ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 10, pp. 20722-20725, October, 2017

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

POPULATION GENETIC DYNAMICS EXPLAIN THE PRESENCE OF THE ARAB MUTATION OF DDR2 GENE IN A MOROCCAN PATIENT WITH SPONDYLO-META-EPIPHYSEAL DYSPLASIA, SHORT LIMBS-ABNORMAL CALCIFICATIONS TYPE

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DOI: http://dx.doi.org/10.24327/ijrsr.2017.0810.0949

ARTICLE INFO

Article History:

Received 05th July, 2017
Received in revised form 08th August, 2017
Accepted 10th September, 2017
Published online 28st October, 2017

Key Words:

spondylo-meta-epiphyseal dysplasia, autosomal recessive, *DDR2* gene, recurrent mutation

ABSTRACT

Spondylo-Meta-Epiphyseal Dysplasia Short Limbs Abnormal Calcifications type (SMED,SL-AC) is a rare autosomal recessive disorder clinically characterized by dwarfism, peculiar facial dysmoprphism, muscular hypotonia, short limbs, small hands and normal intelligence. Main radiological findings are broad and short bones in the extremities and pelvis, vertebral and costal abnormalities, metaphyso-epiphyseal changes and abnormal calcifications. Mutations in *DDR2* gene are known to be responsible for this disease with recurrence of the arab mutation (p.Arg752Cys) at exon 17. By reporting this recurrent mutation for the first time in a Moroccan patient with SMED,SL-AC, we reveal the transfer of this mutation from arabian peninsula to morocco through migration of population.

INTRODUCTION

Spondylo-Meta-Epiphyseal- Dysplasias (SMED) are a heterogeneous group of bone disorders including several entities defined by radiological abnormalities of spine, epiphyses and metaphyses with different clinical features, evolution and modes of inheritance (1-6).

Spondylo-Meta-Epiphyseal Dysplasia, Short Limbs-Abnormal Calcifications type (SMED,SL-AC) (MIM 271665) formerly known as Spondylo-Meta-Epiphyseal Dysplasia, Short Limbs-Hand Type is a very rare bone dysplasia with autosomal recessive inheritance and variable progression (1, 7-9). This genetic disorder was first reported in three patients in 1993 by Borochowitz *et al* who also provided the first histologic description for the disease (10, 11).

SMED,SL-AC is clinically characterized by short stature, shortening of the lower and upper limbs, narrow chest, facial dysmorphism, normal intelligence and muscular hypotonia (1, 6, 8, 9).

Major radiographic findings include platyspondyly, short ribs, shortened long tubular bones with irregular metaphyses and epiphyses and premature calcification of cartilaginous structures (9, 11).

SMED, SL-AC is due to mutations in *DDR2* gene, a member of the receptor tyrosine kinase family involved in signal transduction (1, 6, 8, 12).

Here, we report the case of a moroccan consanguineous patient with clinical and radiological features specific to SMED,SL-AC who had the arab recurrent mutation.

Case report

Clinical description

The patient was two-year-old girl born of a healthy consanguineous Moroccan couple, aged 24 and 31, she is a unique child. Pregnancy course was normal and delivery was uneventful. The family history was unremarkable. There were no miscarriages. The girl was referred at the age of 22 months

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to the consultation of medical genetics for diagnosis of achondroplasia, which was excuded by molecular analysis.

On clinical examination at 22 months, her head circumference was 50 cm (+2SD), length 64 cm (-4SD) and weight 8kg (-4SD). She presented with generalized hypotonia, delayed motor development and poor head control. Dysmorphic examination shows prominent forehead with mid-face hypoplasia, hypertelorism, low set ears, short nose, anteverted nares and long philtrum. There was narrow chest, short limbs with bowed lower limbs, small puffy hands and short fingers (Fig 1)

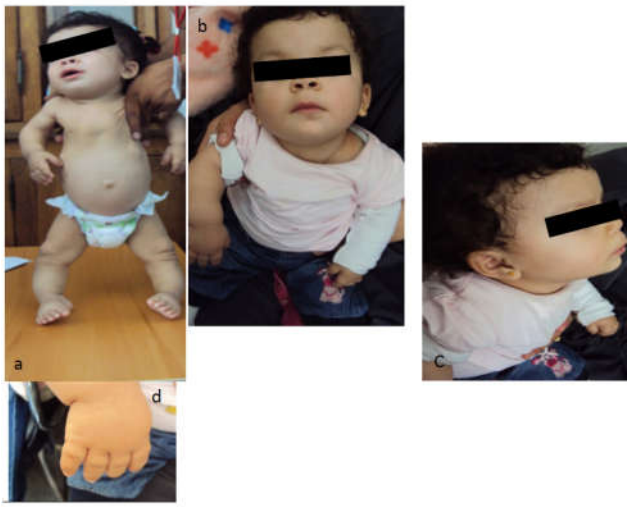

Fig 1 Physical features of the patient showing short stature, short limbs, narrow chest, bowed lower limbs (a) dysmorphic face (b,c), and short puffy hands (d).

Radiographs taken at this age showed: a wide cranial sutures, short ribs, platyspondyly with wide intervertebral spaces, shortened long tubular bones with irregular metaphyses and epiphyses, markedly shortened broad metacarpals and phalanges and odontoid hypoplasia (Fig 2).

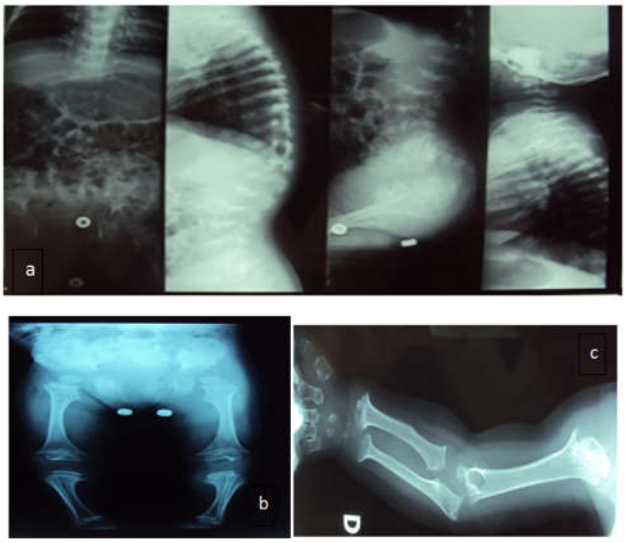

Fig 2 Twenty two months of age. Odontoid hypoplasia, platyspondyly, wide intervertebral spaces; short ribs (a) pelvis deformity (b)shortened long tubular bones of the upper and lower limbs with metaphyseal widening and epiphyseal irregularities (b,c)

Based on clinical and radiological data, diagnosis of SMED, SL-AC was evocated.

METHODS

EDTA blood samples were collected after informed consent from the patient and her parents. DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Inc.) Targeted amplification of exon 17 of *DDR2* gene was performed by Polymerase Chain Reaction (PCR). Then, amplified fragments were purified and sequenced on an automated ABI prism 3130 DNA sequencer (life technologies) using Big Dye Terminator Kit (life technologies, Foster city, CA). Obtained sequences were aligned to the *DDR2* reference genomic sequence (GenBank: NM_001014796).

RESULTS

We identified a single homozygous base substitution c.2254C>T in coding exon 17, that results in Arginine to Cysteine amino acid change: p.Arg752Cys. It is the Arab recurrent mutation (Fig 3).

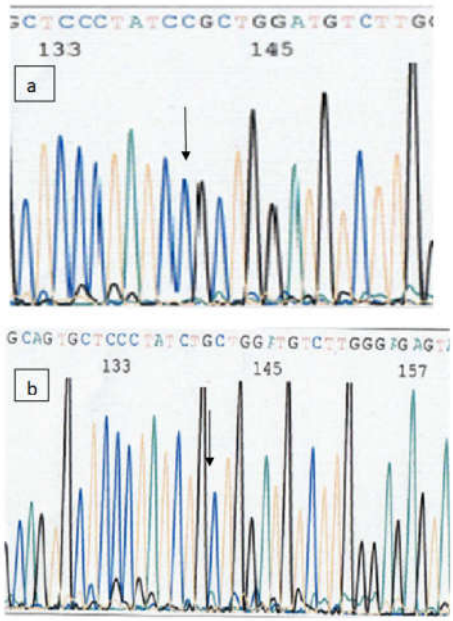

Fig 3 The electrophoregrams show the exon 17 sequences of DDR2 gene of a normal control (a)and the proband (b). The patient was homozygous for the arab recurrent mutation c.224C>T (p.Arg752Cys).

This mutation was present in heterozygous state in both of the girl's parents.

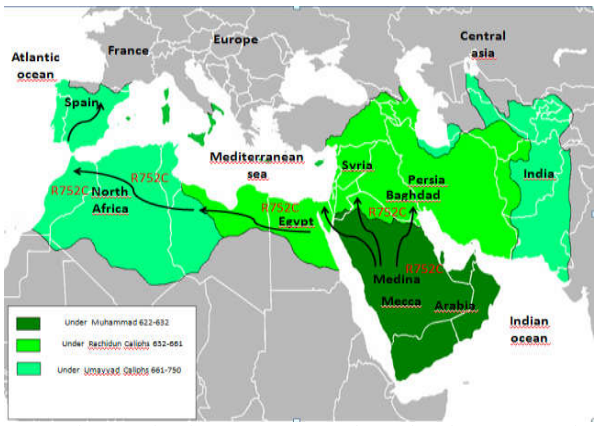

Fig 4 Arab expansion from 622 to 750 and transfer of R752C mutation from Arabian Peninsula to North Africa

DISCUSSION

SMED,SL-AC is a very rare autosomal recessive bone disease of unknown prevalence. To date 27 patients have been described mainly in Jerusalem, Egypt, UAE, Oman, Algeria, Pakistan and Puerto-Rico (6, 7).

A wide phenotypic variation is observed but characteristic clinical features are facial dysmorphism, muscular hypotonia, short stature, short limbs and hands with a narrow chest (1, 6, 8, 9).

Early Radiological abnormalities are flattening of vertebral bodies with wide intervertebral spaces, short ribs, open fontanelles, broad and short pelvic bones, broadening and shortening of the long bones as well as tubular bones of the hand and flared metahyses. Some patients may show massive C2 vertebral body or narrowing of the spinal canal (9, 11, 13). Disease progression is highly variable and characterized by C1-C2 level cord compression, kyphoscoliosis, bowing of the limbs, metaphyseal and epiphyseal changes and abnormal calcifications (9). Calcifications of costal cartilages and epiphyses occur at the age of around one year in most patients (11). However, according to a review of the literature, the time of onset and severity of calcifications are highly variable and their absence should not exclude the diagnosis of SMED,SL-AC even in children aged 2 years (6, 9, 11).

Most patients show motor development delay with normal intelligence. However some patients with mental retardation are reported (11, 14, 15).

SMED,SL-AC is due to mutations with loss of function of *DDR2* gene on chromosome 1q23.3. This gene comprises 19 exons and encodes a DDR2 protein: Discoidin Domain Receptor 2, consisting of 855 aa and belonging to the protein kinase super family, which is involved in signal transduction, regulation of migration, proliferation and cellular differentiation (1, 6, 8, 12, 16). A recent role as regulator of ovarian function was revealed for this protein (17, 18). A total of seven mutations are reported in the literature including 5 missense, one small deletion and a splicing mutation, with a hotspot at the exon 17. The c.2254C>T (p.Arg752Cys) mutation was previously described in 8 patients of Arabic origin, namely 6 patients from 5 different Arab Muslim families from the Jerusalem area and two affected children from an Emirati family of Egyptian background. The parental consanguinity was present in most of these cases (1, 6, 8, 19). The chromosomes carrying the p.Arg752Cys mutation found in the Palestinian families described by Bargal *et al*. share a common haplotype, suggesting a founder mutation (1).

Early deaths were reported in many patients with SMED,SL-AC due to spinal cord compression or respiratory failure. Regular monitoring for these complications is essential (2, 9, 13, 15).

Few conditions are similar to SMED,SL-AC. Achondroplastic patients demonstrate decreased interpediculated distance, which is not present in the patients with SMED,SL-AC; cartilage calcification is not present, the ribs are longer and the configuration of the acetabulum differs (9).

Autosomal recessive Rhizomelic chondrodysplasia punctata type 1 can be excluded on clinical and radiological features: stippled calcifications are an early finding in this condition which is also expressed by cataract, skin disease and congenital heart defects. Metatropic dysplasia is easily distinguished from SMED,SL-AC (2, 9).

Clinical and radiological findings of the proband mainly facial dysmorphism suggested the diagnosis of SMED,SL-AC. This rare disease can be considered even if abnormal calcifications are not yet present.

Targeted sequencing of exon 17 of *DDR2* gene identified the Arab recurrent mutation p.Arg752Cys in the proband, from a Moroccan consanguineous couple of Arab origin.

The clinical phenotype and the degree of chondral calcification of the patients with arab recurrent mutation were very severe in comparison with other mutations (1, 8). The proband presented also severe clinical features (hypotonia, delayed motor development and C1-C2 instability) except precocious and extensive abnormal calcifications.

The present case is the second reported from Morocco, the first one was described by Mansouri *et al* in a Moroccan girl in whom whole exome sequencing led to the identification of a novel homozygous missense mutation in *DDR2* gene (6).

The parents of the patient are first cousins. Genealogical tree evocating a recessive inheritance can help to differentiate SMED, SL-AC disease from other SEMD as well as other bone diseases with different inheritance pattern.

Our proband is at risk for developing severe neurological complications due to odontoid hypoplasia and may need surgical decompression.

We reveal here the presence of the Arab mutation c.2254C>T (p.Arg752Cys) of *DDR2* gene in the Moroccan population. Arab expansion began in the 7th century with the Islamic prophet Muhammad and conquests of the Maghreb took place from 670 to 742 under Umayyad caliphs. Thus, migration, centuries ago, of population from the Arabian Peninsula to Morocco promoted the transfer of c.2254C>T mutation and contributed to the genetic diversity of moroccan population(20)(Fig 4).

Clinical diagnosis of SMED,SL-AC disease in this patient was confirmed by molecular analysis and allowed us to propose an accurate genetic counseling and prenatal diagnosis for this family.

Abbreviations

PCR: Polymerase Chain Reaction.
UAE: United Arab Emirates
DDR2: Discoidin Domain Receptor 2
SD: Standard deviation

Author's contribution

WJ, MM carried out the molecular genetic study and drafted the manuscript. AC provided clinical data. AS participated in the design of the study and in the draft of the manuscript.

Acknowledgments

We are grateful to the patient and her family for their collaboration.

Author Disclosure Statement

The authors declare that they have no competing financial interests.

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How to cite this article:

Jdioui W *et al*., Population Genetic Dynamics Explain The Presence of The Arab Mutation of ddr2 Gene In A Moroccan Patient With Spondylo-Meta-Epiphyseal Dysplasia, Short Limbs-Abnormal Calcifications Type. *Int J Recent Sci Res.* 8(10), pp. 20722-20725. DOI: http://dx.doi.org/10.24327/ijrsr.2017.0810.0949

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