was presented directly to the craniofacial surgery clinic at Dental school of Shahid Beheshti University of Medical Sciences (SBMU) at the age of 13 for treatment of malocclusion (crowded teeth) and mandibular dysfunction. The family referred to the Genomic Research Center at SBMU for genetic counseling to learn the probability

of abnormalities in their next child as well as options for prenatal diagnosis.

The subject was born to apparently healthy parents and was delivered full term by caesarean section with birth weight (3.250 kg), height (55 cm), Apgar score (10) and with no clear symptoms at birth. Dentition erupted at 9 months and walking started at 18 months normally. He showed no symptoms and was completely healthy until stunt growth and low weight appeared at 10 months of age. Soon after, he presented irregularities in fingers followed by gradual restriction of mobility.

At the age of 14, thorough clinical examinations revealed short height (143 cm) and low weight (38 kg) with normal head circumference. He had low-set ears, temporomandibular joint (TMG) dysfunction with a minor double chin, round bulbous fingers, proptosis, prominent cheeks, irregular teeth, dental crowding and progeric appearance. Degeneration of subcutaneous fat was evident in the entire body but more predominant in fingers and toes. Musculoskeletal examinations

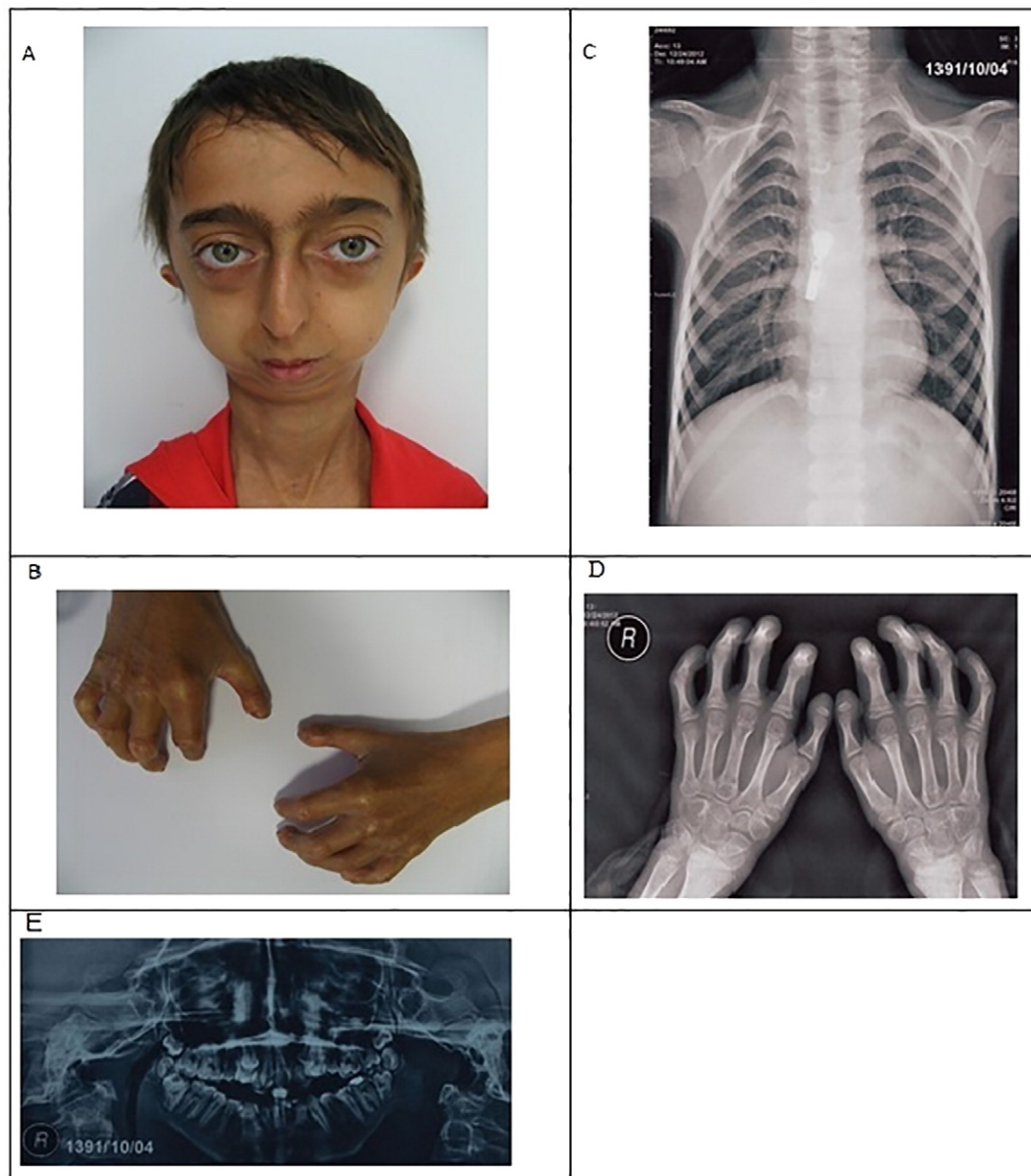


Fig. 1. Clinical and radiology features of the patient. A) The patient has a small nose, thin light brown hair, prominent cheeks, low-set ears, micrognathia, and slight double chin with drooping shoulders. B) Bulbous round fingers consistent with acroosteolysis. C) Chest X-ray shows bilateral absence of clavicles. D) X-ray film of the distal phalanges of the hands shows irregularity of the tufts of all terminal phalanges, consistent with acro-osteolysis. E) Dental X-ray reveals malocclusion and overcrowding teeth.

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